The University of Hull

From Bench to Bedside:

The Development of a Location Indicating Nasogastric Tube

being a Thesis submitted for the Degree of

PhD in Nursing

The University of Hull

Faculty of Health and Social Care

By

Barbara Elaine Elliott

MSc (University of Manchester) BNurs (University of Manchester)

December 2014

Acknowledgements

This thesis has been completed with the generous advice, support and encouragement of my supervisors, Dr Peter Draper and Professor John Greenman. Their knowledge and experience was invaluable and I am extremely grateful for their guidance. I would also like to acknowledge the support given by all members of the project team at University of Hull, Prof John MacFie, Dr Monika Schoenleber, Dr Rob Singh and Dr Jay Wadhawan and further afield Prof Linda Shields in Australia.

Dr Monika Schoenleber advised and assisted with experiments for chapter 4 and conducted extensive testing of the prototype tubes informing decisions regarding the final design of the medical device. I am sincerely grateful to her and for the contributions of Sandra Burley and Margaret Crawley, formerly of the University of Hull, to discussions regarding the user carer network. Pam Locker from Lincoln University gave valuable advice on initial hand painting techniques and Prof David Young shared his extensive knowledge and experience of regulatory approvals and commercialisation of medical devices. In addition I would like to acknowledge the statistical advice provided by Eric Gardiner.

Both professional and lay members of User Advisory Network have given their time and experience to ensure that the research remained rooted in and informed by clinical need. I appreciate the time and effort that they have devoted to the project. I am grateful for the support and advice given by R&D Manager, James Illingworth, and clinical staff at the research sites. The project could not have succeeded without the support of the consultant surgeons, Peter Sedman and Prashant Jain, who allowed me access to their patients, and the anaesthetists, theatre and ward staff and research nurses who made me welcome and facilitated the collection of samples. Most importantly without the tissue and fluid samples donated by patients the development of the device could not have taken place and I am extremely grateful for the generosity of the patients who gave consent for their samples to be used for the project.

The research was significantly aided by the generous funding from Yorkshire Concept and the National Institute for Health Research, Invention for Innovation programme. The award of these grants enabled the project to progress from laboratory based experiments with hand adapted nasogastric tubes to clinical studies involving manufactured prototypes.

Finally I would like to thank my family for their unfailing support. My husband, William, has provided endless encouragement as well as practical help. I am eternally grateful to him and my daughters, Louise and Laura, for their patience and love over the years, for keeping me focussed and giving me the space and time to complete this PhD thesis. Their belief and that of my parents has provided a constant source of encouragement and motivation.

Abstract

From Bench to Bedside: the development of a Location Indicating Nasogastric Tube

Background

Nasogastric tubes are frequently used in clinical practice. Correct placement in the stomach must be verified on passing the tube and before every feed or administration of medicine. Current methods of confirming placement are limited and complications related to incorrect placement are well documented. The need for an easy, safe, reliable bedside method for verifying nasogastric tube placement has been identified.

Aim

To develop a manufactured prototype of an effective, sensitive and reliable nasogastric tube which self-indicates its position and is ready for clinical investigation in patients.

Methods

A pH sensitive redox polymer, vitamin K_1, was applied to the tip of 40 hand adapted nasogastric tubes (iteration 1) that were then assessed in pH solutions and clinical samples. Results were used to inform the design of manufactured prototype tubes (iteration 2). A total of 60 iteration 2 tubes were prepared and evaluated in a range of fluids, resected stomach tissue, gastric fluid and sputum. Documentation for regulatory approval of the new device was prepared and the intellectual property protected in preparation for licensing with a commercial partner. A User Network was established to inform the design and development of the device.

Results

A total of 100 prototype tubes were evaluated. One third of iteration 1 prototypes and all of iteration 2 manufactured prototypes, generated a measurable current. Variation in the size and nature of the gastric tissue samples limited definitive conclusions that could be drawn from these experiments, but guided design choices in an iterative manner. However experiments with human gastric fluid demonstrated that, using linear sweep voltammetry, zero current potential gave clearer distinction of pH than amperometry in the desired pH range. Patent protection (granted in Australia, USA and Canada and pending in Europe) of the associated intellectual property and completion of the regulatory approvals process enabled negotiations with a number of companies interested in manufacturing the novel medical device for clinical trials. A User Network was established and a range of communication strategies developed to ensure that the development of the device was informed by current experience of lay and professional users.

Conclusion

This thesis documents a translational research study in which understanding of electrochemistry was applied to a current clinical problem generating new knowledge. It was demonstrated that, when a redox polymer is applied to the distal tip of a nasogastric tube, the electrochemical reaction can be measured at the proximal end and assessment of the zero current potential distinguishes fluids of different pH values. New understanding of the reality of user involvement in the development of medical devices was generated and a flexible approach of a User Network is advocated. A commercially manufactured device, with appropriate regulatory approvals was produced ready for clinical trials and patents granted or pending across the globe.

Presentations and Awards Resulting from the Thesis

2007 June
UK Patent Application GB 2,438,873 replaced by PCT Application WO 2007/141579 A1 'Catheter with a Sensing Region For Redox Reactions'

2008 November
Elliott, B., Shields, L., Greenman, J., Wadhawan, J., Imrie, C., El Habal, M., Development of Enteral Feeding Tubes, **Yorkshire Concept Proof of Commercial Concept Fund and Yorkshire Enterprise Fellowship Showcase and Networking Event**, Leeds

2010 June
Elliott, B., Singh, R. Location Indicating Nasogastric Tubes, **Business Angels Event**, University of Bradford.

2011 July
National Institute for health Research (NIHR), Invention for Innovation (i4i) programme.
Principal Investigator **Barbara Elliott** - Location Indicating Naso-Gastric Tube **£834,428 (full economic costs)**

2013 July
Schoenleber, M., Wadhawan,J., MacFie, J., Singh, R., Shields, L., Greenman, J. and **Elliott B**. Random Arrays of Vitamin K1 Modified Electrodes for pH Sensing, Poster presentation at **"Faraday Discussion 164: Electroanalysis at the Nanoscale"** Conference, Durham University, 1 – 3 July 2013

2013 September
Elliott, B., Singh, R., Schoenleber, M., Greenman, J., Wadhawan, J. and MacFie, J. The Development of a Location Indicating Nasogastric Tube
European Universal Biotech Innovation Awards – finalist

2013 October
Elliott, B., Singh, R., Schoenleber, M., Greenman, J., Wadhawan, J. and MacFie, J. The Development of a Location Indicating Nasogastric Tube
Medipex NHS Innovation Awards, Yorkshire and Humber region "Medical Devices and Diagnostics" category – finalist

2014
Elliott B, Shields L, Schoenleber M, Wadhawan J, Greenman J and MacFie J. From bench to bedside: the development of a location indicating nasogastric tube, oral presentation at **3rd Biennial Australian Capital Region Nursing and Midwifery Research Centre Conference,** Canberra Australia, 16-17 Oct. **Awarded $200 prize for best oral presentation**

Contents

List of Figures

List of Graphs

List of Tables

Chapter 1: Thesis Introduction

1.1 Introduction

There are over 500,000 medical devices in use worldwide for the diagnosis, monitoring and treatment of almost every health condition (European Medical Technology Industry (Eucomed) 2012a). However these represent just a small fraction of the number of devices invented and developed with only an estimated 4% becoming commercially successful products (Dymond et al. 2012). Initial inventions require proof of concept and prototype testing and this thesis chronicles the invention, development, proof of concept studies and prototype testing of a new medical device, namely a Location Indicating Nasogastric Tube (LINGT). The development of the medical device from initial identification of clinical need through to the preparation for clinical trials of the final manufactured prototype is discussed in detail.

This introductory chapter summarises the need for such a device and the establishment of a multi-disciplinary team to achieve its development. The importance of innovation and translational research in health care is discussed and the aim, research design and structure of the thesis presented.

1.2 Nasogastric Tubes

Tubes inserted into the stomach through the nose (nasogastric) or mouth (orogastric) are frequently used in clinical practice. Nasogastric tubes are used in patients of all ages for the delivery of nutritional support and/or medication, decompression of the gastrointestinal tract in cases of obstruction, severe pancreatitis or gastrointestinal surgery, or diagnosis and assessment (Phillips 2006). Such tubes are also used for gastric lavage in the management of patients with drug overdose, poisoning or haematemesis (Chen et al. 2014). Orogastric tubes are less well tolerated and are used when the nasal passages are inaccessible for example after facial injury or surgery and most commonly in neonates who are obligate nose breathers. Naso or orogastric feeding is used

extensively with babies in neonatal units who have absent or weak suck and swallow reflexes and is the preferred method for providing nutritional support for patients of all ages who cannot take sufficient nutrition orally. This may be due to decreased ability to swallow, for example after a stroke. The treatment of some conditions such as cystic fibrosis and extensive burns require patients to consume a significantly increased amount of calories (Medlin 2012). Such high levels of nutrition are difficult for patients to consume orally and may be delivered through a nasogastric tube often at night whilst the patient is sleeping.

Passing nasogastric and orogastric tubes is therefore a very common clinical procedure in a range of clinical areas and enteral feeding of patients by either the nasogastric or orogastric route is a common practice in nursing. It is suggested that the placement of nasal or oral enteral tubes is one of the most frequently performed procedures in critically ill children (Ellett, et al. 2005b, Ellett, Maahs & Forsee 1998). Thousands of tubes are passed each day, most often by nurses although other health professionals and in some situations relatives, in particular parents, also pass tubes. The actual number of nasogastric tubes in use is difficult to determine and suggested figures vary. The National Health Service (NHS) Purchasing and Supply Agency in 2005 estimated that 170,000 nasoenteric tubes were supplied to the NHS in the United Kingdom each year (National Patient Safety Agency 2005b) but by 2010, the latest date that figures could be found, this figure had increased to 275,000 (Yardley, Donaldson 2010). It has been estimated that around a million tubes are passed through the mouth or nose into the stomachs of adults and children each year in the United States of America (Ellett, et al. 2005a, Halloran, Grecu & Sinha 2011). Although thousands of feeding tubes are passed each day without incident (National Patient Safety Agency 2011b) there is a wide variation in practice and education regarding the management of nasogastric tubes (Cannaby, Evans & Freeman 2002) and this common procedure carries risk for the patient and uncertainty for the practitioner.

The key issue for nurses and carers is verification of the correct placement of the tube which must be checked after insertion, before every feed or administration of medication, following bouts of coughing or vomiting or if there is external evidence that the tube has moved (National Patient Safety Agency 2011a).

Placement is most frequently intended to be in the stomach and gastric placement is the focus of this thesis although placement in the small intestine is discussed in the literature review. The methods used to verify correct placement of tubes in the stomach are of concern to nurses and other clinicians across the world and the research conducted in a range of countries including the United States of America (USA), United Kingdom (UK), Turkey, Japan, Singapore, Australia and Switzerland, is discussed in the review of the literature. Since the late 1980's a vast amount of research on the use of nasogastric tubes has been conducted by Norma Metheny in the USA, mainly with adult patients, and her work is considered to be seminal in this area and is reviewed in detail in chapter 2.

Nurses must evaluate the literature regularly and develop practice in accordance with clinical practice guidelines and the evidence (Stepter 2012). However the National Patient Safety Agency statement that none of the existing methods for testing the position of gastric feeding tubes are totally reliable (National Patient Safety Agency 2005b) confirms the difficult position that clinicians are in when passing and using feeding tubes. A review of methods of verifying correct placement in the stomach concluded that there was no definitive, non-radiographic method to differentiate between respiratory, oesophageal, gastric and small bowel placement of blindly inserted feeding tubes in the fed and unfed state (Metheny, Meert 2004). Recent evidence suggests that the situation is even worse than this with none of the methods of determining the location within the human body of enteral tubes inserted through the nose or mouth, including X-ray, which is widely considered to be the "gold standard", are reliable (National Patient Safety Agency 2011b).

When parents and other relatives are undertaking nasogastric feeding for their sick baby or child, especially at home, the fear of delivering feed into the child's lungs may create huge anxiety and is not conducive to promoting parents' confidence as carers and facilitating early discharge. Thus an easy and certain verification method for determining tube position is a crucial component of care in avoiding serious patient harm and distress to patients, carers and health professionals. It has been stressed that an effective bedside test for nasogastric tube placement must be found (Metheny, Meert 2014b). New devices and

techniques for correct placement of enteral tubes must be developed in order to ensure both easy and accurate insertions (Sparks et al. 2011) and there must be large scale prospective clinical studies to evaluate these emerging technologies (Hanna et al. 2010).

1.3 Medical Devices

Good ideas are often generated by clinical need and the idea for this study started with discussions regarding the frustration and uncertainty with current methods of verifying correct placement of nasogastric tubes. The clinical need for an easy, safe, reliable bedside method for verifying nasogastric tube placement is clearly apparent from the literature reviewed in chapter 2 and was discussed with colleagues working in the Chemistry and Biological Sciences departments of the University of Hull. When considering how to improve the procedure for verifying correct placement of nasogastric tubes it became clear that a new medical device had to be developed. The author explained the need for a nasogastric tube that once inserted into the stomach would immediately indicate its correct position and suggested that ideally a visual indicator such as a light would appear at the external end of the tube. If the tube was incorrectly placed, in the oesophagus, small intestine or respiratory tract, the light would not come on or a different coloured warning light would appear.

This was considered to be “blue sky” wishful thinking, as such a tube would be either impossible to manufacture and/or prohibitively expensive. If such a simple solution to the problem of placement verification was available, it was believed that a current manufacturer of nasogastric tubes would already be undertaking the research and development required. However, as discussed in chapter 3, an electrochemical method of pH measurement is available and it was believed that this could be applied to a nasogastric tube in order for it to be able to self-indicate its position. Colleagues in the University’s Knowledge Exchange Office were involved to help with patent searches and it appeared that this solution might indeed be novel and worthy of protection through patent applications. The issues of protecting intellectual property are discussed in chapter 5.

The European Medical Device Directives define a medical device as:

> *"any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of: diagnosis, prevention, monitoring, treatment or alleviation of disease; diagnosis, monitoring treatment, alleviation of or compensation for an injury or handicap; investigation, replacement or modification of the anatomy or of a physiological process; control of contraception"*

(The Council of the European Communities 1993, p 5).

They further specify that

> *"A medical device does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but it may be assisted by such means"*

(The Council of the European Communities 1993 p 6).

The time required to develop an idea into a medical device that is marketable varies greatly depending on the complexity of the device, clinical and market place need and hence the money available for its development (Dymond et al. 2012). The time taken to develop the Location Indicating Nasogastric Tube (LINGT) from the initial idea in 2005 to the commencement of clinical trials has been almost a decade. Following discussion of the initial idea for a novel nasogastric tube, a presentation was given by the author and 2 colleagues to a panel of local senior business executives and academics representing a funding body "Yorkshire Concept" to request funding for proof of concept studies and prototype testing. A grant of £35,000 was awarded. The initial proof of concept experiments were conducted by the author, with advice from a research chemist, and are discussed in chapter 3. Additional experiments were conducted by the research chemist and the combined data formed the basis of a grant application for further funding from the National Institute for Health Research (NIHR) Invention for Innovation (i4i) programme. This award of £834,428 (full economic costs) facilitated the iterative development of the LINGT and the establishment of

a project team including the full time employment of a Post Doctoral Research Associate (PDRA). The author was named as Principal Investigator on the grant application and continues in this role, managing a specialised team of academic and clinical colleagues from diverse backgrounds. Reports on the progress of the project have been written by the author and submitted to NIHR every six months. An example of these reports, Interim Report 5, is included in Appendix 1.

In 2013 the author entered the project for two prestigious Biotech competitions: the European Universal Biotech Innovation Awards and the Yorkshire and Humber region Medipex NHS Innovation Awards. The project was selected as one of five finalists (from over 200 applications) for the European award and one of four finalists in the "Medical Devices and Diagnostics" category of the regional award (Medipex Innovation Healthcare Hub 2013). In September 2013 the author and a colleague from the Knowledge Exchange at the University of Hull presented the project before a panel of judges from Global Biotech Industries in Paris and, whilst the project did not win either of the awards, selection as a finalist was significant recognition of the value of the project and provided important commercial exposure discussed further in chapter 5.

1.4 Innovation and Translational Research

Innovation is the process of turning research outputs into real applications and in order for a good idea to be turned into an innovation additional "drivers" and the co-ordinated activity of a specialised team are required (Dymond et al. 2012). It has been suggested that medical device innovation involves a highly interconnected "ecosystem" in which public expectations, clinical trials, regulatory processes and investment decisions interact (Krucoff et al. 2012). To this may be added clinical need, protection of intellectual property and commercialisation procedures. Innovation requires a team effort involving academic, clinical, scientific, financial and industry partners (Dymond et al. 2012).

A specialised team for this project evolved through meetings with academic colleagues in other faculties who had the scientific knowledge and expertise to

develop the sensor for a location indicating nasogastric tube and the Knowledge Exchange who had understanding of the legal and financial aspects of innovation. Medical practitioners, equally concerned with the issue of nasogastric tube placement, also joined the team. However the main motivation for the innovation was the conversations the author had with parents of children with nasogastric tubes who were unable to take their children home from hospital until they were competent and confident delivering feeds through their child's tube. The need to make the procedure easier and safer for these children and less stressful for their parents remained the key driver throughout the study and representatives of such parents remained involved in the project through the "User Advisory Network" discussed in chapter 6.

Translational research is the term applied when findings from basic scientific research are transferred into clinical and healthcare practice, often termed "from bench to bedside", thus facilitating the application of the results from laboratory experiments through clinical trials to patient interventions and applications (Callard, Rose & Wykes 2012). The notion of translational research was first used in oncology in the 1990's with the endeavours to find new drugs and was later used with a wider application, first by the USA in 2003, followed by other countries including the UK. The focus on translational research resulted from concerns that the enormous advances in basic science in recent years have not been reflected in similar advances in the management and cure of diseases. It can take 10-20 years to translate research findings into clinical practice (Sussman et al. 2006) and it has been proposed that a "valley of death" has emerged between basic scientific research and clinical research. Clinician-scientists have been suggested as a means of bridging this gulf and barriers to and facilitators of good translational research are considered (Roberts et al. 2012). It is hoped that translational research will cross that valley and reduce the incidence of scientific research findings being "lost in translation" (Mankoff et al. 2004).

Efforts to prevent delays and promote the faster adoption of research findings by directing resources to this area have been undertaken in the UK and USA. In the UK the NIHR now has 11 biomedical research centres and 16 research units focussed on translating fundamental biomedical research into clinical research of benefit to patients (National Institute for Health Research (NIHR) 2014). Similarly

in the USA the National Institutes of Health Roadmap established new initiatives to hasten the transfer of scientific research findings into practical health care delivery (Chesla 2008). The NIHR funding for the development of the LINGT is evidence of the commitment of the NHS to translating research findings into increased patient safety and comfort.

Translational medicine is not simply a one way process “from bench to bedside” but rather a complex two way process (Marincola 2003) and it is increasingly realised that knowledge must also be transferred back to the laboratory from the bedside. This thesis considers the two way process in chapter 6, where the methods of sharing information between researchers, clinicians, patients and relatives in order to develop a device that is effective but also meets the needs of both lay and professional users are discussed.

1.5 Aim of the Thesis

The overall aim of this PhD research is to develop a manufactured prototype of an effective, sensitive and reliable nasogastric tube which self-indicates its position and is ready for clinical investigation in patients.

1.6 Research Design

Research may be defined as systematic enquiry which utilizes defined and explicit methods to answer questions and expand knowledge (Polit, Beck 2010). There are two broad approaches to research design: quantitative and qualitative. Both have their strengths and weaknesses and increasingly mixed methodologies are being developed which combine the two approaches (Bryman 2008). This study utilised both quantitative and qualitative measures in developing a nasogastric tube that reliably self-indicates its position. Purely quantitative methods were used in the laboratory and clinical evaluation of the device discussed in chapters 3 and 4. However the need for such a tube evolved from qualitative evaluation of nursing care as well as studies highlighting problems with current placement detection methods which are discussed in the

literature review. Chapter 6 explores the development of the User Network and the qualitative data that emerged from group and individual meetings with members of that User Network. These qualitative data reinforced the need for a new medical device and informed the design of such a device.

Clearly there is a place for both qualitative and quantitative approaches in the study of nursing care and patient experiences. When designing a research study it must be decided what type of evidence is needed to answer the particular research question or test a particular theory in a way that is acceptable and convincing. The key to successful and sound enquiry is that whether it is a quantitative or qualitative study it is approached in rigorous and systematic manner so that results can be explained and justified by the most appropriate methods. At the same time it is important to remain sceptical and be mindful that all scientific knowledge is provisional (De Vaus 2001). It can be argued that social research and research in nursing is a moral act whereby the researcher is responsible for ensuring that any change, which is an outcome of the research, is for the better and the researcher is working for social good (Clough, Nutbrown 2002). This can be challenging in experimental research as, whilst the motivation of the researcher may be to develop improved practices and devices for delivering care, the outcome is uncertain and developments may be costly and inconvenient. Thus it was crucial that the quantitative aspects of the study were informed by a qualitative element through the engagement of lay and professional users to ensure the end product met their needs.

The two main approaches to quantitative research design are observational and experimental. It may be claimed that the experimental design is the most rigorous of all research designs indeed it is considered to be the gold standard against which all other designs are judged because of its internal validity (Trochim, Donnelly 2007). This study used an experimental design where a hypothesis was tested in a carefully controlled environment. Control of environmental factors is essential in order to assess the interaction between the concepts being studied, that is, the variables (Polit, Beck 2010). Variables are described as independent or dependent; variations in the dependent variable being conditional on variations in the independent variable. In this research, variation in the electric current (dependent variable) depended on variation in the pH and chemical composition

of the body fluid (independent variable). The researcher's ability to control the environment in the clinical setting was limited and the issues arising from this are discussed in chapter 4.

Important measures in quantitative research are sensitivity and specificity. These issues are crucial in developing a new medical device as it must be at least as sensitive and specific as previously used devices and ideally much better in order to justify the research programme and change in practice. An instrument's sensitivity is the ability to correctly identify a case or diagnose a condition and specificity is the instrument's ability to correctly identify non-cases that is the instrument's rate of yielding "true negatives" (Polit, Beck 2010). In the laboratory demonstrating sensitivity and specificity may be considered relatively straight forward, however in human beings the situation is far more complex presenting challenging practical and ethical dilemmas. The sensitivity and specificity of the device influence the number of patients required for clinical evaluation and statistical advice was sought in order to meet the requirements for robust clinical evaluation of the device. This is discussed in chapter 7.

1.7 Structure of the Thesis

This doctoral thesis explores the design, development, laboratory and clinical testing of a novel nasogastric tube. The complexity of the device is discussed as well as the clinical and market place need and the regulatory processes necessary to bring a new medical device to market. The research was completed with the final design freeze and manufacture of the prototype system consisting of prototype nasogastric tubes and an indicator box to identify placement. This system will be trialled on patients as part of the clinical investigation for the NIHR funded project but such a trial is beyond the scope of this PhD.

The thesis is structured as follows:

- Chapter 1 introduces the research problem and the importance of innovation and translational research in health care.

- Chapter 2 discusses the history and development of nasogastric tubes and the current literature on the issues surrounding the use of nasogastric tubes considering the limitations of methods of placement verification and justifying the need for this study. A wide ranging contextual review of the literature on nasogastric tubes and wider issues of enteral feeding is followed by a configurative review of the literature on the problems associated with blind placement of nasogastric tubes and methods of placement verification.

- Chapter 3 describes the initial prototype development of hand adapted nasogastric tubes (iteration 1) to test the hypothesis that

  "the chemical reaction between acid stomach contents and a specific electrochemical coating on a nasogastric tube will create an electric current which can be measured externally".

  The laboratory and clinical experiments to test these handmade tubes in pH solutions and human gastric mucosa to determine the proof of concept are discussed.

- Chapter 4 considers the laboratory and clinical assessment of the manufactured prototype tubes (iteration 2) and the decisions made to reach a design freeze.

- Chapter 5 discusses the process of gaining regulatory approval to market a new medical device including the establishment of a Quality Management System in accordance with ISO 13485:2012 Medical Devices Regulation, risk assessment, establishing intellectual property rights and commercialisation of the device. Commercialisation of the product was an aim from the outset and there had to be protection of the Intellectual Property (IP) through patent applications.

- Chapter 6 explores patient and public involvement (PPI) in the study through the establishment of a User Advisory Network of lay and

professional users of nasogastric tubes. An important aspect of medical device development is the involvement of users to ensure that the device meets their requirements in terms of design and ease of use.

- Chapter 7 discusses the final manufacture and future development of the LINGT and the planned clinical evaluation studies necessary to meet the requirements for Conformeté Européenne (CE) marking and market introduction. The final prototype of the medical device will be tested in patients and such clinical investigations require ethical approval and user evaluation. Whilst these trials are beyond the scope of this thesis this chapter considers the work planned to develop the device further as well as the limitations of the thesis.

For ease of discussion throughout the thesis the term “nasogastric tube” will be used as the generic term for a tube which can be inserted into the stomach via the nose or the mouth. When there are specific issues to be considered relating to the nasal or oral route this will be made clear and the term “orogastric tube” used to differentiate tubes only inserted through the mouth. Other terms used in the literature, such as naso-enteral or naso-enteric tubes or nasogastric enteral access device (NG-EAD), are not in common use in spite of the latter term being preferred by the American Society of Parenteral and Enteral Nutrition (ASPEN) (Bankhead et al. 2009) and “nasogastric tube” remains the most commonly used and understood term in international literature and practice.

Chapter 2: Literature Review

2.1 Introduction

This chapter presents two reviews of the literature. Firstly a wide ranging historical and contextual review of the literature on the development, types and uses of nasogastric tubes is presented (sections 2.2 - 2.5) in order to explain the context of the issues and the magnitude of the problem of placement verification. Alternative methods of feeding are described briefly in order to justify why nasogastric feeding remains an important aspect of patient care and treatment (section 2.6). Additional risks associated with nasogastric tubes are summarised before the main consideration of the issues associated with misplaced nasogastric tubes. The purpose of this PhD is to develop a nasogastric tube which can self-indicate its position in the stomach in order to avoid the problems associated with misplaced tubes. Therefore a configurative systematic review of the literature on these problems including a review of the evidence for the range of methods of verifying correct placement is presented (sections 2.8 – 2.11).

The range of the quality of literature, from individual case reports to large scale empirical studies and aggregative systematic reviews, means that the quality of the evidence reviewed varies and this is discussed as part of the review. Whilst a systematic approach to the review of this literature was used with clear search terms defined, the selection of studies to be included remained broad as it was considered important to review all aspects of nasogastric tube misplacement and the variety of placement verification practices.

A configurative approach to reviewing the literature as described by Gough, Oliver and Thomas (2012) was adopted as a method of organising data from a range of studies selected for the literature review. Configurative reviews synthesise research studies that may be based on different interpretations of reality mediated by varying perceptions and beliefs (termed “critical realism”) (Gough, Thomas 2012). Such an approach was necessary as definitions of misplaced tubes vary greatly from one study to another and methods of identifying misplaced tubes have improved considerably over the last 80 years

from simple observation for respiratory distress in the 1920s (Scott 1930) to sophisticated 3 dimensional scanning techniques available today (Chen et al. 2014). Thus perceptions of misplacement have become more sensitive with increased ability to interpret the patient's experience. The configurative approach enabled the inclusion of the widest possible range of literature exploring the historical context of the issues and demonstrating the slow change in practices. Literature relating to the other aspects of the thesis, namely regulatory approvals and user involvement, is discussed in the relevant chapters relating to these topics.

2.2 History and Background

2.2.1 Enteral Feeding

Early nasogastric tubes were used only for feeding, their use in decompressing the stomach and for diagnostic tests developed later. Feeding nutrients through a tube directly into the human body was first described 3,500 years ago when ancient Egyptians and Greeks used enemas to deliver nutrients into the rectum to preserve health when the bowel was inflamed or the patient had diarrhoea (Chernoff 2006). Rectal feeding was the method of choice for thousands of years due to the inaccessibility of the upper gastrointestinal tract (Chernoff 2006) and it was not until Levin (Levin 1921) invented a flexible nasogastric tube made out of rubber that nutritional support via the gastrointestinal tract began to gain preference over nutrient enemas (Clevenger, Rodriguez 1995).

Prior to this there were attempts to feed patients through tubes into the oesophagus such as by Capivacceus in 1598 (Randall 1984) and in the 17th century by Von Helmont who developed a flexible leather tube for oesophageal feeding (Harkness 2002). The first reported use of a flexible, hollow tube to deliver nutrition directly into the stomach via the nose or mouth was by John Hunter in 1790 (Clevenger, Rodriguez 1995) although it has been suggested that it is impossible to discern who passed the first tube into the stomach and for what reason (Paine 1934).

In the twentieth century increased rates of patient survival due to improved acute care techniques led to more patients requiring nutritional support and by the 1930's nursing textbooks discussed techniques for passing tubes via the nose into the stomach for the purpose of administering bolus artificial feed (Phillips 2006). During this time developments were also being made in the nutrient formulas being fed to patients through nasogastric and nasojejunal tubes making this type of nutritional support an important aspect of post- operative care (Mulholland et al. 1943). A controversial use of nasogastric feeding tubes also developed during the early part of the 20th century when they were used to administer nutritional support to prisoners on hunger strike beginning with the suffragettes protesting for the right to vote (Crosby, Apovian & Grodin 2007). Such practice is now illegal (see section 2.5) but in all other situations early introduction of enteral feeding is now advocated particularly for the critically ill (Heidegger, Dawson & Pichard 2008) as it is believed that enteral feeding protects the gut mucosal barrier (Jiang, Li & Li 2003), reduces infective complications (Kalfarentzos et al. 1997) and reduces the length of hospitalisation (Marik, Zaloga 2004).

2.2.2 Decompression

The practice of inserting tubes into the stomach to release gas or liquid has occurred for 300 years as a therapeutic intervention in patients with distension and vomiting due to bowel obstruction (Verma, Nelson 2007). In the last 100 years passing a nasogastric tube for decompression has become standard practice for prophylaxis in patients having abdominal surgery, it being thought to reduce the incidence of nausea and vomiting, pulmonary aspiration and pneumonia, wound separation and infection and to promote earlier return of bowel function and earlier hospital discharge (Verma, Nelson 2007). However a Cochrane Review of 37 trials found that routine use of nasogastric decompression after abdominal surgery may slow rather than hasten recovery and increase the risk of some post-operative complications (Verma, Nelson 2007).

Tubes inserted for decompression carry less risk for the patient than those inserted for feeding, as they are often inserted under direct vision by the surgeon or anaesthetist and, as nothing is being inserted down the tube, the risks

associated with misplaced tubes are considered to be minimal. However serious problems have been reported when tubes inserted for decompression are misplaced in the trachea or bronchi. Placement of nasogastric tubes in the trachea or bronchi of ventilated patients can result in airway leakage and ventilatory failure if not promptly detected and corrected (Hung et al. 2007).

Tubes inserted for drainage are usually intended for short term use and made from polyvinylchloride (PVC) and so are not suitable for feeding patients (see section 2.3). It is therefore recommended that, if a patient subsequently requires nasogastric feeding, the tube used for decompression should be removed and an appropriate feeding tube should be inserted (National Patient Safety Agency 2011b).

2.3 Types of Tubes

Nasogastric tubes vary in size, material and cost and selection of the most appropriate tube depends on the age and size of the patient and the intended use. There are two main categories of tubes used currently; firm, usually large bore PVC tubes and softer narrow bore polyurethane tubes. The cheaper, stiffer PVC tubes are only used for drainage, decompression or short term feeding (less than a week) as they have been associated with ulceration and bleeding of the nose, pharynx and stomach in long term use (Jackson, Payne & Bacon 1990) and have been found to stiffen after 7 days of use (Taylor et al. 2014). In adults these are usually large bore tubes although finer tubes are produced in the same materials for use with babies and children (see Table 1 for definition of sizes).

French Gauge (Fr) is the internationally accepted method of denoting the external diameter of medical catheters developed by Charriere in the 19th century (Iserson 1987). The basis for the Fr number is diameter multiplied by 3 and table 1 gives the corresponding diameter in inches and millimetres for sizes 3Fr to 18Fr.

French Gauge	External Diameter *(mm)*	External Diameter *(inches)*
3	1	0.039
4	1.33	0.053
5	1.67	0.066
6	2	0.079
7	2.3	0.092
8	2.7	0.105
9	3	0.118
10	3.3	0.131
11	3.7	0.144
12	4	0.158
13	4.3	0.170
14	4.7	0.184
15	5	0.197
16	5.3	0.210
17	5.7	0.223
18	6	0.236

Table 1: French Guage size and corresponding diameter of catheters

Large bore tubes are considered to be 14 Fr or above and narrow-bore 5 Fr – 12 Fr with very few nasogastric tubes manufactured less than 5Fr due to the viscosity of feeds causing blockages in smaller tubes. Narrow bore, soft, PVC tubes were introduced by Dobbie and Hoffmeister in 1976 as a means of reducing the trauma caused by the earlier stiffer tubes but they were not without risks themselves as they required a stylet for insertion and tracheopulmonary injuries associated with insertion of these tubes were reported soon after their introduction (Valentine, Turner 1985).

In the 1990's small bore, soft, polyurethane and silicone tubes that remain flexible when exposed to gastric fluid were introduced to improve patient comfort (Sriram et al. 1997, Payne-James, Grimble & Silk 2001). Such tubes remain the preferred choice for prolonged feeding as they are less likely to cause complications (Payne-James, Grimble & Silk 2001) and, being narrower, they do not affect the competency of the lower oesophageal sphincter thus reducing the risk of aspiration (Phillips 2006, Sriram et al. 1997). Polyurethane tubes are also considered to be easier to see on X-ray than PVC "Ryles" tubes and are the preferred choice if X-ray confirmation of placement is required (Taylor et al. 2014). A European survey of 380 adult intensive care units found that the majority of tubes used were polyurethane (49%) followed by silicone (29%) and poly vinyl chloride (20%) (Fulbrook, Bongers & Albarran 2007). The number of

tubes used which require a stylet for insertion is not known but anecdotal reports suggest that the majority of tubes inserted into children require a stylet because of the softness of the tubes used in this patient group (Irving et al. 2014).

Particular patient groups such as very low birth weight infants may require more expensive silastic tubes as they reduce the risk of oesophageal perforation associated with PVC tubes (Yong et al. 2014). As long as the tubes are inserted into the correct location they cause minimal trauma, however small bore tubes are easier to insert into the wrong location and to become displaced during use (Williams, Leslie 2004, Ellett, Beckstrand 1999) .

2.4 Feeding practices

Nursing text books describe the procedure for passing nasogastric tubes in adults (Griffin 2011) and children (Howe, Forbes & Baker 2010) and this procedure is taught to all nursing and medical students in the UK. NHS Hospital and Community Trusts also have their own procedures and protocols for passing tubes and verifying correct placement for example (Cornwall Partnership NHS Foundation Trust 2013, Gateshead Health NHS Foundation Trust 2012) but all are based on the National Patient Safety Agency guidelines (National Patient Safety Agency 2005a, National Patient Safety Agency 2005b, National Patient Safety Agency 2011a, National Patient Safety Agency 2011b).

Feeding through a nasogastric tube may be continuous or intermittent pump feeding or bolus feeds delivered through a feeding syringe (Barker 2004). Continuous feeding has been associated with lower risk of aspiration and bolus feeding was only recommended in patients with a competent cough and gag reflex and a normal level of consciousness (Metheny 2002). However recent studies suggest that bolus feeding is probably safer than previously thought and could be used more widely (Medlin 2012). Verifying correct placement is essential prior to each bolus feed but there is a range of practices with regard to the frequency of placement verification with continuous feeding, although it is suggested that placement should be verified at least once per shift (Metheny, Stewart 2002).

Tube feeding is an important part of nutritional support for babies born before the development of a co-ordinated suck and swallow reflex, which develops between the 32nd and 34th week of gestation (Dodrill et al. 2008). It is essential that enteral feeding is established as soon as possible after birth in order to avoid atrophic changes to the gastrointestinal tract (Lucas, Bloom & Aynsley-Green 1983) and stimulate secretion of gastrointestinal hormones and bile flow (Aynsley-Green 1983). Such preterm infants may be fed continuously or by intermittent bolus feeds, through an oro-gastric or nasogastric tube; the evidence for the selection of the method and route of feeding being inconclusive (Maggio et al. 2012). Whilst it is suggested that the oral route may be preferable as neonates are obligate nose breathers and thus nasal tubes may restrict respiratory effort, there is insufficient evidence to determine whether oral route is better than nasal in preterm or low birth weight infants and a large scale randomised controlled trial is required (Watson, McGuire 2013a). Babies are particularly vulnerable to trauma caused by the passing and presence of the tube and accurate placement in the body of the stomach is essential to avoid gastric bleeding, aspiration and gastro-oesophageal reflux (Maggio et al. 2012).

Breast fed babies who cannot gain sufficient nutritional support from breast feeding alone may be given supplementary feeds via a nasogastric tube to avoid “nipple confusion” associated with supplementation by bottle feeding (Renfrew, Woolridge & McGill 2000) and save time (Taylor et al. 2009). However these are not justifiable reasons to subject a baby to the risks of nasogastric feeding and unless it is essential due to their medical condition less invasive methods of delivering supplementary feeds should be considered to avoid potential harm to the baby and associated parental distress (Taylor et al. 2009).

In 2007 the National Patient Safety Agency issued a Patient Safety Alert concerning the incorrect intravenous administration of liquid medicines intended for the oral or enteral route (National Patient Safety Agency 2007). At this time syringes could be connected to both feeding tubes and intravenous cannulae and 3 deaths and 33 incidents were reported between 2001 and 2004 due to oral medication being inserted intravenously. Incidences of feed being administered into venous cannulae were also reported and now all feeding syringes are purple in the UK with specific connectors that can only connect to feeding tubes to avoid

inadvertent injection of feed or medication into the wrong site. In spite of these measures **"**wrong route administration of oral/enteral treatment" is seventh on the most recent list of Never Events in the NHS (NHS England Patient Safety Domain Team 2013).

2.5 Ethical Considerations

Consideration of the use of nasogastric tubes would not be complete without some discussion of the ethical issues associated with their use in feeding patients against their will. Providing nutritional support to patients unable or unwilling to give their consent is a complex and emotive topic. Nasogastric feeding against a patient's wishes is contentious particularly with regard to children and adolescents (Neiderman et al. 2001). In Europe and America the provision of artificial nutrition is a medical intervention and as such requires the verbal consent of the patient, or if the patient is a minor, their parents (Griffin 2011). Nutritional support becomes "force feeding" if a competent patient does not give consent (Simmonds 2010). If a patient lacks capacity to give informed consent to medical treatment their care and treatment comes under the Mental Capacity Act in England and Wales and any treatment given must be in their best interests (HM Government 2005). Patient consent for nasogastric feeding may be problematic in cases where mental confusion, such as with dementia, or incapacity, such as with anorexia nervosa, are an issue and in end of life care (Simmonds 2010). Restraining patients in order to deliver care is difficult to justify and in the UK attempts have been made to develop a lawful policy for restraint in order to feed (Sayers, Gabe 2007).

Excellent ethical and legal guidance is given by the Royal College of Physicians and British Society of Gastroenterology (2010) and practitioners must always ensure that they act within the law when deciding to deliver nutritional support with nasogastric feeding (Royal College of Physicians and British Society of Gastroenterology 2010). Nasogastric feeding is the preferred procedure for delivering essential nutritional support in many eating disorder units. The subjective experiences of nasogastric feeding of patients with eating disorders and their parents have been explored, providing unique insights into their

experiences and offering recommendations for good practice (Neiderman et al. 2001).

People who are detained in prison and use refusal of nutrition as a means of protest, often referred to as “hunger strike”, cannot be considered to be lacking in capacity. However the use of nasogastric tubes to forcibly deliver food and medication to them has been regularly documented over the last 100 years, beginning with the women suffragettes in England demonstrating for the right to vote (Crosby, Apovian & Grodin 2007). The hunger strikes in the Maze prison in 1980 and 1981, where 10 out of 30 Irish prisoners were allowed to die, as force feeding was not considered an option, in contrast to the treatment of hunger striking prisoners in Guantanamo Bay, where force feeding has been permitted, have created debate in the medical literature regarding the appropriate use of force feeding in prisoners (Crosby, Apovian & Grodin 2007, Smith 1984, Gregory 2005, Rubenstein, Annas 2009).

Force feeding by definition involves physical force including physical and/or chemical restraint to immobilise the hunger striker and the placement of a nasogastric tube and can result in physical and psychological trauma as well as a group of physiological problems including electrolyte depletion, fluid retention and hyperglycaemia collectively referred to as Refeeding Syndrome (Crosby, Apovian & Grodin 2007). Force feeding of hunger strikers has been considered to be unacceptable in UK since the mid 1970’s (Rubenstein, Annas 2009) and the World Medical Association Declaration of Tokyo (1975) and Declaration of Malta (1991 updated 2006) prohibits such practice (World Medical Association 2014). However its use continues in some situations causing difficult and disturbing dilemmas for the personnel involved (Crosby, Apovian & Grodin 2007, Rubenstein, Annas 2009).

2.6 Other Methods of Patient Feeding

Feeding through a nasogastric tube is not the only option for nutritional support for patients unable to feed normally. Whilst nasogastric feeding is considered the initial first choice for the majority of patients unable to feed normally (Kirby et al

1995) other options may be considered for those requiring long term feeding or in particular circumstances.

2.6.1 Total Parenteral Nutrition (TPN)

Total parenteral nutrition (TPN) occurs when nutrition is given intravenously often into one of the large veins and is used when patients have an inaccessible or non-functioning gastrointestinal tract (Hearnshaw, Thompson 2007). However this method of feeding carries a number of risks and is only undertaken in intensive care or specialist units and wherever possible early enteral (via naso or oro gastric tube) is preferred as the risk of atrophy of the gastrointestinal tract is decreased (Heymsfield et al. 1979). Enteral feeding is considered to be safer and associated with better outcomes than TPN, infectious complications are less frequent (Moore et al. 1992), it is also cheaper (Chellis et al. 1996), has fewer complications and safer access (Chernoff 2006). There has been a shift in practice in the last 20 years in recognition of the risks of TPN. In the 1990's TPN was often the preferred method of nutritional support in intensive care units but by the start of the 21st century enteral feeding via nasogastric tubes was the recommended and most common method of feeding patients (Fulbrook, Bongers & Albarran 2007).

2.6.2 Small Intestine Feeding

In some patients small intestine feeding is desired and the tube needs to be placed beyond the pylorus and into the jejunum, delivering feed directly to the main site of nutrient absorption. Although there are conflicting data regarding gastric and small bowel feeding (Neumann, DeLegge 2002, Heyland et al. 2002), naso-jejunal feeding is advocated for patients who are at particular risk of regurgitation and pulmonary aspiration or who have gastroparesis, superior mesenteric artery syndrome, post-operative ileus, pancreatitis or require medication that slows gastric motility (Ellett, Beckstrand 2001, Boivin, Levy & Hayes 2000).

A recent retrospective analysis of a large data set (n=428) of mechanically ventilated patients found that, when compared to stomach placement, the percentage of aspiration was 11.6% lower when feeding tubes were in the first portion of the duodenum, 13% lower when in the second/third portions of the

duodenum and 18% lower when in the fourth portion of the duodenum and beyond (Metheny, Stewart & McClave 2011). The data had been collected prospectively in 5 adult Intensive Care Units (ICUs) over 2 time periods as part of a series of studies examining aspiration in critically ill, mechanically ventilated patients and the relationship remained significant even when controlling for variables such as severity of illness, level of sedation and head of bed elevation (Metheny, Stewart & McClave 2011).

This type of feeding has been increasingly advocated as an alternative to TPN in critically ill patients who do not tolerate nasogastric feeding (Meyer et al. 2007). However it bypasses the gastric phase of digestion impairing the secretion of intestinal hormones and growth factors as well as the bacteriacidal properties of gastric acid (Maggio et al. 2012) and so for patients who are not critically ill or at risk of aspiration nasogastric feeding remains the preferred option.

A Cochrane review of the use of transpyloric versus gastric feeding in preterm infants found no advantage in terms of short and long term growth and that the transpyloric route was associated with an increased incidence of gastrointestinal disturbance and increased mortality (McGuire, McEwan 2007, Watson, McGuire 2013b). Similarly a randomised controlled comparison with adult patients found no clinical advantage to small bowel feeding compared to gastric feeding (White et al. 2009). Meert, Daphtary et al. (2004) conducted a randomised controlled trial of 74 critically ill patients under 18 years of age receiving mechanical ventilation to evaluate the influence of feeding tube position, stomach (n=32) or small bowel (n=42) on nutrient delivery and feeding complications. Twelve patients had to exit the study as the tube could not be passed into the small bowel at the bedside and the 2 groups were similar in terms of age range, risk of mortality score and percentage of ideal weight (Meert, Daphtary & Metheny 2004). The study found that small bowel feeds allowed increased nutrition to be delivered successfully to the critically ill children but they did not prevent aspiration of gastric contents (Meert, Daphtary & Metheny 2004).

In spite of some advantages of small bowel feeding passing tubes beyond the pylorus is difficult and may consequently discourage the use of nasojejunal feeding (Meyer et al. 2007). Various techniques have been described to facilitate bedside positioning of tubes in the jejenum or duodenum including palpation of

the abdomen in lean patients (Sekino et al. 2012). Real-time fluoroscopic transpyloric placement was considered to be the gold standard for passing naso-jejunal tubes with up to a 97% success rate (Pobiel, Bisset & Pobiel 1994). However methods of blind placement have been explored in order to avoid exposing patients to radiation. These methods utilise peristalsis to spontaneously move the tip of the feeding tube out of the stomach and into the duodenum or jejunum. Determining the extra length of tube required for this process to work has been the focus of a number of studies and the appropriate technique is described (Ellett, Beckstrand 2001). Limited success of the use of external magnetic guidance to aid placement has been reported by Boivin, Levy et al (2000) who found a 60% success rate in 156 tube placements over 10 hospital sites. Greater success was reported with a structured training programme for nursing staff on a paediatric intensive care unit supported by the multidisciplinary team and regular audit cycles (Meyer et al. 2007).

2.6.3 Gastrostomy Feeding

National Institute for Health and Clinical Excellence (NICE) recommend that nasogastric feeding is used in the short to medium term (up to six weeks) and longer term feeding should be delivered via gastrostomy tubes, jejunostonomies or gastrostomy buttons (National Institute for Health and Clinical Excellence (NICE) 2006). These feeding methods require insertion of the tubes through a surgical incision through the abdomen into the stomach or jejunum thus giving direct access. Whilst such feeding methods are now the commonest route for long term enteral feeding in adult patients (75%) nasogastric feeding is still the commonest form of home enteral feeding in children (72.6%) with an increasing trend in nasogastric feeding at home (British Association for Parenteral and Enteral Nutrition, Advancing Clinical Nutrition 2010).

It was considered that gastrostomy feeding might be associated with a reduced rate of aspiration in critically ill patients however a review of a number of studies found that aspiration rates are similar in patients fed through gastrostomies and those fed through nasogastric tubes and those patients who aspirate during nasogastric feedings often continue to do so following conversion to gastrostomy feeding (Metheny 2002). More recent comparison studies of gastrostomy versus nasogastric feeding for critically ill patients is not available and therefore the NICE

guidelines should be considered applicable for this group of patients. Further discussion of the issues of gastrostomy and other types of enteral feeding are beyond the scope of this thesis.

2.7 Risks Associated with Nasogastric Tubes

Having a feeding tube passed is unpleasant for both adults and children and may also be distressing for the health care staff involved (Holden et al. 1997). Comforting strategies employed by nurses to support patients through this unpleasant procedure have been described (Penrod, Morse & Wilson 1999) but it can be difficult to distract patients from the procedure.

Inserting a nasogastric tube is a complex procedure requiring skill and expertise and, irrespective of age, patient group or purpose, the procedure carries inherent risks of serious or fatal consequences. In the UK it is recommended that a full patient assessment, balancing the risks and benefits associated with inserting a nasogastric tube for feeding, must be made and documented by at least 2 competent healthcare professionals including the senior doctor in charge of the patient's care (National Patient Safety Agency 2011b). It has been suggested that placement of nasogastric tubes should be approached with the same care and caution as the placement of urinary catheters or central venous devices and that health care professionals should avoid complacency with this procedure (Irving et al. 2014). Misplacement of tubes is the most common risk to patient safety but there can also be the risk of other complications within the gastrointestinal tract, such as diarrhoea, nausea and vomiting (Adam, Batson 1997) and tube occlusion as well as the more serious risks discussed below.

2.7.1 Trauma

Patients receiving nasogastric tubes may be at risk due to trauma during placement such as epistaxis or more seriously perforation of the gastrointestinal tract (Jackson, Payne & Bacon 1990) or pneumothorax (Lo et al. 2008, Kaufman, Hughes & Kerstein 2001) and the presence of the tube can cause ulceration of the nasal passages and nasopharyngeal trauma (Jackson, Payne & Bacon 1990, Wu et al. 2006). Problems in neonates have also been described with tube

insertion causing distress, bradycardia and apnoea (Metheny, Meert & Clouse 2007) and oesophageal perforation being reported (Yong et al. 2014, Maruyama, Baum et al. 2008, Shiojima & Koizumi 2003). It was suggested that recent changes in the texture of nasogastric tubes instituted by one manufacturer led to an increase in the occurrence of oesophageal perforations in neonates (Yong et al. 2014). However following manufacturer guidelines for softening the tubes in warm water, gently manipulating them and using lubricants reduced this risk. The rare complication of knotting of the nasogastric tube around the patient's nasotracheal tube has been reported and it is recommended that any difficult insertion or removal be investigated as in this situation blind removal could lead to life threatening obstruction of the nasotracheal tube (Melki et al. 2010).

2.7.2 Gastro-oesophageal Reflux and Aspiration

The presence of a nasogastric feeding tube may predispose the patient to increased gastro-oesophageal reflux (GER) and risks of aspiration as the tube passes through the lower oesophageal sphincter (Kazi, Mobarhan 1996, Ibanez et al. 2000, Marik 2001, Peter et al. 2002). The influence of the size of the tube on this problem is not clear (Metheny 2002) although some authors suggest that using small bore feeding tubes prevents aspiration (Castell 2000). A study of 16 preterm infants with 8Fr nasogastric tubes *in situ* found that they increased GER when placed in the stomach but the risk was reduced if they were withdrawn into the oesophagus between feeds which the authors suggest as a possible solution (Peter et al. 2002).

The presence of a nasogastric tube is only one of a number of factors understood to increase the risk of aspiration and consequent pneumonia in critically ill patients and the research evidence for the detrimental impact of other factors such as mechanical ventilation and prolonged supine position is much clearer (Metheny 2002). A study of 19 intubated patients receiving mechanical ventilation randomised in a 2 period crossover trial to assess the impact of patient positioning on the risk of aspiration found that patients in the supine position were at greater risk of aspiration than those nursed semi recumbent (45° head of bed elevation) and the risk of aspiration increased the longer the patients remained supine (Torres et al. 1992). Metheny and Franz (2013) provided a review of studies examining the relationship between head of bed elevation and aspiration

or aspiration pneumonia in critically ill patients and conclude that 45° elevation is preferable to supine but the evidence for 30° elevation is lacking even though it is frequently recommended in practice settings (Metheny, Frantz 2013). Head of bed elevation impacts on other patient risks such as the development of pressure ulcers and thromboembolism and the optimum head of bed elevation to balance all of these risks is unknown although there are guidelines from expert panels and recommendations which should be considered (Metheny, Frantz 2013).

Critically ill patients with nasogastric tubes are at risk of a series of clinically silent microaspirations during the course of their treatment and the more often the microaspirations the greater the likelihood of the patient developing pneumonia (Metheny 2006b). Pepsin, which is considered as a proxy for aspiration of gastric contents, was found in almost one third of 6,000 tracheal aspirates from 360 critically ill, mechanically ventilated adult patients receiving nasogastric feeds in 5 intensive care units suggesting that aspiration is common in these patients (Metheny et al. 2006). Efforts have been made to identify early those patients who are aspirating feed from correctly placed nasogastric tubes in order to implement corrective interventions before serious damage occurs (Metheny et al. 2005).

2.7.3 Misplacement

In spite of the above concerns the main cause of harm, including the majority of fatalities, is due to feeding through misplaced tubes (Yardley, Donaldson 2010). Preventing the misplacement of tubes through assistive placement techniques is one possible solution. Ultrasound has been shown to be effective in guiding the placement of nasogastric tubes in critically ill adult patients (Hernandez-Socorro et al. 1996). However in neonates it was found that in only one out of ten cases could the tip of the nasogastric tube be identified by ultrasound (Tamhne, Tuthill & Evans 2006).

More complex procedures using electromagnetic sensing devices (EMSD) (Taylor et al. 2014, Roberts, Echeverria & Gabriel 2007, Rao et al. 2009, Windle et al. 2010, Windle 2010, Kaffarnik et al. 2013) and electocardiographic guidance (Green et al. 2011) have been described as being successful. However these procedures require expensive equipment and highly trained and skilled personnel

and so are not suitable for use with routine nasogastric feeding and home care. Such techniques may be more readily justified in patients who have already suffered a misplaced tube (Sparks et al. 2011) or with the more difficult placement procedure required for naso-jejunal tubes which have to be passed through the pyloric sphincter (Boivin, Levy & Hayes 2000, Windle et al. 2010, Gray et al. 2007).

Roa, Kallam et al. (2009) studied the Cortrak EMSD (Corpak MedSystems, Chicago, IL, USA) and found that it was safe, quick and effective in assisting the placement of 10 naogastric and 12 nasojejunal tubes but stressed that further studies addressing the cost benefit analysis would be required to support the introduction of such a costly procedure. Clinical and cost advantages resulting from the earlier introduction of enteral feeding, avoidance of parenteral feeding and reduced need for X-rays, were identified with the Cortrak system by Windle et al. (2010). A study of 70 feeding tube placements in 51 patients in a surgical ICU over a 12 month period found that the Cortrak system enabled a fast, safe and reliable method for the placement of post-pyloric feeding tubes (Kaffarnik et al. 2013). Another similar system using magnets is the Syncro Blue Tube (Syncro Medical Interventions, Ohio) but in spite of claims of efficacy both these systems suggest that X-ray confirmation should be performed after guided placement (Gabriel, Ackermann 2004). An audit of electro-magnetic tracing to guide the placement of nasogastric tubes in 127 tube placements in 113 patients in an intensive care unit (ICU) found that this method was successful in accurately confirming placement and gave early warning of lung misplacement before trauma occurred (Taylor et al. 2014). Evaluation of the value of these systems in aiding safe nasogastric tube placement is ongoing.

In the past confirmation of nasogastric tube placement was guided by tradition rather than being research based (Shiao, Difiore 1996). Having to have the unpleasant procedure of nasogastric tube insertion repeated because the tube is in the wrong place or the location cannot be verified is costly in both nursing time and distress to the patient. However in recent years methods of ensuring nasogastric tubes are in the correct place prior to feeding have been the focus of many research studies (Metheny, Meert 2004, Irving et al. 2014). Potential failures in the process of passing nasogastric tubes have been studied using a

triangulated approach of literature review, observation and interviews of both healthcare staff and patients in order to develop a systems approach to assessing risk and identifying contributing factors to that risk (Anderson, Buckle & Hanna 2012). Projects aimed at improving and developing bedside methods of verifying correct placement of nasogastric tubes, including this thesis, continue to be a research priority.

2.8 Literature Search Strategy

Confirming correct placement of tubes and detecting tube misplacement is the rationale for this research and therefore the focus of the literature review is on this aspect of nasogastric tube management. In order to understand the current problems associated with nasogastric tube placement and verification of position in the stomach a configurative literature review was undertaken. It is recognised that systematic reviews of the literature have become increasingly important in the last 20 years as a crucial component in establishing the evidence basis for health care and that two approaches, aggregative or configurative, may be adopted (Gough, Thomas 2012).

A configurative approach was selected to the review of the literature for this thesis whereby interpretation and synthesis of the results from primary research studies occur simultaneously as the results from one study are compared with another (Gough, Thomas 2012). In configurative reviews homogeneous types of studies are not sought out, as would be necessary for aggregative reviews, but rather differences between studies are a positive aspect of their synthesis. Configurative reviews include studies that provide richness to the summary of evidence presented through developing and exploring theory (Gough, Thomas 2012). Inclusion criteria need not be set in advance but develop in an iterative way throughout the review. This was considered important as previous aggregative systematic reviews in this subject area had inevitably had to exclude relevant studies. A number of aggregative systematic reviews of studies of tube misplacement and placement verification have been conducted in the last 5 years and the author contributed to a Cochrane review protocol on pH testing as a method of verifying nasogastric tube placement. It was therefore not necessary

to conduct another such review but adopt a broader approach which includes these systematic reviews as well as a range of primary research studies in this area.

A literature search was performed in 4 stages with the terms detailed in Table 2.

	Boolean term	search terms
Stage 1		enteral feed*, enteral nutrition, feeding tube*, feeding catheter*, orogastric tube*, nose* tube, nasal* tube, naso* tube, ng tube, ng intubat*, stomach intubate*, stomach decompress*, gastr* tube*, gastric decompress*
Stage 2	AND	placement, cofirm*, verif*, detect*, misplac*
Stage 3	NOT	Percutaneous, nasobiliar, small bowel, small intestine, jejen*, duoden*
Stage 4		English language, peer reviewed articles, not animal studies, exclude Medline results for CINAHL search

Table 2: Search terms for structured review of the literature

The following databases were searched from 1984 – July 2014: CINAHL, Medline, EBSCO academic search premier, Cochrane. These databases were selected as the most appropriate to access nursing and medical literature in this area. Previous systematic reviews of the literature such as that conducted by Chau, Thompson et al., (2009) had revealed the lack of good quality studies in this area so a further systematic review was not conducted. Instead a range of literature was accessed and used to inform this research project. Table 3 provides a summary of the number of papers identified from the databases searched.

Database	Number of initial hits	Refined search hits		
	Stage 1	Stage 2	Stage 3	Stage 4
CINAHL	7,871	940	705	39
Medline	24,238	2,985	1,013	174
EBSCO academic search premier	5,489	795	198	198
Cochrane	53			

Table 3: Results of structured literature search

Titles and abstracts were read in order to identify the relevance of the papers and exclude duplicates. Full papers were downloaded and printed for one hundred and thirty-two references and the reference lists of these selected papers were hand searched in order to identify further papers.

Grey literature was accessed through OpenGrey, a European multi-disciplinary database which includes The European Association for Grey Literature Exploitation (EAGLE). This is a co-operative network for identification, location and supply of grey literature through national centres participating in Systems of Information for Grey Literature in Europe and includes technical or research reports, doctoral dissertations, conference papers, official publications, and other types of grey literature.

Twelve dissertations were identified but only 2 were relevant to the topic (Ellett 1996, Bourgault 2012) and results from both of these doctoral projects had been published in peer reviewed journals (Ellett, Beckstrand 1999, Bourgault et al. 2014) and so the published papers were accessed.

2.9 Incidence and Risks of Incorrect Placement

Insertion of nasogastric tubes is a common procedure with a relatively low rate of complications, often undertaken by more junior staff who may not be aware of the potential serious consequences of misplacement. This has led to concern that the potential risks of misplacement do not receive the attention they deserve

(Roka et al. 2010) and there is a risk of complacency with verification of correct placement (Irving et al. 2014). When nasogastric tubes were first used in regular nursing practice misplacement in the larynx was discussed but considered highly unlikely due to the strong spasm of the epiglottis and if the tube was inadvertently inserted into the trachea it was considered that this would be clearly evident by signs of asphyxiation in the patient (Scott 1930). Aligning an external mark on the tube with the opening of the nostril and checking that this remained aligned was the only method of monitoring correct placement (Scott 1930) and incidents of misplacement were not recorded. Current practice is very different with correct placement verified when the tube is passed and before every feed or administration of medication (National Patient Safety Agency 2011a, National Patient Safety Agency 2011b). Thus there are two issues to be considered regarding placement verification: firstly ensuring that initial placement in the stomach is confirmed and secondly that there is ongoing verification that tube tip remains in the stomach and does not migrate out of position.

A nasogastric tube may be considered to be misplaced if the feeding ports are in any location other than the stomach that is; in the oesophagus, beyond the pylorus or in the respiratory tract (Khilnani 2007). Although rare, misplacement has also been reported in the brain (Metheny 2002) and eustachian canal (Wynne et al. 2003). Misplacement may occur on initial insertion or a tube may become displaced over time. The cited incidence of misplacement varies depending on the definition of what actually constitutes a misplaced tube but past studies suggest that in adults it varies from 1.9% to 89.5% and in children from 20.9% to 43.5% (Ellett 2004). This is a very wide range, particularly in adults and reflects the difficulties encountered when comparing studies. The majority of incidents of mal-positioned tubes cause little or no physical harm to the patients as misplacement is most frequently in the oesophagus, particularly in children, with the unsuspected placement of nasogastric tubes in the respiratory tract left in situ for feeding considered to be rare (Ellett et al. 2005b).

However insertion of a nasogastric tube into the respiratory tract is the cause of greatest concern because, if undetected prior to feeding, results can be disastrous. Cases of nasogastric tubes misplaced in the respiratory tract continue to be reported (Sparks et al. 2011) indeed it has been claimed that they

are the most frequently reported (Metheny, Meert & Clouse 2007). The majority of such misplacements are detected before any feed or medication is inserted down the tube and consequently the harm caused to patients is considered to be minimal, although such errors cause patient distress and discomfort. It is impossible to quantify the number of misplaced tubes that are detected prior to feeding and reinserted as there is no reporting mechanism for such errors. Some patients may have a number of tubes incorrectly placed before a tube is correctly inserted into the stomach and there are considerable clinical costs associated with misplaced tubes, including the use of multiple tubes and costs of repeat X-rays, even if there are no clinical complications. If, in addition, the patient suffers complications due to a misplaced tube then there will be costs associated with the treatment and management of their clinical condition as well as legal defence costs (Sparks et al. 2011).

Certain factors predispose patients to tube misplacement. In children it is suggested that age, level of consciousness (alert or unconscious being riskier than semiconscious), abdominal distension, vomiting and orally placed tubes increase the risks of tube misplacement (Ellett, Maahs & Forsee 1998). In adults it is suggested that patients who are alert and comfortable are more co-operative and therefore less likely to have a tube misplaced (Roberts, Echeverria & Gabriel 2007). Patients who are unconscious, have impaired swallow reflex or recurrent retching and vomiting as well as those with anatomical malformations such as oesophageal fistula are considered most at risk of tube misplacement (National Patient Safety Agency 2011b). It is also suggested that the risk of misplacement is cumulative in patients so that those who have already experienced a misplaced tube are more likely to have subsequent tubes misplaced and are at higher risk of complications and therefore should be considered for the assisted placement techniques discussed in 2.7.3 (Sparks et al. 2011).

Differing definitions of misplacement and poor reporting mean that the total incidence of misplaced tubes is difficult to determine with accuracy. It is suggested that poor reporting of misplacement has hindered the adoption of protocols to prevent such mistakes (Metheny, Meert & Clouse 2007). A review of all cases of nasogastric tube misplacement in adults reported to the National Reporting and Learning System database between October 2003 and the end of

February 2009 found 104 cases of documented tube misplacement (Hanna 2010). Table 4 shows the results of these tube misplacements and confirms that misplacement of nasogastric tubes continues to be an issue for practitioners.

Effect on Patient	Number of Cases
Death	6
Severe Harm	15
Moderate Harm	23
Low Harm	17
No Harm	43

Table 4: Patient harm associated with feeding tube misplacement (Hanna, Phillips et al, 2010 pp 57)

The different areas for misplacement are considered in detail below.

2.9.1 Gastrointestinal Misplacement

It is suggested that many tubes are not inserted far enough within the gastrointestinal tract and the feeding ports sit in the oesophagus causing irritation and increasing the risk of pulmonary aspiration (Metheny, Smith & Stewart 2000) especially if the patient has other risk factors for regurgitation and aspiration (Metheny 2006b). Feeding tubes can also be inserted past the pylorus into the duodenum and, if unintentional, such placement can cause feeding intolerance (Metheny, Smith & Stewart 2000). Inadvertent post pyloric feeding, when gastric feeding was intended, was associated with severe recurrent postprandial hypoglycaemia in an 18 month old infant (Allen 1988).

Early studies in adults found that 13 – 20% of nasogastric tubes were incorrectly placed in the gastrointestinal tract or migrated out of position over time (Neumann et al. 1995) and that naso-intestinal tubes were out of position 27-50% of the time (Metheny, Spies & Eisenberg 1988). The research with children was even more worrying with 39-55% of naso-gastric or oro-gastric tubes being incorrectly placed in neonates (Weilby et al. 1987).

Misplacement in the gastrointestinal tract is much more common in children and neonates because of the relative small size of the stomach and consequent reduced margin for error. This is particularly problematic in very low birth weight neonates where a difference of 0.5 -1.0 cm can be crucial and can be 5-10% of

the total length of the tube used (Tedeschi, Atimer & Warner 2005). The incidence of incorrect placement of feeding tubes in neonates was found to be 59% in a study of 381 consecutive X-rays of 173 infants (Quandt et al. 2009). In a sample of 72 children aged 3 days to 7 years Ellett, Croffie et al (2005) found that 15 (20.8%) of tubes were out of place as confirmed by X-ray. The need for better guidance on the length of tube to be inserted as well as improved methods of verifying correct placement are acknowledged (Quandt et al. 2009) and are discussed in detail in section 2.10.

Tubes initially correctly placed in the stomach have been found to move up or down the gastrointestinal tract and so become misplaced over time (Metheny, Spies & Eisenberg 1988). A study of 201 critically ill adult patients found that 25 (12.4%) tubes that had been correctly placed initially became displaced over time, 23 from the small bowel to the stomach and 2 from the stomach to the oesophagus (Metheny et al. 2005). Normal peristalsis of the gastrointestinal tract aims to move food along the system towards the large bowel so this could not account for the migration of the tubes which in all cases was in the opposite direction towards the nose. Vomiting or coughing can cause tubes to migrate upwards or the tubes may have been inadvertently pulled by the patient or carer. Confused patients may pull tubes out of place and they may become accidently dislodged during movement or nursing care procedures (Eisenberg, Spies & Metheny 1987). Such partially removed tubes, where feeding ports lie in the oesophagus can be an undetected problem with continuous feeding when placement may only be verified once per shift (Metheny, Stewart 2002).

It was suggested that a simple bedside test for displacement of a previously correctly placed tube was assessment of the length of tube outside the patient and this has been found to be effective in some cases (Metheny et al. 2005, Metheny, Titler 2001). External observation of the tube may be the only placement verification method possible in specific situations where patients are on frequent medications, continuous feeding and antacid medications and it is impossible to get aspirate with a pH reading less than 5.5 (see section 2.10.4) and it is not safe or practical to obtain daily X-rays (see section 2.10.6) (National Patient Safety Agency 2011b). It is recommended that the tube length should be recorded on a daily basis (National Patient Safety Agency 2011b), however it is

recognised that the tip of the tube may spontaneously migrate out of position without any change in the external length of the tube (Metheny, Stewart 2002).

In recent years the use of “nasal bridles” has been advocated to prevent patients from pulling their nasogastric tubes out of position or out completely (Medlin 2012). These devices secure the tube in place by means of tape looped behind the nasal septum and have been used increasingly in recent years since a method of attaching them at the bedside using a magnetic device was developed, but complications, such as the removal of a patient’s septum, have been reported (Young, Leedham 2011). However a study of 140 patients with nasogastric tubes secured by nasal bridles found that they were effective and safe and, although they caused some nasal trauma, they prevented the unplanned removal of tubes and consequent distress to patients of replacement or unnecessary gastrostomy placement (Webb et al. 2012).

2.9.2 Intracranial Misplacement

Misplacement of nasogastric tubes in the brain is extremely rare, however results are frequently fatal with a reported mortality rate of 64% (Genu et al. 2004) or lead to severe neurological deterioration (Metheny 2002). Even if fluid is not inserted through the tube attempts to verify placement by injecting air or aspirating fluid can cause severe damage to delicate brain tissue. The first case of intracranial insertion was reported by Martinelle et al in 1974, however only 34 cases were reported in the international literature in the following 30 years (Genu et al. 2004) suggesting that, with approximately one case per year, this is indeed a rare event.

Intracranial placement may follow cranial surgery (Metheny 2002, Vahid 2007), head injury (Roka et al. 2010, Genu et al. 2004, Fremstad, Martin 1978), cranio-facial trauma (Ferreras, Junquera & Garcia-Consuegra 2000, Chandra, Kumar 2010) and iatrogenic causes (Araimo, Caramia & Meschesi 2011, Freij, Mullett 1997). The most common cause of intracranial placement is trauma and it is recommended that the orogastric route be used in all cases of faciomaxilliary injury and fractures of the anterior cranial fossa unless direct insertion by an anaesthetist using laryngoscopy is available (Roka et al. 2010).

Very unusual cases have been reported where a nasogastric tube has been inserted into the brain of patients through malformations in the cribriform plate caused by previous sinusitis or meningitis (Freij, Mullett 1997, Glasser, Garfinkle & Scanlon 1990). Although this is a relatively rare event caution is recommended when passing nasogastric tubes on patients with previous medical history that might suggest a cranial defect (Freij, Mullett 1997).

2.9.3 Respiratory Tract Misplacement

Apart from intracranial misplacement the most serious problems occur when there is unintentional placement of feeding tubes in the tracheopulmonary system. If not detected prior to feeding such misplacement can cause considerable physiological damage and serious complications for the patient including death. The level of pulmonary injury is dependent on the amount, osmolarity and characteristics of the feed (Metheny 2006a).

There is considerable variation in the reported rates of pulmonary complications related to insertion of narrow bore nasogastric tubes, but it is suggested that they are more frequent than previously thought occuring in 1.2% - 2.4% of all attempted blind placements and leading to “pneumonia, acute respiratory failure, pneumothorax, tracheal perforation, vocal cord paralysis and even death” (Sparks et al. 2011). Others suggest that the rate of pulmonary misplacement in adults may be as high as 3.2% (Sorokin, Gottlieb 2006) or even 4% (Ellett et al. 2005b).

Case reports of the associated mortality have been published (Dyer 2003) and litigation for malpractice has succeeded in the US (Metheny, Aud & Ignatavicius 1998). The majority of misplaced tubes in the respiratory tract are inserted via the right main bronchus (Sorokin, Gottlieb 2006, Metheny et al. 1990a) and are sometimes referred to as “aspiration by proxy” (Metheny 2006b). Whilst the incidence of fatalities from respiratory placement is considered to be low, estimated at 1 per 100,000 intubations (Taylor, Clemente 2005) respiratory misplacement continues to be reported (Hussain 2006) and remains the major concern when verifying tube placement.

The first report of a nasogastric tube inserted into the pleural space was in 1978 (James 1978) followed 3 years later by the first reported death due to feeding into

the intrapleural space (Torrington, Bowman 1981). Further case reports of nasogastric tubes misplaced in the respiratory tract were later published with advice on how to avoid such errors (Theodore et al. 1984). Five cases of misplacement in the respiratory tract were reported in an intensive care unit over a 28 month period and it was suggested that the use of fine bore feeding tubes with stylets to facilitate insertion increased the risk of unrecognised tracheal intubations (Valentine, Turner 1985).

A prospective study of all narrow-bore feeding tube placements in an intensive care unit over a 2 year period found that 14 (2%) of the 740 tubes passed were wrongly inserted into the tracheopulmonary system resulting in serious complications in 5 patients (0.7%) and death in 2 (0.3%) cases (Rassias, Ball & Corwin 1998). Worryingly all of these misplaced tubes were thought to be placed correctly in the stomach based on the recommended bedside test of auscultation of the abdomen during air insufflations through the tubes. This method is discussed in detail in section 2.10.6. Although X-ray examination identified misplacement in 12 cases this verification method was not infallible with two of the misplaced tubes not identified by X-ray and in one case feeding was given for 24 hours into the left pleural space before the misplacement was identified. This patient died as a direct result of the malpositioning of the feeding tube as did another patient who sustained a tension pneumothorax and three other patients developed serious complications as a direct result of the misplacement of their feeding tube (Rassias, Ball & Corwin 1998).

An earlier study had found that inadvertent placement of small-bore feeding tubes in the respiratory tract was identified in 10 patients over a 2-year period in five intensive care units and two general wards (Metheny et al. 1990a). The most frequently used methods for detecting tube placement at that time were observation for respiratory distress and auscultation. It was concluded that these commonly used bedside methods often gave false reassurance that the tubes were properly positioned (Metheny et al. 1990a).

A review of over 2000 nasogastric tube insertions over a 4 year period identified 50 tubes wrongly inserted into the respiratory tract (Sorokin, Gottlieb 2006). Of these 34 entered the right bronchus and 26 the left, the misplacements resulting in serious complications including pneumothorax (n=8) and pneumonia (n=5) for

14 (28%) of patients (Sorokin, Gottlieb 2006). Two patients died as a direct result of the malpositioned tubes however the introduction of specific policies and procedures for placement of feeding tubes resulted in no further misplacements in the following 15 months (Sorokin, Gottlieb 2006).

In February 2005 the National Patient Safety Agency (NPSA) issued a patient safety alert following an investigation into the death of an 8 year old girl who had had enteral feed inadvertently administered into the pleural cavity and 10 further deaths related to misplaced nasogastric tubes reported to them (National Patient Safety Agency 2005b). This alert prohibited the use of blue litmus paper and auscultation as methods of verifying placement and stated that pH indicator paper or X-ray should be used to confirm placement prior to feeding (National Patient Safety Agency 2005b). In spite of this action being a requirement 210 further incidents due to misplacement of nasogastric tubes were reported to the NPSA in the following 30 month period including 26 where feed was delivered into the lungs; five of these patients dying and 6 experiencing severe harm (Yardley, Donaldson 2010).

Between 2005 and 2011 staff in England and Wales reported 21 deaths and 79 cases of harm resulting from feeding into the lungs through misplaced nasogastric tubes (National Patient Safety Agency 2011a). Misinterpretation of X-rays was the cause of the majority (45) of misplaced tubes not being detected prior to feeding and resulted in 12 deaths. The NPSA therefore issued a further safety alert in March 2011 focussing on the safe interpretation of X-ray images (National Patient Safety Agency 2011a). Insufficient radio-opacity of the tube is considered to be contributing factor in the misinterpretation of X-ray images (Taylor et al. 2014). Misinterpretation of X-rays has been found to be an issue in other countries for example in Japan 38.5% of 512 hospitals answering a survey reported incidences of nasogastric tubes inserted into the respiratory tract and found that X-rays were misinterpreted by junior doctors in a number of cases and deaths due to such errors were reported (Haga et al. 2008).

A critical review of the published literature from 1 July 1959 to 1 July 2009 was conducted by Sparks, Chase et al (2011) who identified 5 separate studies investigating the association between misplacement of narrow bore enteral tubes and pulmonary complications. Data were extracted from the studies relating to

the blind placement of 9,931 narrow bore nasoenteric feeding tubes and analysed by an independent epidemiologist using commercial statistical software. One hundred and eighty seven tubes were wrongly inserted in to the respiratory tract giving a malposition rate of 1.9%, 35 of the misplaced tubes led to pneumothorax (18.7%) and 5 caused patient death (Sparks et al. 2011).

Information about pulmonary misplacement in children is scarce and the incidence of tubes misplaced in the lungs of children has been assumed to be similar to that of adults (Metheny, Meert 2014b). However studies suggest that it may be lower with only 1 such misplacement occurring in a recent study of 276 children having gastric tubes inserted (Ellett et al. 2014). A study which reviewed 381 radiographs of neonates found no such misplacements (Quandt et al. 2009). However even if the incidence is low in children the frequency of nasogastric feeding in this population means that respiratory misplacement is still of concern and there is evidence that when tubes are misplaced serious injury and death may occur.

Similar to the review of adult studies conducted by Sparks, Chase et al (2011), Metheny and Meert (2014) conducted a review of published case reports over the last 20 years where blindly inserted nasogastric tubes had been inadvertently inserted into the respiratory tract of children (Metheny, Meert 2014b). Fifteen published case reports were identified where the placement in the respiratory system was confirmed by X-ray, initial bedside testing of placement had involved auscultation in nearly half the cases (n=7) leading the operators to believe that the tubes were correctly placed in the stomach. Four of the patients died as a result of the misplacement, 5 developed a pneumothorax and at least 4 required mechanical ventilation. The reviewers suggest that although the incidence of respiratory misplacement appears to be low additional cases of misplacement during the review period may have occurred but not been reported (Metheny, Meert 2014b)

A recent report reviewed the effectiveness of EMSDs (discussed in section 2.7.3) in detecting inadvertent placement of nasogastric tubes in the respiratory system identified through an OVID Medline search, which identified 6 published peer reviewed studies, and events reported to the US Food and Drug Administration (FDA)'s Manufacturer and User Facility Device Experience (MAUDE) database

between 2007 and 2012 (Metheny, Meert 2014a). The 6 studies had a total of 1,725 patients and in 5 of the studies the investigators reported being able to identify tube misplacement in the respiratory tract before lung damage occurred and no cases of pneumothorax were reported (Metheny, Meert 2014a). However in these studies the practitioners using the EMSD were highly experienced in placing fine bore feeding tubes and using EMSD and the excellent results were at odds with the adverse events reported to MAUDE, where 20 of the 21 cases involved misplacement in the respiratory tract and of these 17 caused a pneumothorax and 2 resulted in death (Metheny, Meert 2014a). The authors of the review conclude that, although electromagnetic devices can improve placement of feeding tubes when operated by skilled and experienced personnel, there remains a significant risk of misplacement when used by inexperienced clinicians and there remains a need for radiologist reported X-ray confirmation before initial use of the feeding tube (Metheny, Meert 2014a).

Conversely when inserting the tube without any special guidance devices the experience of the person passing the tube does not appear to influence the incidence of malpositioning. Whilst the majority of nasogastric tubes in UK are inserted by nurses, doctors insert some, particularly if placement has been difficult and many of the incidents of malpositioned tubes reported to the National Patient Safety Agency (NPSA) were inserted by medical rather than nursing staff (Yardley, Donaldson 2010). The risk of tracheopulmonary placement in adults is increased by endotracheal intubation (Rassias, Ball & Corwin 1998). In children the risk of feeding tubes being placed incorrectly is increased by coma, inactivity, dysphagia and the use of Argyle tubes (Ellett, Maahs & Forsee 1998).

Particular problems can arise with specific groups of patients such as the very young (neonates) and critically ill patients who are paralysed and ventilated. The presence of an inflated, cuffed endotracheal tube does not prevent the passage of a nasogastric tube into the lungs (Valentine, Turner 1985, Theodore et al. 1984). It is generally considered that the risk of placement in the respiratory tract is only present on initial placement but there have been reports of tubes correctly inserted into the stomach and securely fixed to the patient's nose with a nasal bridle being displaced into the lung by coughing or vomiting without any change in the external fixation of the tube (Young, Leedham 2011).

2.10 Current methods of detecting placement of nasogastric tubes

The harm described in section 2:9 caused by misplaced tubes is considered entirely preventable and in March 2010 misplaced nasogastric tubes not detected prior to feeding was confirmed by the Department of Health as being a "Never Event" (National Patient Safety Agency, National Reporting and Learning Service 2010). Never Events are serious avoidable events that cause patients harm and should never happen because there are guidelines in place to ensure that they are avoided. Between 2009 and 2010 forty-one never events relating to misplaced nasogastric tubes were reported in the UK making this the second most common "never event" after wrong site surgery (57 incidents) and confirming that this was an issue for patients and healthcare providers (National Patient Safety Agency, National Reporting and Learning Service 2010). The most common events on the core list of Never Events were surgery performed on the wrong site, retained instrument post-operation, wrong route administration of chemotherapy and misplaced naso or orogastric tube not detected prior to use (National Patient Safety Agency, National Reporting and Learning Service 2010).

Analysis of incidents suggests that misinterpretation of X-ray images was the largest contributory factor but in addition healthcare professionals were not following NPSA guidance and in some instances were not checking tube placement by any method (National Patient Safety Agency, National Reporting and Learning Service 2010). Table 5 gives a summary of the reported incidents related to misplaced feeding tubes between September 2005 and March 2010. Similar concerns were raised in the US where nasogastric tube insertion into the respiratory tract became a sentinel event in 2006 (Catalano 2006). Misplaced nasogastric tubes remain on the list of "Never Events" 2013/14 (NHS England Patient Safety Domain Team 2013) although it has become less common in recent years moving from 4th on the list in 2010 to 19th in 2013 suggesting that current guidance and protocols may be having a positive effect on improving practice.

Checking method where error occurred	Total number of reported incidents	Number of reported deaths (out of total)
X-ray misinterpretation	45	12
Fed despite aspirate tested pH 6-8	7	2
Fed after apparently obtaining aspirate with pH 1- 5.5 (almost none of these were contemporaneously recorded but were recalled later during investigation)	9	1
Water instilled down tube before obtaining aspirate for pH testing	2	0
Not checked at all	9	1
Apparent migration after initial correct placement	8	1
No information on checking method used	17	4
Other		
• Placed under endoscopic guidance	1	0
• Visual appearance of aspirate	1	0
• Bubble test	1	0
Total	**100**	**21**

Table 5: Summary of reported incidents relating to misplaced nasogastric feeding tubes (NPSA, 2011)

In the past a variety of methods have been used to verify the position of feeding tubes, the majority of which are now considered unsafe. In early reviews of popular methods of verifying feeding tube placement it was concluded that there was little published research to support them (Metheny, Spies & Eisenberg 1988) and those studies that have been conducted have found such clinical indicators to be unreliable (Metheny, Meert 2004, Rassias, Ball & Corwin 1998). A systematic review of all literature between 1966 and 2003 acknowledged the lack of well-designed randomised controlled trials to identify the best method of placement verification and recommended a combination of a number of bedside methods (Williams, Leslie 2004). In 2009 Chau, Thompson, Fernandez, Griffiths and Lo published a meta-analysis of twenty-six studies exploring methods for determining the correct placement of nasogastric tubes and found that the limited evidence obtained did not provide a sound evidence base for the development of practice guidelines (Chau et al. 2009). Another systematic review of studies examining bedside verification methods between 1988 and 2007 identified only

12 pertinent studies and found that levels of evidence varied depending on the method but the level of evidence was low, being either indeterminate (preliminary research which may be promising or premature) or class III which is considered unacceptable or potentially harmful (Bourgault, Halm 2009).

This section discusses the range of methods used to identify correct placement of feeding tubes and the available evidence to support them with consideration of current guidelines for practice.

2.10.1 Length of tube to be inserted

In the past individual differences in length of tube required to reach the stomach were considered negligible (Scott 1930) but today the length of tube to be passed is assessed for each individual patient and, whilst not strictly a method of verifying placement in the stomach, it is an essential first step in ensuring the tip of the tube reaches the desired location. Every attempted insertion of a feeding tube commences with an estimation of the length of tube required to be inserted in order to guide the practitioner and avoid stopping the procedure with the feeding ports still in the oesophagus or continuing the insertion so that the tip goes beyond the pylorus and into the duodenum. In children and particularly neonates the estimation of the length to be inserted is not standardised and errors frequently occur (Ellett, Maahs & Forsee 1998, de Boer, Smit & Mainous 2009).

A commonly used measure in both adults and children is the distance from the tip of the nose (for nasogastric tubes) or corner of the mouth (for orogastric tubes) to the inferior attachment of the earlobe and then to the Xiphoid process, the Nose-Ear-Xiphoid (NEX) method (Griffin 2011, Howe, Forbes & Baker 2010, Great Ormond Street Hospital for Children 2014, Freeman, Saxton & Holberton 2012). In a telephone survey of 113 nurses in 5 hospitals in the midwest of North America in 1996, 98% of nurses stated that they used the NEX method to determine the length of tube to be inserted (Shiao, Difiore 1996) and this remains the recommended method when inserting a nasogastric tube (National Patient Safety Agency 2011b, Dornan 2006). However this method has been associated with placement errors in both adults and children and new imaging techniques are highlighting the shortcomings of this previously accepted practice. In a small study of 30 patients with nasogastric tubes who received whole body positron

emission tomography with computerised tomography (PET-CT) scan, 29 patients did not have the nasogastric tube placed correctly in the stomach, only one patient having all 4 feeding ports located in the stomach (Chen et al. 2014).

Estimation of correct tube insertion length is particularly problematic in infants and neonates because of the very small size of their stomachs which leaves very little margin for error. In newborn infants morphological measures have been found to be unreliable, frequently underestimating the length of tube to be inserted resulting in a high rate of tubes positioned in the oesophagus. Studies using the NEX method in neonates found malposition rates as high as 47.5% (de Boer, Smit & Mainous 2009) and 59% (Quandt et al. 2009) and it has been recommended that this method is no longer used in this population (Ellett, Maahs & Forsee 1998, Ellett et al. 2011). A small study of the placement of 43 gastric tubes on a Neonatal Intensive Care Unit found that the distance from the tip of the nose (or corner of the mouth) to the ear lobe then to the midway point between the xiphoid process and umbilicus, the Nose-Ear-Mid Umbilicus (NEMU) method was more successful in this population with 95% of tubes place gastrically (Tedeschi, Atimer & Warner 2005). More recently a randomised clinical trial involving 173 neonates found that 92% of naso or orogastric tubes were placed correctly using the NEMU method but only 61% were correctly placed using the NEX method (Ellett et al. 2011).

Other studies to compare the NEX and NEMU methods in children have found that the NEMU method produces less errors, (Beckstrand, Ellett & McDaniel 2007). However age-related height based measures are superior to both (Beckstrand, Ellett & McDaniel 2007, Klasner, Luke & Scalzo 2002). A study of 20 external measures to predict insertion length in 494 children aged 2 weeks to 19 years found that age related height based (ARHB) measures were the best predictors of optimal placement, being able to predict correct placement in 98.8% children aged 0.5 – 100 months and 96.5% of children over 100 months (Beckstrand, Ellett & McDaniel 2007). Previously Klasner, Luke et al. (2002) conducted a prospective, randomised, double blinded study with a convenience sample of 89 children aged 6 months to 18 years and found that a method of using height to estimate length of tube to be inserted was a better predictor of correct placement as confirmed by X-ray than the NEX method. Further research

by Ellett, Cohen et al. (2011) developed a regression equation to calculate the tube insertion length from the length of neonates, aged from birth to 1 month, corrected for age and the authors provide a table of appropriate insertion lengths for use by practitioners. However further research is required to verify ARHB formulae in infants (Freeman, Saxton & Holberton 2012).

Attempts to develop a weight based formula for determining length of tube to be inserted in neonates have been made. Freeman et al (2012) studied 218 radiographs relating to 87 infants and found that tubes were incorrectly positioned in 26% of occasions consistent with other studies. Their weight related formulas correctly predicted 60% of misplaced orogastric tubes and 100% of misplaced nasogastric tubes. Whilst this was a small single centre study the development of weight based formulas, similar to those used to determine endotracheal tube and umbilical catheter insertion length, is a possible method of enhancing current methods of ensuring correct placement of feeding tubes in neonates (Freeman, Saxton & Holberton 2012). In adult studies the limitations of the currently used body surface measurement techniques (usually NEX) is recognised and the need to develop a better predictor of tube insertion length through large scale studies involving men, women and children of all ages is acknowledged (Chen et al. 2014).

2.10.2 Observation of Patient Reaction

Observing the patient for signs and symptoms of respiratory distress such as choking, coughing, cyanosis, dysphagia and lack of ability to speak or cry during insertion is considered to be an obvious indication of misplacement in the lungs, although there is little research evidence of the effectiveness of such responses in correctly indicating misplaced tubes (Metheny, Titler 2001). However it is unlikely that a nurse or health care practitioner would continue with an attempted placement and indeed they should remove the tube if the patient exhibits such symptoms which are likely to indicate misplacement in the respiratory tract (Ellett et al. 2005b). Observation for signs of respiratory distress is the first item on the list of expected practice for bedside methods to predict tube location during blind insertion of feeding tubes, see Appendix 3 (American Association of Critical Care Nurses 2010a).

For many years the lack of such symptoms were the only verification of correct placement required (Scott 1930) but the use of softer, finer bore feeding tubes has meant that patient reaction cannot be relied upon as an indication of misplacement with many reports of patients appearing comfortable, with normal vital signs and being able to speak in spite of tubes misplaced in their lungs (D'Souza et al. 1994). Small bore tubes can enter the respiratory tract with few if any symptoms (Metheny et al. 1990b) and large bore tubes can enter the respiratory tract with no symptoms particularly if the patient is unconscious (Rassias, Ball & Corwin 1998). Thus there is a need for an objective measure to determine the placement of naogastric tubes.

2.10.3 Obtaining and Observation of Aspirate

Aspirating fluid through a nasogastric tube positioned in the stomach is necessary for some of the other verification tests described below but has also been considered as a means of verification of placement in itself. Ten years ago it was claimed that the appearance and pH of aspirate were the only available bedside tests for gastric placement (Huffman et al. 2004). However obtaining aspirate fluid from the stomach is not always easy as, even if the tip of the tube is in the correct location, the feeding ports may not be sitting in a pool of gastric fluid (Ellett et al. 2014) and fine bore tubes tend to collapse when negative pressure is applied with a syringe (Crocker, Krey & Steffee 1981). Very few of the research studies on assessment of aspirate address the difficulty that can occur when trying to obtain aspirate from patients although Metheny, Wherle et al (1998) in their study of over a thousand feeding tubes found that this was often challenging, particularly if the patient was dehydrated, the tip of the tube was high in the stomach or not in a pool of gastric fluid.

This is particularly a problem in neonates when gastric residual content is dependent on positioning, gastric emptying and gastric motility (Premji 2005). In their study Nyqvist, Sorell and Ewald (2005) obtained aspirate in only 62% of infants, babies born before 32 weeks being particularly difficult to obtain aspirate from. They acknowledge this problem and considered a variety of reasons for this including the tubes being in the stomach but not in contact with gastric fluid, collapse of the fine bore tube and adherence to the stomach wall. However they concluded that in the majority of cases where no aspirate was obtained tubes

were positioned incorrectly (Nyqvist, Sorrell & Ewald 2005). Inability to obtain tube aspirate was found to be the best predictor of naso or orogastric tube misplacement in 276 children with feeding tubes aged from under 1 month (n= 173) to 215 months (n=103) (Ellett et al. 2014). Inability to obtain aspirate to test is a real concern for neonatal nurses and methods to assist in the aspiration of fluid from neonates are set out in clinical guidelines at national level (National Patient Safety Agency 2005).

Manufacturers of a number of fine bore feeding tubes require a 20 or 50cc syringe to withdraw aspirate as it is stated that smaller syringes may exceed the bursting pressure of the tube. Authors warn against the risks of using small bore syringes and advocate large (minimum 30mL) syringes be used when aspirating nasogastric tubes (Wilkes-Holmes 2006). However there is some confusion about the relationship between the positive and negative pressures exerted by syringes of different sizes. Syringe size impacts on the negative pressure applied when used for aspiration in the opposite way to its impact on positive pressure applied when injecting fluid (Boyd 2005). Most of the research in this area has been conducted with intravenous devices but the physics and calculations are the same. When fluid is injected through a small syringe greater force in pounds per square inch (PSI) is applied than with a larger syringe (Macklin 1999) so manufacturers provide information on the size of syringe to be used with specific tubes in order to prevent too great a positive force being applied to the tube causing it to burst. However the negative force needed to withdraw fluid without creating a vacuum is smaller with the smaller the syringe used (Macklin 1999). It has been calculated that the vacuum created by a 20mL syringe is 8 times that created by a 2.5mL syringe (Boyd 2005). When aspirating fluid into a tube clinicians do not want to create a vacuum and so smaller syringes are more successful in withdrawing fluid and it is advocated that if aspiration attempts are unsuccessful smaller syringes can be safely used (Macklin 1999).

If aspirate cannot be obtained the protocol for obtaining fluid states that larger tubes with multiple ports should be tried, the baby turned on their side and if this is unsuccessful 1-2ml of air should be injected to dislodge the tube from the stomach mucosa and the tube advanced or retracted by 1-2cm (National Patient Safety Agency 2005). The injection of a small amount of air through the tube

has been reported as leading to successful aspiration of sufficient gastric fluid for pH testing in 94.4% (n=72) of children (Ellett et al. 2005b)and 92.5% (n= 181) of adult patients (Metheny et al. 1989). It is acknowledged that aspiration from fine bore tubes often takes several attempts and regardless of the size of the tube it has been suggested that in adult patients 30mL of air should be injected into the nasogastric tube with a 30mL or 60mL syringe prior to withdrawing fluid (Metheny, Titler 2001, Metheny, Titler 2001, Metheny et al. 1993) but repeated failure (after 3 attempts) to withdraw fluid should result in the tube being withdrawn or X-ray confirmation sought (Metheny, Titler 2001, Metheny et al. 1998).

Examining the appearance of aspirate for colour and consistency has been suggested as indicative of its source (Metheny et al. 1998) however the appearance of aspirate alone is not reliable as gastric contents can look similar to respiratory secretions (Theodore et al. 1984). A study of 30 staff nurses found that they had difficulty in distinguishing between photographs of gastric fluid, pleural secretions and tracheobronchial secretions and were able to distinguish between gastric and respiratory secretions in less than half of cases (Metheny et al. 1994). However aspirate appearance was found to be useful in distinguishing between gastric and small bowel placement in a study of 80 patients aged 18 -87 years where aspirate from the small bowel was bile stained in over half the samples from the small bowel and in only 7% of gastric samples (Metheny, Stewart 2002). The authors acknowledge that this was a small study and using the colour of aspirate alone is not recommended. Indeed appearance of aspirate was found to be the worst predictor of nasogastric tube placement in a study comparing the accuracy and predictive value of a range of bedside tests in 276 children (Ellett et al. 2014). Nevertheless colour of aspirate features as an aspect of the process of placement verification in some protocols (Tho et al. 2011).

2.10.4 pH Tests

The measurement of pH is a measure of the acidity or basicity of an aqueous solution through the assessment of the activity of hydrogen ions within the solution (Covington, Bates & Durst 1985). The pH scale is derived from a set of internationally agreed standard solutions and is defined mathematically as the decimal logarithm of the reciprocal of the hydrogen ion activity (Covington, Bates & Durst 1985). In practice this means that each step in the pH scale relates to a

10 fold increase, or decrease, in hydrogen ion activity, so a solution of pH 5 has 10 times the hydrogen ion activity of a solution of pH4.

The majority of research into the use of pH measurement of tube aspirate as a method of verifying feeding tube placement was conducted by Norma Metheny and colleagues and published in a number of papers between 1989 and 2001. Their research, discussed in the following section, used a well designed protocol in 6 acute care hospitals with strict inclusion and exclusion criteria. Whilst these studies may be criticised for using tracheobronchial secretions as surrogates for aspirates from tubes placed in the respiratory tract and having the same principal investigator and thus being open to potential bias, they remain the most notable body of research to date (Hanna et al. 2010).

2.10.4i pH of body fluids

The acid-base homeostatic control of the pH of human cells, organs and body fluids is essential for the normal functioning of body chemistry including the functioning of enzymes (Griffin 2011). Body fluids have different pH values with blood being pH 7.4, gastric fluid 0.7- 5.5 and pancreatic secretions 8.1 (Griffin 2011). Thus testing the pH of nasogastric tube aspirate is considered a suitable method of verifying correct placement in the stomach (Metheny, Smith & Stewart 2000, Taylor, Clemente 2005, Metheny et al. 1998). Indeed it is claimed that, of the verification methods that have undergone scientific investigation, observation of aspirate and testing of its pH are the most reliable (Metheny, Titler 2001). The pH of tube aspirate has been found to be better than other bedside methods in predicting both correct and incorrect placement of tubes inserted either into the stomach or intestine (Ellett, Beckstrand 1999).

Normal tracheal pH is 7.81 ± 0.71, pleural pH is 7.92 ± 0.28 and gastric pH 3.52 ± 2.02 (Metheny et al. 1999). A mean value of 4.4 for stomach aspirate and 6.9 for post-pyloric aspirate was found in a cross sectional descriptive study of 53 critically ill children not receiving antacid or proton pump inhibiting (PPI) medication (Gharpure et al. 2000). A similar study of 39 acutely ill neonates found a mean gastric pH of 4.3 compared to a mean intestinal pH of 7.8 (Metheny et al. 1999) These studies suggest that pH of aspirate can be confidently used to distinguish placement in the stomach from that in the small intestine or respiratory tract.

Testing the pH of feeding tube aspirate has been used for many years and this is the first line method of verification advocated by the National Patient Safety Agency in United Kingdom (National Patient Safety Agency 2005b, National Patient Safety Agency 2011b, National Patient Safety Agency 2011a, National Patient Safety Agency 2005a), the USA (American Association of Critical Care Nurses 2010b) and in Clinical Practice Guidelines in a number of hospitals in Australia (Peter, Gill 2009). Whilst it is claimed by some researchers that pH testing of aspirate is a simple, low cost and easy test in the clinical setting (Westhus 2004) there are problems with this method, not least the difficulty in aspirating fluid discussed in the section 2.10.3 which can be time consuming and frustrating.

Over twenty years ago studies in adults reported that a pH reading of 4 or less was a reliable indicator of tube placement in the stomach (Metheny et al. 1998, Metheny et al. 1994). Later studies confirmed that, excluding radiographic confirmation, this method was the most reliable bedside test (Metheny, Titler 2001, Metheny, Titler 2001, Metheny, Aud & Ignatavicius 1998) and such methods could be adapted for use with children (Westhus 2004). A simple bedside assessment of gastrointestinal aspirate, colour, pH and bilirubin content were claimed to be useful indicators of feeding tube placement in children (Westhus 2004) and neonates (Nyqvist, Sorrell & Ewald 2005, Metheny et al. 1999).

2.10.4ii Safe thresholds for pH measurement

There is debate about the safe cut off level with pH values ≤ 4 often being impractical as the use of antacid medication and continuous feeding can increase the pH value of gastric fluid causing unnecessary doubt in the correct placement of the tube (Wilkes-Holmes 2006, Freer, Lyon 2005). Pooled results of a systematic review of 7 studies investigating the diagnostic accuracy of pH found that pH ≤ 4.0 had the ability to predict only 63% of correct placements in the stomach but a pH value of ≤5 showed a sensitivity of 0.89 and a specificity of 0.87 (Fernandez et al. 2010). It is suggested that aspirate with a pH value ≤5 is indicative of placement in the stomach of fasting adults and a pH value ≤6 indicates placement in the stomach of a fed adult (Metheny, Smith & Stewart 2000, Metheny et al. 1993) and neonate (Freer, Lyon 2005).

The accepted value recommended by the NPSA is pH between 1 and 5.5 (National Patient Safety Agency 2005b, National Patient Safety Agency 2011b). However it is stressed that whilst this value can reliably exclude respiratory placement it cannot guarantee gastric placement as there is a small risk that the tube may be in the oesophagus putting the patient at greater risk of aspiration (National Patient Safety Agency 2011b). Although this value has been suggested as indicating gastric placement in the vast majority of patients of all ages including those on acid inhibiting medication (Metheny et al. 1994) it is suggested by some authors that with pH values between 5 and 6 additional verification methods be used (Huffman et al. 2004, Freer, Lyon 2005). In 2010 the NPSA discussed reducing the threshold with the professional bodies and a sample of hospitals in England and Wales and found that any benefits of reducing the risk of placement in the oesophagus were outweighed by concerns regarding the consequent increase in X-rays and delays to patient feeding (National Patient Safety Agency 2011b).

This was strongly disputed by Hanna, Phillips et al. (2010), who were commissioned by the NHS Patient Safety Research Portfolio (PSRP) to determine a consensus guideline for the safe verification of feeding tube position. They used a multi-modality approach including a systematic review of the literature, a Bayesian belief network model and decision analysis, involving a steering group of experts to give feedback and guidance comparing their recommendations to current practice and historical adverse events (Hanna et al. 2010). They argue for a cut off value of pH 4, recommending that all patients with tube aspirate greater than pH4 be X-rayed to confirm the position of the tip of the tube. Whilst they recognise that this will expose a group of patients to unnecessary X-rays, they consider that the risk of delivering feed into the oesophagus or lung is reduced from 9.38% at pH5.5 to 0.62% at pH4 and cite 5 incidents from the National Reporting and Learning System database where feeding tubes misplaced in the respiratory tract were considered safe to feed with a pH cut off of 5.5, but would have been correctly identified as misplaced if pH4 cut off had been used (Hanna et al. 2010). However the authors recognise that their work was limited by the lack of good quality research studies in this area.

A recent prospective observational study by Gilbertson, Rogers et al (2011) aimed to determine a reliable and practical cut off value for pH to determine nasogastric tube placement by comparing the pH values of gastric and endotracheal aspirate. They studied 4,330 gastric acid samples from 645 children aged 0.3 – 5.2 years (mean age 1.0 years) and found a mean pH of 3.6 (standard deviation 1.4) and the mean pH of 65 endotracheal aspirate samples collected from 19 patients aged 0.4 – 5.2 years to be 8.3 (standard deviation 0.8) (Gilbertson, Rogers & Ukoumunne 2011). This study found that a misplaced tube coiled in the oesophagus, gave a pH aspirate of 5.5 and the lowest pH value for endotracheal aspirate was 6 and so concluded that a pH value of ≤5.5 was not conservative enough to confirm placement in the stomach and suggested a safer value of ≤5 (Gilbertson, Rogers & Ukoumunne 2011). The authors estimate that this value would give a 90% confirmation rate for correctly placed nasogastric tubes and a cut off value of ≤5 is supported by other research studies (Ellett et al. 2005b).

2.10.4iii Neonates

Guidance is specific to adults, children and infants (National Patient Safety Agency 2011a, National Patient Safety Agency 2005a) with guidance for neonates being considered separately (National Patient Safety Agency 2005b). Neonates pose specific considerations as they have an intrinsically higher gastric pH (Freer, Lyon 2005). As in adults medications and continuous feeding may affect the gastric pH. Intestinal and pulmonary aspirate has a pH greater than 5 so pH cannot be used to differentiate between these two locations. The pH of aspirate cannot distinguish between oesophageal and gastric placement if oesophageal reflux is present as this can result in both acidic and alkaline readings (Khilnani 2007). It is suggested that the increased incidence of incompetence of the lower oesophageal sphincter in neonates contributes to increased levels of gastro-oesophageal reflux in this population with consequent low pH levels (≤5) of fluid aspirated from the oesophagus, making measurement of pH alone a poor predictor of correct placement in the stomach (Ellett et al. 2014).

2.10.4.iv Methods for measuring pH

In the past blue litmus paper has been used to test the pH of aspirate in the UK and other countries as it indicates acidic fluid by turning pink. Nyqvist, Sorell and Ewald (2005) examined the clinical use of litmus tests for the verification of feeding tube location in infants born prematurely. A convenience sample of 60 infants was used and data were obtained from 2,970 tube feeds. They concluded that litmus paper was a useful clinical test for the verification of feeding tube position having obtained positive results in 97% of the sample.

Testing pH of aspirate with litmus paper became usual practice in UK with adults, children and neonates (Smith 2006). However practice had to change following the death of an 8 year old girl who had received nasogastric feeds into her lung in spite of litmus paper indicating that the tube was in her stomach. (Yardley, Donaldson 2010). The NPSA Patient Safety Alert 05 recommended a more precise measure of pH using pH indicator strips or paper, rather than litmus paper (National Patient Safety Agency 2005a). It was found that blue litmus paper was not sufficiently sensitive to distinguish between bronchial and gastric secretions as it turns from blue to pink regardless of the level of acidity ie any pH <7. The change in practice from the routine use of litmus paper to pH indicator strips was not smooth in all hospitals and units but successful, well managed approaches to education and change have been reported (Smith 2006) and pH indicator paper/strips are now used throughout the NHS.

Whilst pH indicator strips are more sensitive and can give a specific level of pH matching colour changes of pH paper to colour pads on a chart may be subjective (May 2007). An important consideration for all tests which use the colour change of indicator pads on reagent strips, is the issue of colour blindness or colour deficiency amongst clinical staff. Protanomaly (red weakness) results in red being mistaken for yellow/amber and purple seen as blue and green seen as white in poor visibility (The Institution of Engineering and Technology July 2013). Deuteranomoly (green weakness) reduces the subtle discrimination of red, orange, yellow and green (The Institution of Engineering and Technology July 2013). Colour vision defects occur in 1 in 12 men and 1 in 200 women and assuming that 90% of NHS nurses are female it is suggested that approximately 1.3% of NHS nurses are colour deficient and may have difficulties identifying the

subtle colour changes on pH indicator strips without being aware of their deficiency (Taylor, Clemente 2005). The NPSA recognise the problems that some staff have in particular distinguishing between pH5 and 6 with the currently available pH indicator paper and recommend that a second competent person verifies all readings in this range (National Patient Safety Agency 2011b).

In the past it was recommended that pH meters be used rather than pH indicator paper to get a truly accurate measure of pH of nasogastric tube aspirate (Dobkin et al. 1990). However improvements in the accuracy of pH indicator paper in the past 20 years has made these an acceptable standard of accuracy as long as they are CE marked and manufactured to test human gastric aspirate (National Patient Safety Agency 2011b). There still remains concern about the accuracy of pH indicator papers in common clinical usage particularly in the critical pH range of 4-6 (Hanna et al. 2010). A full review of the studies that have been undertaken to validate the accuracy of pH indicator paper compared with calibrated, hand held pH meters and intra gastric pH probes using clear buffered solutions and gastric aspirates is provided by Hanna, Phillips et al (2010).

Tubes with built in pH probes that do not rely on obtaining aspirate have been developed and used clinically. They were originally used to distinguish between placement in the stomach and small intestine rather than between gastric and pulmonary placement (Berry et al. 1994). Such tubes are expensive and require special training of clinicians in their use and they cannot distinguish between gastric and oesophageal placement and gastric and pulmonary placement if the gastric pH is greater than 6 (Metheny, Meert 2004).

In 2012 a device, the NG Pod, was developed by a UK based company Westco Ltd and received substantial investment over the next 2 years (Invest in Cheshire 2012). This simple device comprises of a disposable fibre optic sensor which is inserted into the nasogastric tube prior to use. Bonded to the tip of the fibre optic tube is a chemical sensor which changes colour at a predetermined pH. A small hand-held light source is applied externally by the clinician who can then view the colour change. Although offering some solution to the problem of placement verification this device was never tested on patients and the company went into administration in April 2014 (Hodgson 2014). This reflects the problems of trying to introduce a new device into an established system of patient care.

2.10.4v Factors that influence gastric pH

The British Society of Gastroenterology guidance for enteral feeding recommends a pH value for aspirate of less than 5 but claims that assessment of pH is of no use if the patient is on acid inhibiting medication (British Society of Gastroenterology 2013). Medications, including H_2 receptor antagonists and proton pump inhibitors, can alter the pH of gastric fluid and it is recommended that the effects of medication on gastric pH be considered when using this method of verifying feeding tube placement (McClave et al. 2009). A cross sectional survey of 52 patients receiving nasogastric or nasointestinal feeds on one day in one hospital Trust found that 42% of patients were taking such medication (Taylor, Clemente 2005). This study suggested that the use of such medication could reduce the ability of pH to confirm nasogastric tube position to only 58% of cases and they suggest that if patients have a safe swallow reflex acidic drinks should be administered to improve the accuracy of this test (Taylor, Clemente 2005). Alternatively it is recommended that pH testing be carried out 2 hours after the administration of H2 blockers (Parviainen et al. 1996) although this may not always be practical and a waiting period of one hour is suggested in nursing textbooks (Griffin 2011).

The impact of gastroenteritis on pH of gastric fluid was studied by Stock, Gilbertson et al (2008) who found that there was no difference in mean pH of gastric aspirate obtained from children with gastroenteritis (n= 294) and children without gastroenteritis (n=99). Children with gastroenteritis were more likely to have aspirate with pH<4 than those children without the condition (Stock, Gilbertson & Babl 2008).

Concern about the impact of continuous feeding on gastric pH is not justified as it has been found that gastric pH levels are similar in patients on continuous feeds to those on intermittent bolus feeds and selection of type of feeding should be dictated by the patient condition and practical issues (National Institute for Health and Clinical Excellence (NICE) 2006). It is recommended that clinicians should wait one hour after the administration of medicines or feed before gastric aspirate is tested for pH (Griffin 2011).

An unusual problem was identified in 2012 with a type of nasogastric tube which had an internal stylet to ease insertion. These stylets must be removed once the

tube is inserted and before feeding commences and water is inserted to ease their removal. The mixture of water inserted to flush the tube and the lubricant in the tube produced an acidic aspirate which was thought to be fluid aspirated from the stomach when in fact the nasogastric tube was located in the lungs. Two patients died as a result and an alert was issued in the UK to all Trusts regarding the safe flushing of tubes to avoid such disastrous errors in future (National Patient Safety Agency 2012). A similar alert, in the form of a Field Safety Notice, was issued with regard to a coating Merck Serono had added to their pH indicator strips as it was found that these strips gave a similar reading with water as with stomach contents. Such notifications are a reminder of the constant vigilance required when manufacturing nasogastric tubes and with verifying nasogastric tube placement.

2.10.5 Combination tests using pH and enzyme measurement and/or bilirubin levels

The gastrointestinal enzymes trypsin and pepsin are present in varying amounts in different compartments of the upper gastrointestinal tract and therefore measurements of these enzymes have been considered as an additional method of identifying placement of feeding tubes. These enzymes are barely present at all in pulmonary fluid whereas gastric fluid has high levels of pepsin and intestinal fluid high levels of trypsin (Metheny et al. 1997). Laboratory tests for pepsin and trypsin have been suggested as more accurate predictors of placement of post-pyloric tubes (Gharpure et al. 2000). A study of 890 adult patients used a combination of pH, pepsin and trypsin to successfully distinguish between respiratory, gastric and intestinal placement but there are no simple and inexpensive bedside tests for these enzymes (Metheny et al. 1997) which limits the usefulness of these measures.

However billirubin can be measured at the bedside using urine reagent strips and a colour scale specifically designed for gastric fluid (Metheny, Smith & Stewart 2000) and a combination test of pH and bilirubin levels of aspirated fluid has been recommended to differentiate between gastric, intestinal and respiratory placement of nasogastric tubes (Metheny et al. 1999). Metheny, Stewart et al.

(1999) measured the pH and bilirubin levels of fluid aspirated from acutely ill, fasting adult patients with nasogastric tubes (n=209) and nasointestinal tubes (n=228). Tube placement was confirmed by X-ray and in addition aspirate obtained from tracheobronchial suctioning (n=125) and pleural fluid aspirate (n=24) was tested for pH and bilirubin levels. This test is highly sensitive to respiratory placement identifying 100% of the respiratory aspirates, however the specificity was lower for non-respiratory aspirates and the predictive value of the test was problematic. There is very little bilirubin in gastric fluid aspirates of neonates (Metheny et al. 1999) and a study of nasogastric tube aspirates from 72 children under 7 years found that bilirubin levels were not useful in predicting tube placement and only pH was helpful in making decisions (Ellett et al. 2005b).

A systematic review of the accuracy of biochemical markers, pH, bilirubin, a combination of pH and bilirubin and a combination of pH, pepsin and trypsin in determining nasogastric tube placement in adults identified 10 research studies which all used X-rays as the reference standard for comparison and found that combined tests of bilirubin and pH had a high specificity of 0.99 but a lower sensitivity of < 0.9 but were more accurate than pH alone (Fernandez et al. 2010). Whilst combination tests including pH and bilirubin remain standard practice in some parts of the USA (Metheny 2011) they have not been adopted in the UK.

2.10.6 Radiography

Radiographic verification using X-rays has long been considered the only definitive determination of the placement of feeding tubes and has been advocated by a number of authors as the only reliable method of determining feeding tube location (Metheny, Meert 2014b, Metheny, Stewart 2002, Metheny, Meert & Clouse 2007, Metheny, Titler 2001, Jolley, Elliott & Williams 2005). Radiological verification is strongly advocated, particularly for initial assessment of newly inserted nasogastric tubes and is considered as the gold standard for many associations including the American Association of Critical Care Nurses (American Association of Critical Care Nurses 2010b) and is recommended in some UK units regardless of a positive pH test (Parmar et al. 2011).

However in the UK the National Patient Safety Agency advocate the use of X-ray verification only as the second line test to be employed if the first line test (pH of

tube aspirate) proves inconclusive (National Patient Safety Agency 2005b, National Patient Safety Agency 2011a, National Patient Safety Agency 2005) . This is because there are implications for cost and availability, points also recognised in the US (Metheny, Stewart 2002) but more importantly exposure to radiation carries significant long term risks. The risk of fatal cancer or hereditary effect is estimated at 0.0002% and 0.0026% per radiograph (Hart, Hillier & Wall 2009) and it has been recommended that X-rays should not be used routinely in neonates to check feeding tube placement (National Patient Safety Agency 2005). However if babies are being x-rayed for other purposes verifying correct feeding tube placement at the same time is recommended, although X-ray request forms must clearly state that the purpose of the X-ray includes verification of feeding tube placement (National Patient Safety Agency 2011a).

In a review of 381 radiographs of 173 neonates with feeding tubes Quandt, Schraner et al. (2009) found that the tip of the feeding tube was not visible in 21% of X-rays. Similarly a study of 113 adult ICU patients found that PVC Ryles tubes could not be clearly seen in the chest in 57% of patients, the abdomen in 73% patients and were not visible at all on X-ray in 23% of patients (Taylor et al. 2014). These authors state that use of PVC Ryles tubes should stop and poluyurethane tubes be used as they were visible in 98% of cases. Similar problems were experienced in Singapore when implementing changes in practice to include X-ray verification of feeding tube placement. It was found that the radio-opaque line on the tubes could not be visualised resulting in a change in the make of tubes used (Tho et al. 2011).

Interpretation of X-rays particularly in the critically ill can be difficult and errors in interpretation can occur resulting in significant morbidity (Rassias, Ball & Corwin 1998, Lamont et al. 2011). Such errors occur particularly at night when there is not sufficient experienced support available to confirm position (National Patient Safety Agency 2011a). In particular radiographic determination of placement of feeding tubes in the stomachs of neonates and extremely low birthweight infants can be problematic and guidelines on interpretation of such X-rays are limited (Cordero et al. 2010) with confusion in the literature about what constitutes correct placement on X-ray (Quandt et al. 2009). As stated previously, of 21 deaths and 79 cases of harm, resulting from feeding into the lungs through

misplaced nasogastric tubes, in England and Wales between 2005 and 2011, 45 serious incidents including 12 deaths were due to misinterpretation of X-rays (National Patient Safety Agency 2011a). The NPSA also estimates only 30% of incidents are reported and recommends that radiographs taken to confirm the position of feeding tubes are interpreted by appropriately trained clinical staff (National Patient Safety Agency 2011a).

Similar problems with the reporting of X-rays have occurred in the USA. For example X-ray reports confirmed correct placement of fine bore feeding tubes inserted with the aide of an electromagnetic placement device in 4 cases when the tubes were in fact placed in the left lung and had resulted in pneumothorax (Metheny, Meert 2014b). Some hospitals in the USA now require that a radiologist review X-ray films to confirm correct placement prior to feeding (American Association of Critical Care Nurses 2010b).

Lesser but still significant problems caused by waiting for an X-ray to be taken and then reported have been discussed in the literature such as the delay to feeding and/or administration of medication (Taylor et al. 2014). Whilst these problems are detrimental to patient health radiographic confirmation of feeding tube placement still remains the gold standard method of verification as long as the tube inserted is sufficiently radio-opaque and the X-ray is promptly reported by an experienced radiologist. Exposure to unnecessary X-rays should be avoided however especially in neonates and certainly in UK this method should only be used if the less hazardous method of pH testing is inconclusive (National Patient Safety Agency 2011a).

2.10.7 Auscultation

Auscultation involves injecting 10-30ml of air into the nasogastric tube and listening through a stethoscope placed over the epigastria, or the left upper quadrant of the abdomen, for the resulting “whoosh” as air enters the stomach (Metheny et al. 1990a, Metheny et al. 1998). It became popular because it was easy to perform and involved minimal cost, being taught as accepted practice in many nursing schools (Farrington et al. 2009).

Auscultation was identified as being unreliable over 30 years ago (Torrington, Bowman 1981, Roubenoff, Ravich 1989) but in 1996 it was still being

recommended as a suitable method of verification (Viall 1996) and found to be used by 98% of nurses in Midwestern US hospitals (Shiao, Difiore 1996). A UK survey in 2002 found that 26% of nutrition specialist nurses were using this method (Cannaby, Evans & Freeman 2002). A postal survey of 380 adult intensive care units spread across the whole of Europe found that auscultation was the most commonly used method of placement verification (Fulbrook, Bongers & Albarran 2007) and it was suggested that this method was still being used by the majority of nurses in the US as late as 2009 (Farrington et al. 2009). A recent review of the literature also concluded that this was the most common verification method used by nurses (Kenny, Goodman 2010) and it was not until 2012 that the Child Health Patient Safety Organisation in USA recommended its immediate discontinuation (Irving et al. 2014).

Practice recommendations in the UK changed in 2005 with the publication of the NPSA guidelines, which stated that this method should not be used (National Patient Safety Agency 2005a). However confirmation of nasogastric tube placement using auscultation is still reported (Gilbertson, Rogers & Ukoumunne 2011) in spite of evidence that this technique has led to the inadvertent placement of feed into the lungs of patients with disastrous results (Metheny, Aud & Ignatavicius 1998). It is suggested that in spite of overwhelming evidence nurses are reluctant to adopt newer more accurate methods of placement verification and facilitating change can be challenging (Huffman et al. 2004). Auscultation is still recommended as a method to verify feeding tube placement in the majority of Turkish nursing textbooks and is used frequently in nursing practice in Turkey (Turgay, Khorshid 2010).

The main problem with auscultation is that insufflated air can be heard through a stethoscope placed over the epigastrium regardless of whether the tube is in the stomach, lung, oesophagus or duodenum or jejenum (Cannaby, Evans & Freeman 2002, Ellett, Beckstrand 1999, Metheny et al. 1998, Metheny et al. 1990). In neonates in particular the stomach and lungs are so close together that it is virtually impossible to distinguish between the sound of air being injected into the stomach and air injected into the bronchi. Metheny, McSweeney et al. (1990) recorded the sounds generated by a series of air insufflations through the nasogastric tubes of 85 acutely-ill adult patients. One hundred and fifteen usable

tape-recordings of sound sequences were played to a team of experienced clinicians who were told from where the sound had been recorded on the patient's body but not the location of the nasogastric tube. The collated results were compared to the actual position of the tube as confirmed by X-ray. The average percentage of correct classifications of each tape was 34.4% and the authors conclude that auscultation should not be relied upon to differentiate gastric from intestinal placement, nor gastric from respiratory placement of feeding tubes (Metheny et al. 1990b). Not only is such practice unreliable but it may also be dangerous if the tube is misplaced. If the tube is placed in the lungs and air is injected directly into the pulmonary parenchyma it is possible to induce a pneumothorax.

More recently Turgay and Korshid (2010) investigated 44 feeding tube placements in critical ill adult patients using auscultation, pH of aspirate and X-ray to determine the position of the tip of the tube. Nurses inserted the tubes at the bedside and checked the placement by auscultation after which a researcher aspirated fluid and tested this for pH before the patient had an x-ray which was reviewed by the attending physician. A pH less than 5 correctly identified 90.4% of the placements but 4 of the 5 tubes identified as not being in the stomach on X-ray were thought to be correctly placed by the auscultation method and 2 were considered to be so by the pH of aspirate (Turgay, Khorshid 2010). Although this was a small study the authors used the extensive American literature on the topic to support their findings that aspirate pH is an effective method of verifying feeding tube placement but auscultation is not.

2.10.8 Bubbling Under Water

Placing the end of the nasogastric tube under water and observing for bubbling when the patient exhales has been documented as a method of placement verification but is considered to be unreliable as the stomach may also contain air and produce bubbling (Ellett 2004). Similarly the absence of bubbling cannot guarantee gastric placement as, if the tube is placed in the lungs, the ports may be blocked by respiratory mucosa or bronchial fluid and so no bubbling will be seen (Roberts, Echeverria & Gabriel 2007).

2.10.9 Endotracheal tube cuff pressure

The particular challenges of passing nasogastric tubes on critically ill patients who may be paralysed and ventilated and the access to a range of technical equipment in intensive care units has lead to a number of techniques being developed which utilise equipment already available for other aspects of patient care such a mechanical ventilation. The most widely researched of these is the use of capnography but other methods have also been studied as a means of detection of the placement of gastric tubes. A German study of 30 patients under general anaesthesia with orotracheal tubes in place found that misplacement of a nasogatric tube in the trachea significantly increased the endotracheal cuff pressure compared to when the tube was correctly inserted into the oesophagus (Fuchs et al. 2007). The authors claim that this constitutes a new, simple and reliable bedside method to detect misplacement of nasogastric tubes in the trachea (Fuchs et al. 2007) but such a test is obviously only available in patients with endotracheal tubes *in situ* i.e. those who are paralyzed and ventilated.

2.10.10 Electocardiographic guidance

Electrocardiographic guidance is available to those patients who are mechanically ventilated with a specific ventilator, the Servo-i ventilator, produced by Marquet Critical Care, Solna, Sweden. A paediatric case series of 20 children requiring placement of a catheter embedded with 9 electordes into the stomach for the measurement of the electrical activity of the diaphragm was reported by Green, Walsh et al. (2011). It was found that the electrical activity of the diaphragm as viewed by the waveforms on the catheter positioning screen on the ventilator was a reliable indicator of correct placement in the stomach confirmed by pH testing or radiograph (Green et al. 2011). Other studies have investigated the use of electrocardiograms (ECG) for the placement of gastric tubes in adults with encouraging results (Diaz-Rodriguez, Esponda-Prado & Ize-Lamache 2004, Barwing et al. 2009). However these verification tests require expensive equipment and experienced health care personnel only available in specialised units.

2.10.11 Capnography

Devices that detect carbon dioxide (CO_2) are used routinely to identify correct placement of endotracheal tubes and monitor patients' respiratory status in theatres, intensive care and accident and emergency units. The exhaled CO_2 is detected or measured by the methods of colorimetry, capnometry or capnography. Although the terms capnometry and capnography are sometimes considered synonymous, capnometry suggests measurement (i.e. analysis alone) without a continuous written record or waveform. Capnography comprises the continuous analysis and recording of CO_2 concentrations in respiratory gases by measuring and recording the absorption of infra red light by CO_2 molecules (Jaffe 2008).

Infrared CO_2 analyzers are able to follow CO_2 changes in a single breath and are used widely for respiratory monitoring (Saisch 1994). In capnometry single use pH sensitive calorimetric detectors display colour changes due to chemical reactions that occur when CO_2 is present. The colour changes from purple, when exposed to room air or oxygen and to yellow, when exposed to 4% CO_2 (O'Flaherty, Adams 1990). False negative results and false positive results, due to gastric contents, mucus, and drugs such as epinephrine, have been reported when capnometry is used to verify ET tube location (Srinivasa, Kodali 2007).

The Royal College of Anaesthetists and the Association of Anaesthetists of Great Britain and Ireland recommend the use of capnography to ensure correct tracheal tube placement in the operating theatre (The Royal College of Anaesthetists 2014). A survey of lead clinicians in every paediatric intensive care unit (PICU) in the UK revealed that 42% of consultants believed that confirming tracheal tube placement by capnography should be mandatory after any intubation whether in PICU, A&E or the ward and that this was even more important in PICU than adult intensive care units due to the increased proportion of junior trainees (Cumming, McFadzean 2005). When CO_2 is absent as measured by these devices, it means either the endotracheal tube is in a wrong position or there is an absent/ decreased presentation of CO_2 to the lungs as in a cardiac arrest.

The use of capnography has expanded over recent years and it is now used in a variety of acute care settings (Ahrens, Sona 2003). A number of intensive care

units in North America, Canada and UK have applied these devices to nasogastric tubes to identify correct placement of such tubes in the gastrointestinal tract by identifying the absence of CO_2. Essentially correct placement of the nasogastric tube is assumed if there is no CO_2 recorded that is the tube is not in the lungs therefore it must be in the gastrointestinal tract.

D'Souza, Kilam et al. (1994) explored the use of capnographs during the insertion of intestinal feeding tubes in 13 anaesthetised adult patients and 7 awake volunteers (medical and healthcare staff). In all 13 patients it was found that when the tube was placed in the trachea or pharynx a normal capnograph was displayed but no CO_2 was detected when the tubes were in the oesophagus of patients or the healthy volunteers (D'Souza et al. 1994). The authors concluded that capnographic measurement of CO_2 form the tip of the feeding tube during insertion is a safe, accurate and cost-effective method and ensuring placement in the stomach (D'Souza et al. 1994). This research was followed by a small study of 10 patients (Thomas, Falcone 1998) and a larger study of one hundred small bore feeding tube placements in a Canadian ICU to compare capnography with a two stage radiographic technique for determining correct placement in the stomach (Kindopp, Drover & Heyland 2001). Eighty-nine tubes were successfully placed in the gastrointestinal tract and no CO_2 was detected in these placements; the capnograph correctly identifying the 11 tubes inadvertently placed in the trachea (Kindopp, Drover & Heyland 2001). The use of the capnographs significantly shortened the time required for placement. A similar two stage procedure was used to test the ability of capnometry to identify the correct placement of nasogastric tubes in 53 mechanically ventilated adult patients (Araujo-Preza et al. 2002). The authors concluded that capnometry was a safe and efficacious new method for identifying correct placement of feeding tubes.

More recently the results of capnometry confirmation of feeding tube placement were compared with capnographic confirmation in a convenience sample of 195 gastric tube pacements in 130 adult patients in a medical intensive care unit (Burns et al. 2006). They found that a calorimetric device was just as accurate as capnogrphy for detecting carbon dioxide and thus airway intubation when adult sized nasogastric tubes were used. They caution that although accurate interpretation of colour change is easily taught and understood additional training

on aspects of the calorimetric device is needed. In particular ensuring that the tube ports are not occluded during tube placement must be taught as this would yield a false positive result with potential disastrous consequences. Also backflow of gastric contents may moisten the calorimetric indicator causing an irreversible colour change and resulting in other methods of verification being required (Burns et al. 2006). Whilst Burns et al (2006) acknowledge that the study findings may not be valid with smaller feeding tubes a small randomised, blinded trial of 20 patients undergoing elective cardiac surgery found that capnogrphy accurately differentiated between oesophageal and tracheal placement of fine bore feeding tubes (Ward et al. 2009). Two studies of mechanically ventilated patients found that there was agreement between capnographs (Burns, Carpenter & Truwit 2001) and calorimetric detectors (Howes, Shelley & Pickett 2005) and x-rays in confirming correct placement in the stomach.

Elpern et al (2007) studied 91 tube placements in 69 adult patients on a medical intensive care unit in USA comparing capnometry and air insufflations (normal practice) with the gold standard of X-ray and found that neither air insufflations nor capnometry provided a failsafe method for determining tube placement. They found that, although air insufflation was better, neither method consistently discriminated gastrointestinal and pulmonary intubation and 16% of the capnometric results incorrectly indicated pulmonary placement (Elpern et al. 2007). However one year later a study of 424 nasogastric tube insertions found that a CO_2 sensor correctly identified feeding tube placement in 99% of cases (Munera-Seeley et al. 2008) and the following year a two stage insertion method using calorimetric capnography on adult patients in intensive care concluded that colorimetric capnography combined with epigastric auscultation was a safe and accurate method of verifying correct gastric tube placement (Meyer et al. 2009). The nasogastric tube was inserted 30cm and connected to the calorimetric capnograph; if no CO_2 was detected insertion was completed to 50cm and placement in the stomach tested by capnograph, auscultation and X-ray (Meyer et al. 2009).

Unfortunately this method does not differentiate where in the gastrointestinal tract the tube is placed so further methods are required to determine whether the tube is in the oesophagus, stomach or duodenum. In addition manufacturers of

capnometers warn of false results due to air being present in the stomach prior to insertion of the feeding tube and to refluxed gastric contents causing inaccurate and misleading colour changes and these have been reported in other studies (Puntervoll et al 2002).

The vast majority of studies of capnography and calorimetric capnometry have been conducted with adult patients. However researchers used a handheld capnograph as the first of four methods of verifying correct placement in a study of 72 children with nasogastric tubes (Ellett et al. 2005b). Carbon dioxide values were obtained for all 72 children and were 0mmHg in 71 cases (98.6%) and 2.00mmHg in one child, well below the cut off level of ≤ 15 mmHg, confirming that no tubes were placed in the respiratory tract which was verified by X-ray (Ellett et al. 2005b). A small pilot study which assessed the CO_2 levels at the open ends of both endotracheal and oral or nasal feeding tubes in 7 premature infants found that capnography may be useful in differentiating between gastrointestinal and respiratory placement of feeding tubes in this most vulnerable patient population (Ellett, Woodruff & Stewart 2007). A Cochrane protocol to determine the diagnostic accuracy of capnometry and capnography for detecting inadvertent respiratory placement of enterogastric tubes in children compared to the reference standard was published in July 2014 and the results of this review will provide important information for the future of this test in children (Smith et al. 2014).

A meta-analysis of the use of end-tidal carbon dioxide detection to determine correct placement of nasogastric tubes was conducted by Chau et al (2011). Nine clinical trials were eligible for inclusion and the authors found that there is evidence to support the use of capnography or calorimetric capnometry in verifying the correct placement of feeding tubes in mechanically ventilated patients (Chau et al. 2011). The limitations regarding the use of capnography or calorimetric capnometry in verifying gastric tube placement including the confinement of the practice to intensive care units mean that it cannot be recommended for general use. A further review of the evidence for the diagnostic accuracy of capnometry and capnography in identifying correct placement of nasogastric tubes in adults is currently being undertaken (Holland, Smith & Penny 2013).

In 2005 the National Patient Safety Agency in UK first issued practice alerts on verification of feeding tube placement and these were reissued in 2011. The possible role of CO_2 monitoring as a method for detecting misplaced tubes was not mentioned (National Patient Safety Agency 2005b, National Patient Safety Agency 2011b, National Patient Safety Agency 2011a). However in the USA updated guidance from the American Association of Critical Care Nurses states that capnography should be used as a bedside test, if available, but this method is not sufficiently sensitive and specific to preclude radiographic confirmation of initial placement of feeding tubes before the first feed is delivered (American Association of Critical Care Nurses 2010a).

2.11 Current Recommendations

It has been suggested that a combination of the simpler and more accurate methods should be used to guide feeding tube placement during insertion and help identify when an X-ray is required to confirm location if there is any doubt as to where the end of the tube lies (Metheny, Meert 2004, Ellett et al. 2011, Ellett et al. 2012). However current advice from the NHS states that clinical decisions should be based on one reliable test (pH indicator strips/paper or radiography) rather than on a combination of tests with varying reliability (National Patient Safety Agency 2005b).

Guidelines for acceptable tests to verify the position of nasogastric tubes and those tests which are no longer considered safe are provided by NPSA (National Patient Safety Agency 2005b, National Patient Safety Agency 2011b, National Patient Safety Agency 2011a, National Patient Safety Agency 2005a). However there is clear evidence that these are ineffective in changing practice with the overall incidence of serious events related to misplaced tubes being largely unaffected by such reports (Yardley, Donaldson 2010). Analysis of incidents of misplacement suggest that healthcare professionals are not always following this guidance and in particular staff are administering feed in spite of obtaining aspirates of pH between 6 and 8, instilling water down tubes before obtaining aspirates, not checking tube placement by any method and not documenting the

checking procedures undertaken (National Patient Safety Agency, National Reporting and Learning Service 2010).

An audit by NPSA in 2010 of 166 junior doctors in 5 pilot hospitals found that there was a low awareness of harm and continued use of unreliable methods such as the “whoosh test” described in section 2.10.7 and the use of litmus paper to test acidity rather than the recommended pH paper. It was also found that less than a quarter of junior doctors were aware of the existing guidance and less than a third of those surveyed had received any training on the interpretation of X-ray images for misplaced tubes (National Patient Safety Agency, National Reporting and Learning Service 2010).

Current guidance states that stomach aspirate should be tested for pH using pH indicator paper and feeding only delivered if pH between 1 and 5.5 (National Patient Safety Agency 2011a). The second line test is X-ray although this is an expensive and hazardous method and therefore not suitable for regular use. There is no regulatory enforcement nor sanctions against NHS Trusts or individuals who do not comply with the NPSA guidance. In Australia Clinical Practice Guidelines are developed and audited but there appears to be no mandatory enforcement there either (Peter, Gill 2009). The situation is similar in Japan where recommendations for evidence based practice have been published but are not always implemented (Haga et al. 2008). Changing clinical practice for the confirmation of feeding tube placement in acute hospital settings in Singapore has also been reported and it suggested that it requires good co-ordination and a multidisciplinary approach and may result in unexpected issues and a staged approach to the implementation of change is recommended (Tho et al. 2011).

Inclusion of pH indicator paper and a procedural checklist in the nasogastric tube packaging have been suggested as relatively easy and cheap methods of improving compliance (Yardley, Donaldson 2010) and such strategies have been adopted by at least one UK manufacturer of nasogastric tubes (Enteral UK personal communication October 2013).

2.12 Conclusion

This chapter has presented a wide ranging contextual review of the historical and current literature on the use of nasogastric tubes with regard to feeding and decompression followed by a configurative review of the literature on the harm caused by misplaced tubes and the range of verification methods available. A structured approach to searching the published literature was conducted and the available evidence for placement verification discussed.

There are a number of methodological issues concerned with research in this area not least the definition of what constitutes misplacement. Clear definitions of when a feeding tube is considered correctly placed are needed, such as whether the tip and all feeding ports or the tip and at least one feeding port need to be in the stomach, must be clarified. The use of X-ray to confirm placement and against which other verification methods are compared in the majority of studies, including those conducted by Metheny and colleagues, is flawed because there is clear evidence that X-ray itself is not a failsafe method of verifying correct placement. The increased use of better imaging techniques such as PET-CT scans will provide more accurate information about the location of the feeding ports of nasogastric tubes and enable enhanced evaluation of new techniques and devices.

It is clear from the current literature that there remains a strong need for a simple, reliable bedside test to confirm correct placement of nasogastric tubes that is quick and simple to perform and does not rely on expensive equipment or medical expertise or experience. The following chapters discuss the development and evaluation of such a device from an early handmade prototype to a fully functioning manufactured trial product ready for clinical evaluation.

Chapter 3: LINGT Iteration 1 Hand Painted Prototypes

3.1 Introduction

Following consideration of the problems of verifying correct placement of blindly inserted nasogastric tubes discussed in chapter 2, this chapter explains the initial development of the Location Indicating Nasogastric Tube (LINGT) to address these problems. The electrochemical principles on which the LINGT was developed are summarised and the early production and experimental testing of hand adapted prototype tubes discussed. The results of initial trials in pH buffer solutions and clinical specimens of 40 hand prepared tubes are discussed and used to inform the next iteration of LINGT explored in chapter 4.

3.2 Hypothesis

Colleagues in the Chemistry Department of the University of Hull suggested a specific electrochemical reaction that could be used to measure pH and this was applied to a nasogastric tube and the following hypothesis tested:

> "the chemical reaction between acid stomach contents and a specific electrochemical coating on the internal tip of a nasogastric tube will create an electric current which can be measured externally."

This hypothesis was tested by producing hand-adapted nasogastric tubes, incorporating the specific sensing material at the tip, which generated an electrical signal when in contact with gastric fluid. A means of transferring the signal along the length of the tube to the external end was developed and a potentiostat to measure the current built. These handmade tubes were tested in various pH solutions in the laboratory and in 5 samples of resected stomach tissue.

3.3 Materials and Methods

The nasogastric tube developed utilises dynamic electrochemistry; that is the electron transfer reactions between electrodes attached to the internal (distal) tip of the nasogastric tube and reactant molecules within the solutions in the stomach. This electrochemical reaction produces a small electric current (less than 1 mA) which passes along the tube via hand painted "wires" and is detected by an indicator box attached to the external (proximal) end of the nasogatric tube. The indicator box, which is in fact a potentiostat, applies a potential difference (PD) between the electrodes as well as displaying the magnitude of the electric current generated.

An amperometric (current-measurement) waveshape pH sensing system has been detailed in the literature (Robinson, Lawrence 2006). The pH detection system used in this study is similar to, but distinct from, that underpinning Oxford University's Senova Systems™ solid state pH sensor, named the pHit™ sensor (Senova Systems 2014) as it is combined with a redox reagent to provide an alternative method of detection of pH measurement. This amperometric pH sensing system was applied to the prototype nasogastric tubes in order to provide an improved method of determining the nasogastric tube location over conventional verification methods described in section 2.10.

When a metallic electrode is inserted into a solution there is a transfer of charge across the interface between the electrode and the solution (Fisher 1996). The electrochemical reaction can be driven by the application of a PD which induces the exchange of electrons between the electrode and the molecules in the solution. The transfer of electrons can be in either direction: a molecule in solution may accept an electron from the electrode and become reduced or an electron can be removed from the solution molecule by the electrode and thus the molecule is oxidised (Fisher 1996). In an oxidative process electrons flow from the solution molecules to the electrode and in a reduction reaction electrons flow from the electrode to the solution molecules (Fisher 1996). A redox reaction occurrs when electrons cause **red**uction then **ox**idation of various components in a reaction, hence the term "redox".

The redox reaction rate depends upon the environment in which the tube is placed and the low pH in the stomach affects the PD across the electrodes enhancing the redox reaction.

3.3.1 "Wires"

This first iteration of the LINGT prototype involved two insulated "wires" hand painted on to nasogastric tubes manufactured by Pennine Healthcare (City Gate, London Road, Derby, DE24 8WY). These "wires" were deployed axially and diametrically opposite one another, along the entire length of the tube. A commercially-available fast curing electrically conductive silver ink that was found to be suitable for medical devices produced by "Creative Materials Inc" (Tyngsboro, Masachusettes, USA) product reference number 119-03 was used. Unlike conventional conductive materials this product is very resistant to flexing and creasing and has excellent adhesion to a variety of surfaces making it ideal for painting on to the naso-gastric tubes.

The distal 3cm of the wires at the tip of the tube formed the electrodes. Traditionally electrodes are made of glassy carbon but it is suggested that electrochemistry at droplet-modified electrodes does not require the use of classic glassy carbon, but may utilise a range of electrode materials (Banks et al. 2003). Whilst a three electrode system is usually used in electrochemical experiments, the simplest method of meausurement of current characteristics involves the use of two electrodes; the working and reference electrodes (Fisher 1996). The reaction of interest occurs at the working electrode and the reference electrode provides a stable and fixed potential so that when a voltage is applied between the two electrodes the drop in potential between the working electrode and the solution is precisely defined (Fisher 1996). It was advised that the currents generated by the LINGT would be small enough to allow measurement to be made using a two-electrode mode, rather than the conventional three-electrode measurement usually undertaken in dynamic electrochemical measurement (Wightamn, Wipf 1989).

The potential can be referenced via a waveshape analytical measurement. This simple two electrode arrangement is perfectly acceptable for the measurement of current/voltage where only a tiny current is passed (Fisher 1996). The two-

electrode potentiostatic system is a feasible measurement procedure that has been demonstrated to be effective when dealing with systems based on interfacial charge transfer at microscopic interfaces (Fisher 1996).

The conductive ink was diluted with thinner product reference number 113-12 also produced by “Creative Materials” by mixing 3 drops of ink with 2 drops of thinner on a petri dish. These were whisked together with a paint brush for 30-60 seconds until a metallic paint with an even consistency was observed (Figure 1). Mixing in this way in a petri dish resulted in the thinner evaporating quickly and the paint becoming too thick for an even application of ink. A small mixing bottle was therefore used and the ink and thinner were mixed by shaking for 30-60 seconds. The top was kept in place whenever possible to avoid evaporation.

Figure 1: Hand mixing paint and thinner to produce optimum consistency

The optimal consistency of the paint mixture was found by trial and error and changes are discussed later in this chapter. Two painting techniques were trialled in order to find the best technique for applying the paint in a consistent thin line. Initially a fine (3mm) short, flat ended, Winsor and Newton, Winton hogs’ hair brush suitable for precision painting oil based inks was used but the artists’ drafting pen in Figure 1 was found to deliver the most precise and consistent

amount of ink. This was set at precisely 3mm width with the adjustment wheel and loaded with ink from a paint brush.

Initially the tubes were held by hand and painted (Figure 2) but it was found that they curled back on themselves smudging the paint and causing the painted wires to touch and so “short out” when tested for electrical conductance. This shorting of the wires was resolved by removing the excess ink with a cotton bud soaked in acetone whilst leaving the two stripes of ink intact. To avoid this problem the tubes were secured to the bench by Blu-tack (Bostick, La Defense, Paris, France) which is a soft putty like adhesive. Although there was some improvement, the Blu-tack did not secure the tubes sufficiently and there remained problems with the painting technique (Figure 3).

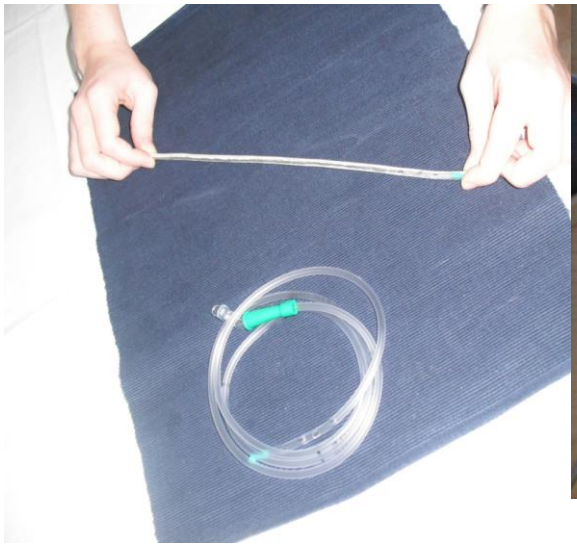


Figure 2: Hand painted tubes

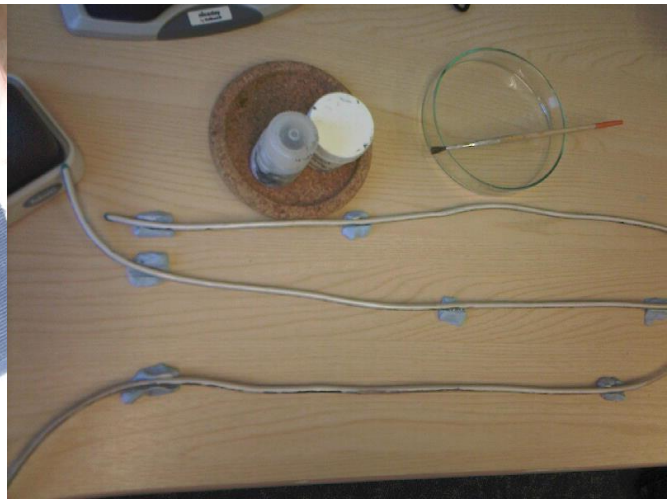


Figure 3: Hand painted tubes secured with “Blu-tack”

Eventually a mould was produced which held the tube at each end and permitted a straight line to be painted along the tube without it bending or curling. Initially this was a modified skirting board with clamps at either end but it was found that this did not hold the tubes securely enough. A colleague at Lincoln University, Alan Gill, designed a frame out of MDF with grooves the exact size of the tubes

which could hold the tube securely along its entire length (picture 4 & 5). This final iteration of the frame ensured the most accurate painting of the wires.

In accordance with the ink data sheet and manufacturer's recommendations the ink was left to air dry for 2 hours and when dry the tube was removed and reinserted so that the other side could be painted. This second stripe of ink was then left to air dry for 2 hours.

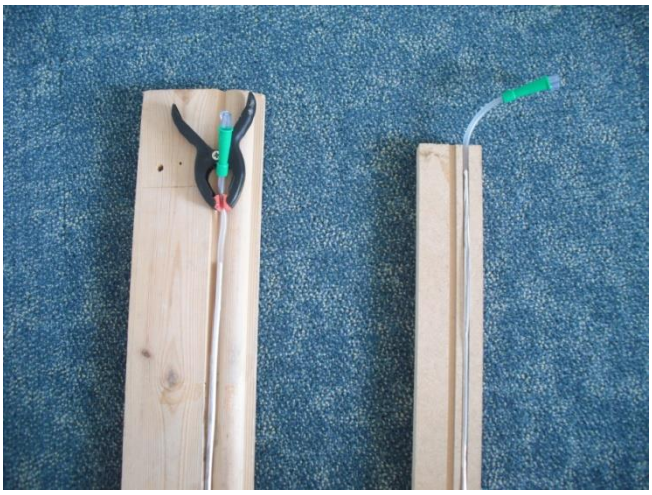


Figure 4: Left: initial frame with clamp to secure tube. Right: final frame which holds tube securely along entire length

Figure 5: Top: Initial frame with clamp to secure tube. Bottom: final frame which holds tube securely along entire length.

Length of both frames = 90cm

3.3.2 Electrodes

The distal 3 cm of the painted wires formed the electrode surface onto which a sensing material was applied. An electrode can be chemically modified by the immobilisation of a layer of material on to its surface and the modified electrode then takes on the surface character of the immobilised material and can be used

to perform electrochemical experiements (Fisher 1996). One example of modified electrodes is polymer coated electrodes. A particular type of polymer, redox polymers, produce electrical conductivity “via self exchange reactions within the polymer and with electrons “hopping” from one site to another” (Fisher 1996).

This was the electrochemical reaction suggested as a measure of pH and the redox polymer to be used in the LINGT prototype was vitamin K_1. Vitamin K_1 is a fat soluble vitamin, also known as phylloquinone, which occurs naturally in green plants where it has an intrinsic role in photosynthesis (Friedrich 1988). Vitamins are organic compounds essential for life as they have a distinct biochemical role in the human body. A number of vitamins are electrochemically active with their redox characteristics being particular to the specific vitamin (Hart 1990). Vitamin K_1 has a phytyl side chain (Figure 6) which is removed by intestinal bacteria producing vitamin K_3 (menadione) which is absorbed by the body. Wain, Wadhawan et al. (2003) give a detailed discussion of the electrochemical studies of vitamin K_1 which are vast due to the biological significance of this redox polymer (Wain, Wadhawan & Compton 2003).

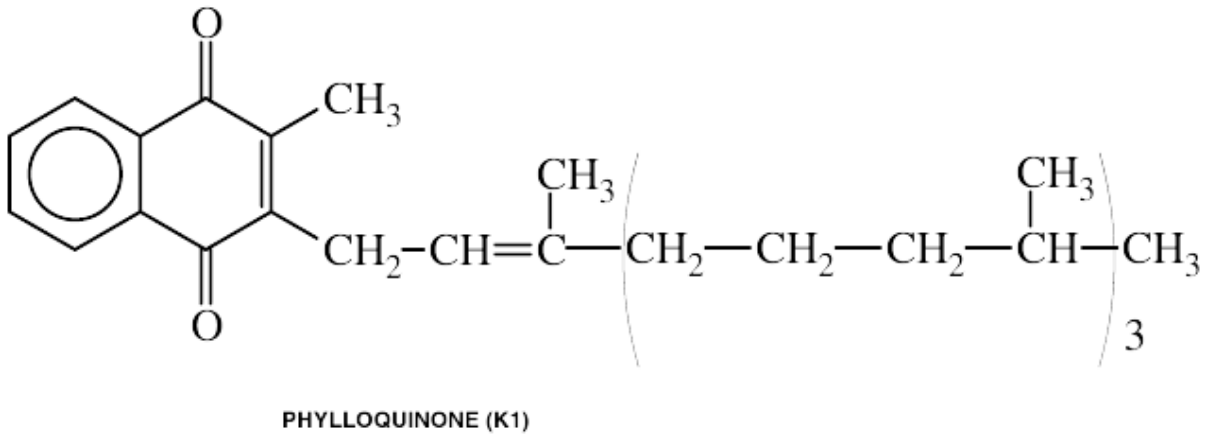


Figure 6: Chemical structure of vitamin K1

The phytyl sidechain of vitamin K_1 contains an olefinic moiety which is readily amenable for covalent chemical attachment to the electrode surface. Since the redox process is pH sensitive, a current characteristic (for example the peak current in a voltammetric measurement) will occur at different potential depending on the pH of the solution into which the measurement is made. This type of

voltammetric measurement can be made further stable by moving towards a monolayer of immobilised vitamin K_1 on the electrode surface.

The redox reaction of vitamin K_1 is a two-electron, two-proton reduction to form the corresponding hydroquinone. In addition, at low pH, the vitamin K_1 droplet interface has a high affinity for the self-assembly of peptides; adherence of these in the stomach, to the electrodes further maintains sensitivity of the system via modulation of redox activity of the vitamin K_1. It is thought that this effect will differentiate the stomach reading from other body compartments as it will not occur in the oesophagus or lungs due to the absence of these peptides nor in the duodenum where intestinal enzymes degrade the vitamin K_1. The basic principle is that peptides generated in the stomach, which contain hydrophobic and hydrophilic parts, self-assemble at the interface between the two immiscible liquids, so as to minimise the interfacial tension. This binding affects the amperometric signal.

In humans Vitamin K_1 contributes to the synthesis of clotting factors in the clotting cascade (Choonara et al. 1985) and has a role in bone and kidney metabolism (European Commision Scientific Committee on Consumer Safety 2010). Vitamin K_1 deficiency produces unexpected bleeding and, as levels are low in the new born, haemorrhagic disease of the new born may result and is treated prophylactically by vitamin K_1 supplementation soon after birth. In 2003 the American Academy of Paediatrics also recommended prophylactic vitamin K_1 for late onset deficiency bleeding (American Academy of Pediatrics Committee on Fetus and Newborn 2003).

In order to achieve a pharmacological effect, vitamin K_1 is given systemically by intramuscular or intravenous injection. There have been reports of severe side effects including fatalities related to administration by these routes, such reactions resembling hypersensitivity or anaphylaxis, including shock and cardiac and/or respiratory arrest (European Commision Scientific Committee on Consumer Safety 2010). Other adverse effects such as hyperbilirubineamia, transient flushing, hypotension and temporary resistance to prothrombin-depressing anti-coagulants, have only been observed after systemic administration of relatively high clinical systemic doses (European Commision

Scientific Committee on Consumer Safety 2010). However the gastric route is not associated with these risks and the potential for gastric absorption of vitamin K_1 applied to the tip of a nasogastric tube is considered to be minimal. In spite of this a full toxicology report was commissioned and calculations were conducted to ensure that, even if the full amount of vitamin K_1 applied to the tubes was absorbed there would be no risk of adverse effects (Appendix 4).

Concerns have been raised about hypersensivity reactions to vitamin K_1 included in cosmetic products and its use in such products has been banned since 2009 (European Commision Scientific Committee on Consumer Safety 2010). The effects on the skin were caused by products containing as high as 8% vitamin K_1, in considerably higher doses than were applied to the LINGT.

Daily requirements of vitamin K_1 in the human diet range from 5 micrograms for 0-6 month olds to 65 micrograms in adult males (55 microgram for females) (World Health Organisation Food and Agricultural Organisation of the United Nations 2002). The amount of vitamin K_1 applied to the nasogastric tubes was sufficiently small so that if it is digested, the amount of vitamin K_1 delivered is less than the recommended daily allowance for infants(<1 microgram).

Vitamin K_1 is a water-immiscible yellow oil which was obtained from Sigma-Aldrich Company Ltd, (Poole, Dorset, England). Vitamin K_1 solution was prepared by mixing the pure vitamin K_1 oil with acetonitrile in a ratio of 1mM in 10 mL solution. Acetronitrile is a colourless liquid and is the simplist organic nitrile which dissolves a wide range of ionic and nonpolar compounds. It is used as a polar aprotic solvent and in the laboratory it is used as a medium-polarity solvent. The vitamin K_1 solution had a formula weight (FW) of 450.70 and density of 0.984 g/mL. Alliquots of 10 mililitre were stored in sealable test tubes.

One side of the distal tip of the painted nasogastric tube was dipped in the solution of vitamin K_1 along a length of 3cm thus coating 3cm of one of the painted wires with vitamin K_1 to form a working electrode. The other wire was left uncoated to form a silver reference electrode. The tubes were left to dry naturally in air for 5 minutes. Figure 7 shows the structure of the tubes with the painted electrodes and vitamin K_1 coating.

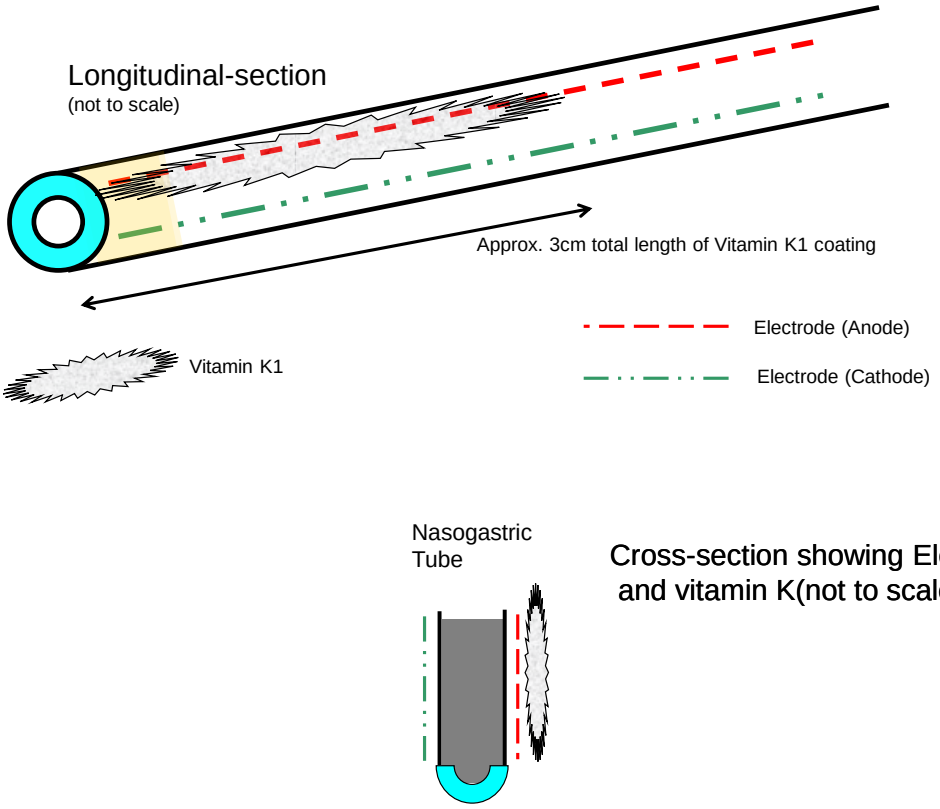


Figure 7: Structure of the tube with painted wires and vitamin k1 coating to form an electrode

3.3.3 Potentiostat

An electrical potential applied to electrodes increases or decreases the energy states of the electrons within the atoms and thus can enhance the electrochemical reaction within the solution. The electrical potential was applied by a very simple potentiostat meter attached to the external end of the tube. This potentiostat also measured the current flow between the two electrodes as a function of the applied potential difference between the electrodes and thus became the initial prototype indicator box (Figure 8).

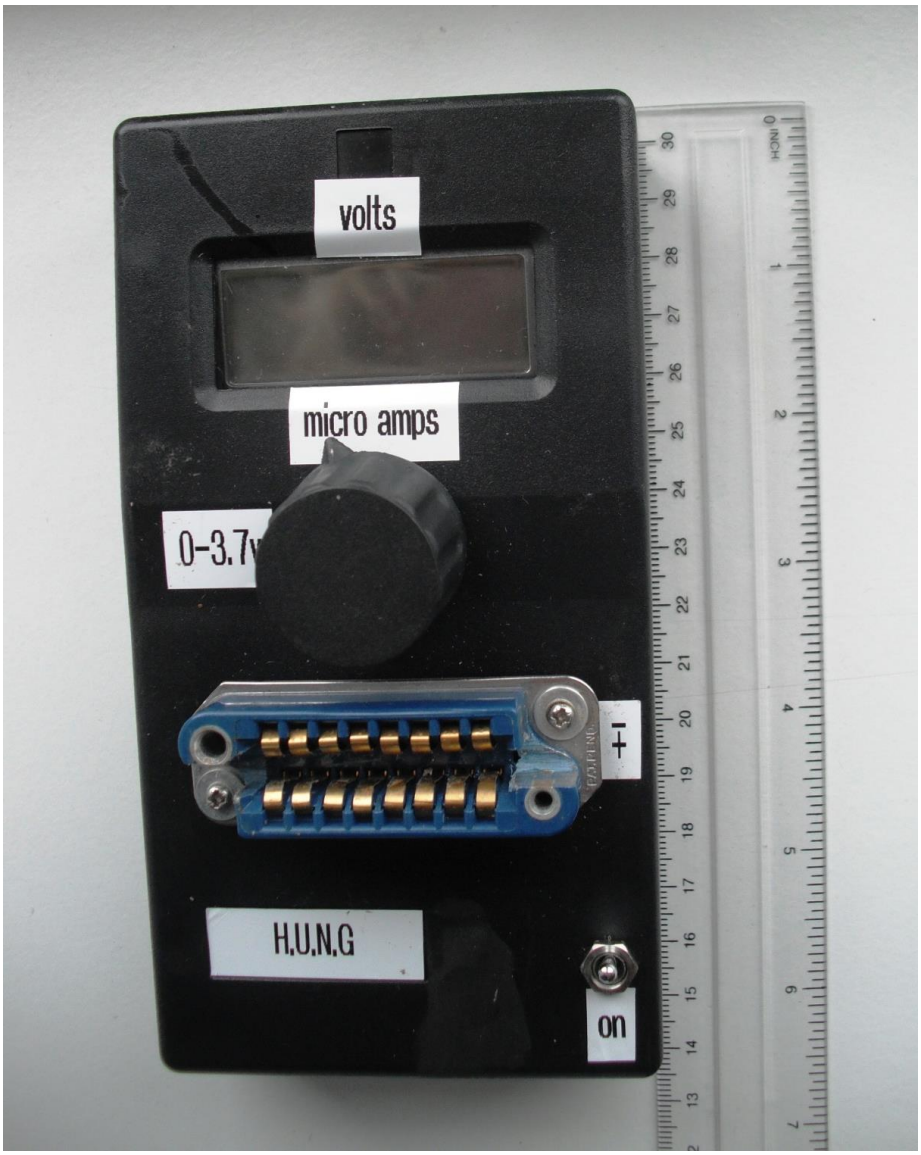


Figure 8: Potentiostat/ Indicator Box

The distal end of the nasogastric tube was inserted into the pH solution or stomach tissue and the proximal end was inserted between the sensors on the potentiostat (Figure 9). The application of a polarising potential to the electodes caused a pH-sensitive redox reaction (2 proton 2 electron reduction and oxidisation sequence) to occur at the base-circumference of the individual droplets of vitamin K_1 (Wain, Wadhawan & Compton 2003). The current that flowed between the electrodes during this redox process and the shift in the observed potential of a particular current feature (e.g. the reduction potential when the observed reduction current reaches maximal value during a voltammetric measument) was the measurement signal. This type of waveshape

analytical measurement is completely different to that used in other pH measurement systems based on quinone/hydroquinone redox equilibria since those are generally based on potentiometry (measurement of electromotive force between two electrodes when the system is under equilibrium conditions, viz. conditions of zero current flow), such as the quinhydrone electrode.

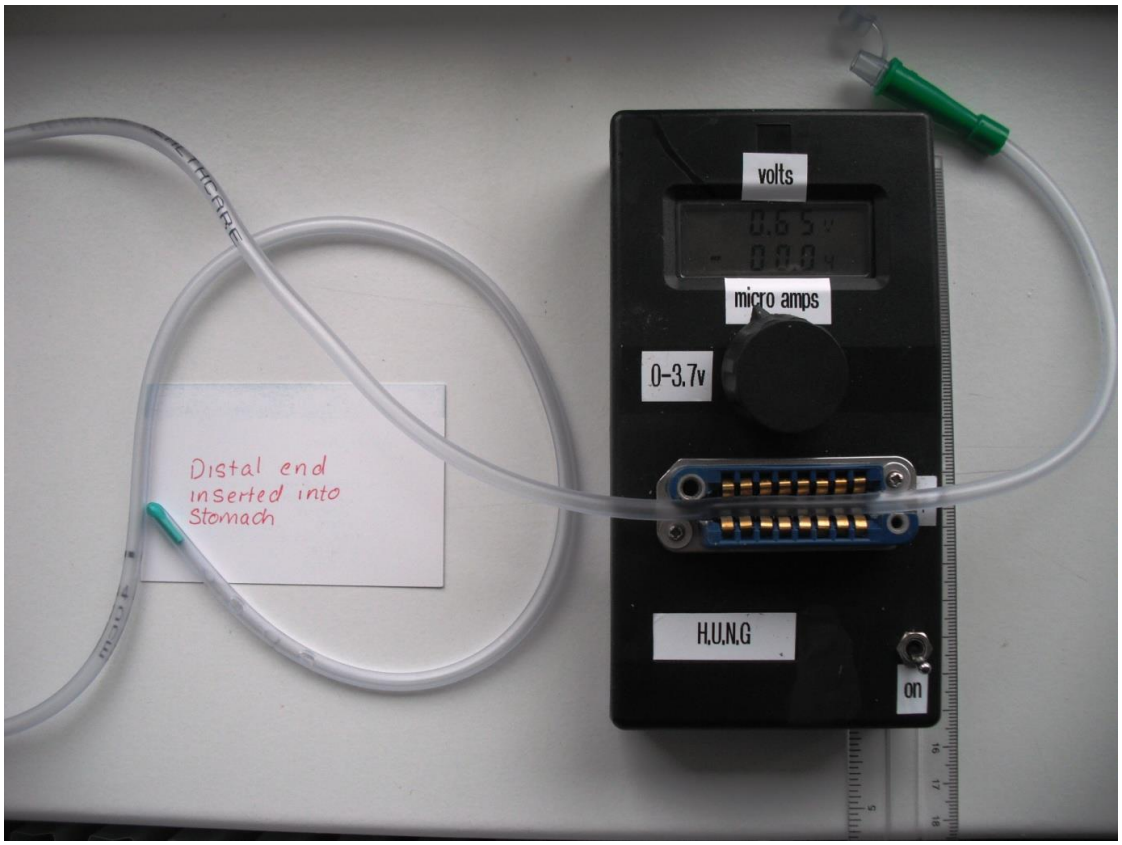


Figure 9: Nasogastric tube inserted into potentiostat with placement of distal end indicated

A total of 40 tubes were prepared in batches of 10 for both laboratory (20 tubes) and clinical experiments (20 tubes). The application of the conductive ink was adjusted in light of the results of each set of experiments as discussed below.

3.4 Laboratory Experiments

Two hundred millilitres of Fluka phosphate buffered saline was prepared by dissolving one tablet in 200ml de-ionised water. Ultrasonic vibration for 1 minute was used to facilitate the process.

Hydrochloric acid was added to produce acidic solutions and sodium chloride as a base to adjust the pH to the required levels of pH 2.00, 3.00, 4.00, 5.00, 6.00 and 7.00. The Mettler Toledo MP220 (Scientific Laboratory Supplies SLS) pH meter was used to test the pH which is accurate to second decimal place.

An aliquot of each pH solution (40 ml) was put into a large test tube which was labelled and placed in order in a test tube rack (Figure 10).

Figure 10: Test tubes containing pH solutions of different acidity with distal tip of nasogastric tube in situ

3.4.1 Test 1

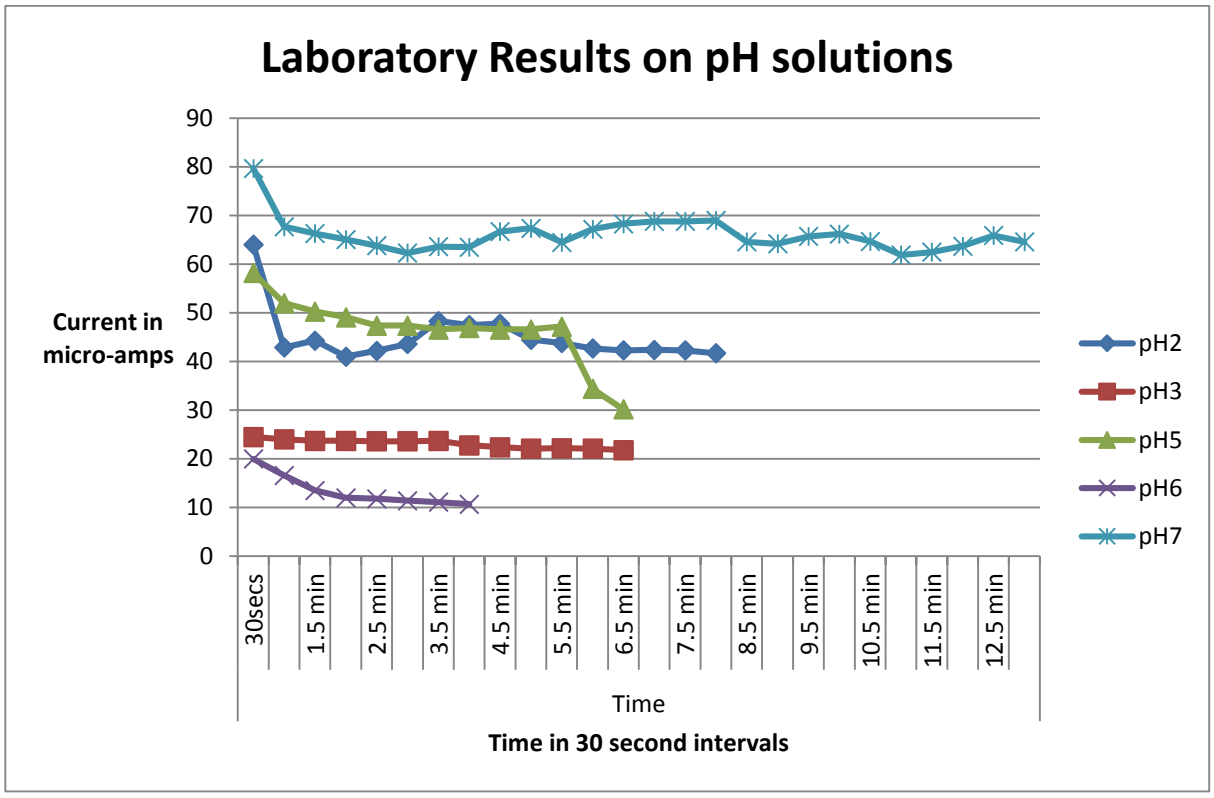
The distal end of the naso gastric tube was placed in the pH solution and the proximal end connected to the potentiostat. The dial on the potentiostat was set to apply a potential difference of 0.64 volts to the electrodes. This optimal potential difference had been determined by analysis of cyclic voltammograms

conducted by the electrochemist and was set on his advice. The position of the tube within the connectors on the potentiostat was adjusted in order to get a reading of the current. Each tube was inserted into each pH solution in turn and current measurements recorded every 30 seconds for 10 minutes. All 10 tubes from the first batch prepared were tested in this way but readings were obtained from only 2 tubes and then only when held carefully in position. The conductivity of the tubes was not good and only background and operator current could be detected. The reasons for 8 of the tubes not to work at all was not clear but It was considered that the conductive ink may have been applied too finely to conduct current along the entire length of the nasogastric tube. In addition the electrochemist suggested that the vitamin K_1 may need to be replenished between each test.

3.4.2 Test 2

The second batch of 10 tubes were painted with thicker paint consistency (3 parts paint to 1 part thinner) and a wider pen setting of 3mm to obtain a thicker "wire" on the tubes for test 2. The first 4 tubes were tested in pH 2, 3, 4, 5, 6, 7, 8 solution in the same way as in test 1. As little or no current was registered from these tubes it was decided to recoat them with vitamin K_1 after each pH solution. The first 3 cm of one side of the tube tip was dipped in vitamin K_1 and allowed to air dry for 5 minutes. It was then inserted into the first pH solution and the proximal end of the tube attached to the potentiostat. Readings were taken every 30 seconds for 10 minutes and the tube tip was then removed, rinsed in distilled water, recoated with vitamin K_1, air dried and positioned in the next pH solution.

Current registered for 3 of the tubes prepared in this way in all pH solutions and for one tube in only 2 solutions (pH4 and pH2). These tubes were tried in all pH solutions but no further currents were registered. The conductivity of the tubes was still not good but those that did conduct showed a steadily decreasing current over time. Graph 1 gives an example of the currents generated by 1 tube in different pH solutions. The increasing current observed at pH2 and pH7 was possibly due to the potential difference being too high and the silver paint breaking down through oxidation to create a silver solution.



Graph 1: Current generated by one tube in 5 different pH solutions

3.4.3 Discussion of Laboratory Experiments

The results of the initial set of experiments (Test 1) were extremely disappointing but demonstrated the need to refine the application of the "wires" to ensure good conductivity and to replenish the working electrode. The second set of experiments (Test 2) with the improved prototypes demonstrated that the system worked and generated a small amount of data which suggested that the current generated varied at different levels of pH. However the difference in values was not linear with the expected steady change in current with the change in pH. A solution of pH7 generated the highest current (60-80 micro amps) and a solution of pH 6 generated the lowest current (10-20 micro amps) with pH 2,3 and 5 generating currents between these ranges.

Further laboratory experiments were clearly required and these were conducted by the post-doctoral research chemist following the author's methods for preparation of the tubes.

3.5 Clinical Experiments in Freshly Resected Human Stomach Tissue

Although results were only obtained by the author for 3 tubes inserted into synthetic buffered solutions of different pH values further studies undertaken by a post-doctoral research chemist funded by the Yorkshire Concept grant with tubes prepared with a refined painting technique, demonstrated that a current could be generated in a range of pH solutions. It was therefore considered important to demonstrate that this would also happen in biological fluids, in particular gastric fluid, preferably *in situ* in stomach tissue. It was not ethical or appropriate to test such crude, hand-made prototypes on human subjects. The solution was to use surgically removed stomach tissue, identified by experienced surgeons and removed from the human body because of disease, to test the tubes thus ensuring certainty that the tubes were in stomach tissue.

The proposed tests on freshly removed stomach tissue were discussed with the consultant surgeons and Chairman Hull Ethics committee. He decided that if resected specimens destined for disposal were used and no patient data were recorded then in his opinion there were no ethical problems. Nonetheless, this proposal was submitted to the Hull Ethics Committee for their information and a letter of agreement was obtained to carry out these initial tests (Appendix 5). A copy of this letter was sent to the University of Hull Faculty of Health and Social Care Research Ethics Committee for their approval.

Permission was granted to test the nasogastric tubes on freshly resected stomach tissue in the upper gastro-intestinal theatre of a local general hospital by the consultant surgeons. All assessments were carried out in theatre immediately after the gastric specimen had been removed by the surgeon. On completion of the assessments the gastric specimen was disposed of in the normal way as directed by the surgeon.

The author was informed of forthcoming gastrectomies by the consultant surgeon and attended theatre on the appropriate days. Having prepared the tubes and indicator box in the theatre sluice, the author was then alerted when the stomach tissue was due to be removed. Appropriate universal precautions were taken and after the tissue had been removed by the surgeon and placed in a large dish

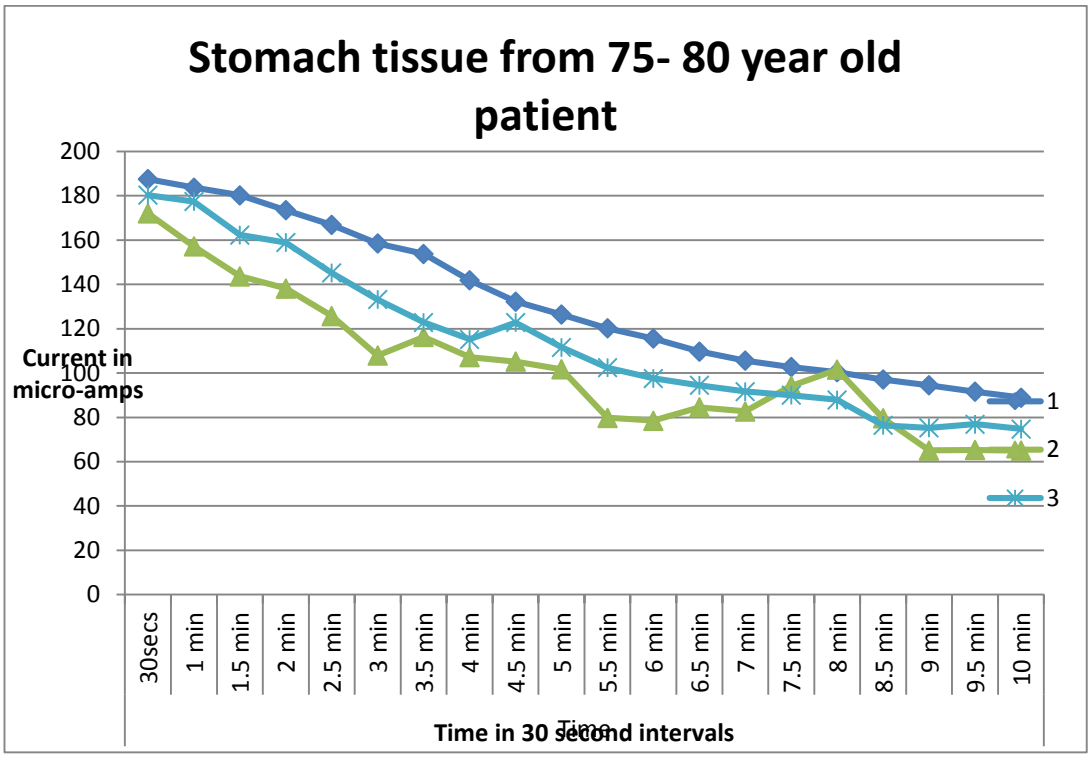
it was passed to the author who transferred it to the theatre sluice. Three tubes were inserted in the stomach tissue through an incision identified by the surgeon. The potentiostat dial was set to give a potential difference of 0.64 volts and readings of the current in micro-amps were recorded every 30 seconds.

No patient tissue or fluid was removed from the operating environment and no patient details were recorded except age in 5 year intervals. The assessments took place on 6 occasions between September and November 2009.

A total of 20 tubes were prepared and 15 placed in 5 stomachs (3 in each stomach) over a 3 month period. The first 5 tubes used were sterilised with ethyl oxide to determine the effect of sterilisation on the detection system. This unfortunately made the conductive ink flake away from the tubes and so no current could be detected. It was therefore decided not to sterilise the remaining tubes as this was not a requirement at this stage of the research.

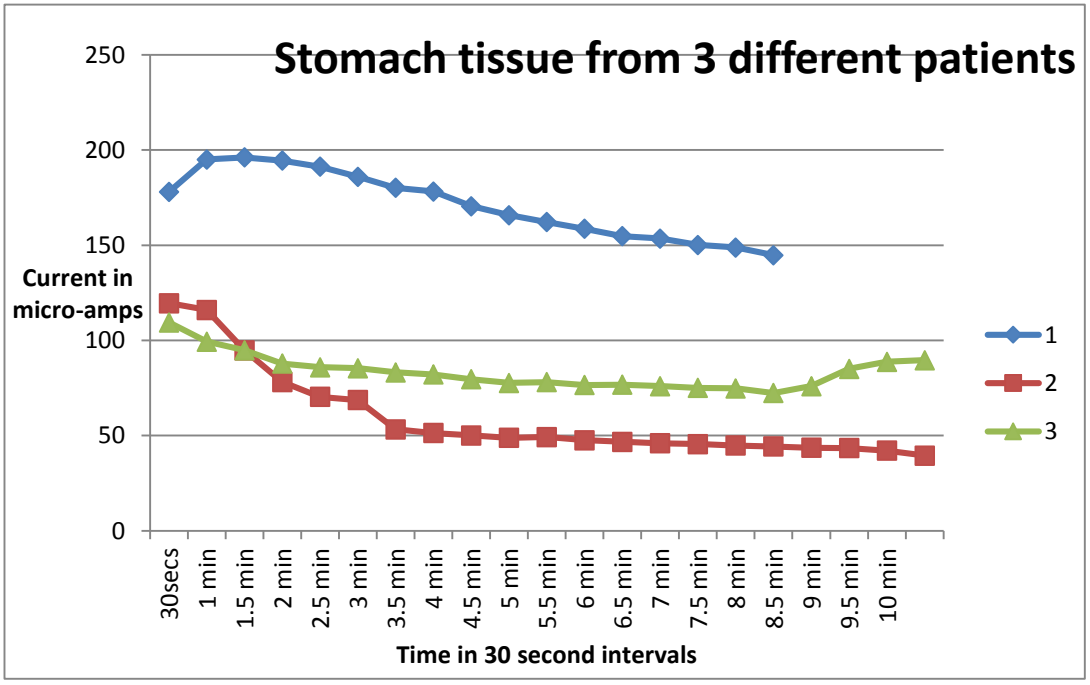
The initial method of inserting 3 tubes simultaneously and moving the indicator box to each one in turn was modified to inserting the tubes one at a time and leaving the indicator box connected to each tube until the 10 minute recording period had been completed. This was because it was difficult to get a good connection between the electrodes and the sensors on the indicator box and once achieved the author was reluctant to break the connection until all the readings had been made. Blood and gastric juice leaked onto the author's gloves making manipulation of the tubes and sensors difficult. There was also some concern that the tips of the tubes could come into contact with each other within the stomach tissue and affect the chemical and electrical reactions.

Of the 15 tubes inserted 8 behaved in a similar fashion, 3 of these being in the same stomach as indicated in Graph 2. All three tubes demonstrated similar readings and a similar rate of decline in current over the 10 minute period with tube 2 showing a brief temporary rise in current at 8 minutes but then returned to the expected level by 9 minutes.



Graph 2: Current generated over 10 minutes by 3 tubes inserted into the same stomach tissue

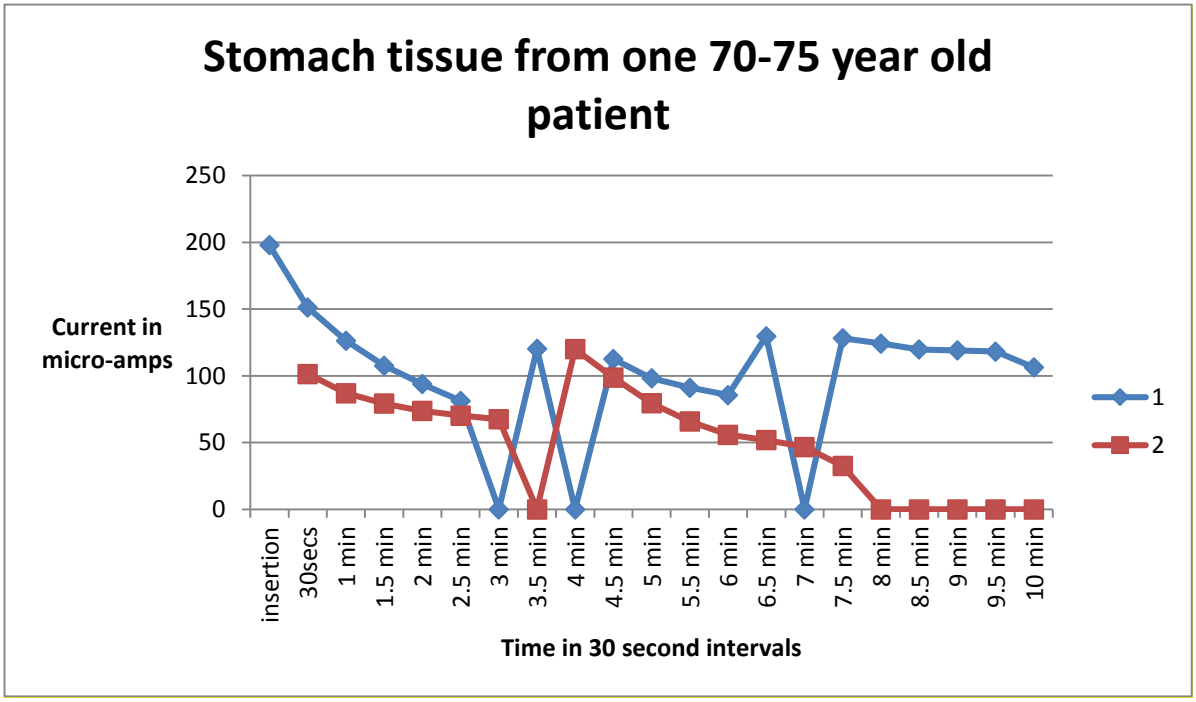
Graph 3 shows how three further tubes (in different stomachs) showed a similar steady decline in readings. Tube 3 showed a much slower decline in current until 8.5 minutes when the current began to increase.



Graph 3: Current generated by 3 different tubes inserted into 3 different stomachs

During one experiment a sudden drop in current at 3.0 minutes alerted the author to the fact that the tube had slipped out of the aperture and so was no longer in contact with stomach mucosa. It was reinserted causing immediate return of the current to higher than pre- removal levels. Due to the size and shape of the incision in the stomach through which the tube was inserted this event occured again at 4.0 minutes as shown in Graph 4 tube 1.

This phenomenon was tested on a further two tubes which were purposefully removed from the stomach at 3.0 and 3.5 minutes and reinserted demonstrating a similar fall of current to 0 when removed and return to high readings on replacement. Graph 4 shows the measurements from one of these tubes.



Graph 4: Current readings from 2 tubes removed and reinserted in one stomach

The remaining 7 tubes either did not show any reading (n=3) or after an initial high reading dropped to 0 micro-amps within 2-3 minutes and did not incease in spite of efforts to move the tubes both within the stomach and within the potentiostat (n=4).

3.6 Summary of Experiments on LINGT Iteration 1

Table 6 shows a summary of the results of the 40 tubes prepared and tested. Sixteen of the twenty tubes used in the laboratory experiments did not register any current neither did eleven of the twenty tubes tested on resected stomachs; five because the sterilisation process had rendered them un-useable. Thus one third (n=13) of the modified nasogastric tubes demonstrated a reaction when placed in either a pH solution or gastric mucosa which generated a current that was conducted along the tube and measured by the indicator box.

<table>
<tr><td colspan="2">20 tubes for lab experiments on pH solutions</td><td colspan="4">20 tubes for experiments on resected stomachs</td></tr>
<tr><td rowspan="2"></td><td rowspan="2"></td><td>5 tubes sterilised</td><td colspan="3">15 tubes not sterilised</td></tr>
<tr><td rowspan="2"></td><td rowspan="2"></td><td colspan="2">9 produced clear readings</td></tr>
<tr><td>16

Did not register current</td><td>4

Produced clear readings.

Graph1</td><td>5

Ink flaked off so not useable</td><td>6

Produced 0 readings or declined to 0 by 3 minutes</td><td>6

Showed steady decline in current over time.

Graph 2 and 3</td><td>3

Showed decline of current which dropped to 0 when tube removed from stomach then returned to expected levels on reinsertion

Graph 4</td></tr>
</table>

Table 6: Summary of results of 40 adapted nasogastric tubes in pH solutions (20) or freshly resected human stomach tissue (20)

In all human clinical specimens the current generated was in the range of 0-200 micro amps which settled to a value of 50-90 micro amps in 5 out 6 cases. Much smaller currents (between 10 and 80 micro amps) were generated in the buffer solutions. The declining levels of current recorded and illustrated in Graphs 1-4 are most probably the result of positive hydrogen ions moving towards the

negative electrode created by the vitamin K_1. Eventually the decline tailed off to a steady level. In electrochemistry, the Cottrell equation describes the change in electric current with respect to time in a controlled potential experiment, such as chronoamperometry. For a simple redox event the current measured depends on the rate at which the analyte diffuses to the electrode. That is, the current is said to be "diffusion controlled". The Cottrell equation is

$i = kt^{-1/2}$ where k is the collection of constants for a given system so $k=\frac{i}{\sqrt{t}}$

I = current in micro-amps t = time in seconds

The Cottrell equation can be used to plot micro-amps against reciprocal square root seconds (time) and a straight line will be obtained.

3.7 Limitations

The technique of adapting the nasogastric tubes was refined throughout the course of the experiments and each batch of painted tubes improved in terms of the consistency of the paint and the application techniques. The initial 10 tubes prepared did not conduct current well but the second batch was better with third and fourth batches improving further. Hand mixing and hand painting is a variable process even if efforts are made to control the amount of ink prepared and applied. Thus an automated procedure had to be found to ensure that the “wires” and electrodes were uniform and the vitmain K_1 applied in a closely controlled way in order to ensure that the precisely same amount was applied to each tube.

The sterilisation process using ethyl oxide had a detrimental effect on the conductive ink causing it to flake away from the tubes. This will need careful consideration in future studies as sterilisation is a requirement for tubes prepared for clinical use.

3.8 Discussion

It has been demonstrated that the system of an adapted nasogastric tube painted with conductive ink and with vitamin K_1 applied to the distal end does generate an electric signal when placed in buffer solutions of different pH values and in stomach tissue and this signal is conducted along the length of the tube and can be detected by the indicator box (potentiostat). Thus these initial experiments on the first iteration of the LINGT have contributed to the overall aim to develop an effective, sensitive and reliable nasogastric tube which self-indicates its position.

The initial part of the hypothesis has been proved that is:

> "the chemical reaction between acid stomach contents and the vitamin K_1 coating on the nasogastric tube will create an electric current which can be measured externally"

However the demonstration that this current is unique to the stomach has yet to be made. There are many factors which affect the dynamics of an electrode reaction including the electrode potential, transport of material between the electrode and the solution, the reactivity of the solution, the nature of the electrode surface and the structure of the interfacial region over which the electron transfer occurs (Fisher 1996).

The objectives of this first phase of the research have been partially met in that:

- hand adapted nasogastric tubes were produced but they did not consistently nor reliably conduct current along their length. The reliability of the system needs further work and will be partly addressed by professional manufacture.
- these handmade tubes were tested in pH solutions in the laboratory but there was insufficient data to confidently determine the current produced at different pH values
- these tubes were tested on resected stomachs and effectiveness in human gastric mucosa was demonstrated in a number of tubes. However these samples varied in size and gastric fluid was contaminated

with blood from the surgical incisions so comparison with insertion into healthy human stomachs is limited.

3.9 Conclusion

These initial experiments on LINGT iteration 1 provided the proof of concept evidence that a chemical pH sensing system could be applied to a nasogastric tube and that the system could be effective in generating a signal in pH buffer solution and stomach tissue.

Further work was clearly needed to refine the design of the LINGT and demonstrate that the sensing system was able to distinguish between placement in the stomach and other body compartments. These initial experiments informed the application to the National Institute of Health Research Invention for Innovation (i4i) programme for funding to undertake this work. The award of £834,428 (full economic costs) enabled the development of the second iteration of the LINGT and the final design freeze discussed in chapter 4. Funding ensured that the LINGT iteration 2 prototypes were professionally manufactured and the appointment of a full time research chemist ensured that the electrochemical evaluation of the system was conducted in a detailed manner. The author took the role of Principal Investigator (PI) for the funded project and continued her doctoral research as detailed in the following chapters.

Chapter 4: LINGT Iteration 2 Manufactured Prototypes

4.1 Introduction

The hand-prepared prototypes discussed and evaluated in the previous chapter were developed into manufactured prototypes during 2012. A number of manufacturers were considered and Arrotek Medical Ltd was selected as the preferred manufacturer on the basis that they were able to manufacture small numbers of prototype tubes at a cost and timeframe within the specification of the project. Contracts were put in place and the following section discusses the development and evaluation of the next iteration of the Location Indicating Nasogastric Tube (LINGT).

4.2 Hypothesis

The manufactured prototypes of LINGT were tested in laboratory and clinical samples in order to test the previous hypothesis:

> "the chemical reaction between acid stomach contents and a specific electrochemical coating on the internal tip of a nasogastric tube will create an electric current which can be measured externally."

And the additional hypothesis that:

> "the current generated in the pH range of the stomach (pH5 or less) will be sufficiently different from that measured in other body compartments (pH6 or over) to enable the calibration of a specific indicator box"

4.3 Design

Table 7 gives a summary of the design decisions that were considered when developing iteration 2 of LINGT with the selected options highlighted in yellow. Decisions regarding the specification of the tube were governed principally by the standard of nasogastric tubes in current use as the LINGT had to be as effective,

as easy to insert and as comfortable for patients, whilst remaining competitive in price. Each decision is justified in turn in the following sections.

Design Decision	Possible Options				
1.Tube Material	Polyurethane (PU)	Polyvinyl chloride (PVC)	Silicone		
2. Incorporation of the conducting wires	Extruded tube with 2 additional lumina either side of the feeding channel into which wires are incorporated	Wires coextruded into walls of the tube	Normal feeding tube with "wires" applied after manufacture by Screen Printing or pad printing	Normal feeding tube with "wires" applied after manufacture by Ink jet electronics or Micro-Pen	
3. Wire Materials	Medical grade Stainless Steel	Titanium	Silver, gold or platinum possible but too expensive	Carbon considered but conductivity limited	Copper- good conductor but corrosion an issue
4. Wire diameter	0.25 mm Good conductivity but increases rigidity of tube	0.1 mm conductivity acceptable			
5. Electrode Position	Wires externalised through hole from lumen to outer surface then 'tucked' in again (Figure 13 & 14)	Wires externalised through hole from lumen to outer surface and marker bands applied externally fitted flush to tube to form airtight seal (Figure 11 & 12)			
6.Electrode Materials	Same as wire	Gold marker band – already available as used in other medical devices	Silver marker band	Surgical stainless steel marker band	
7.Application of Vitamin K1 to working electrode	Exposed wire tip (electrode) sputtered, sprayed or spotted	Dipped in vitamin K1			
8. Application of Ag/AgCL to reference electrode	Hand painted	Exposed wire tip (electrode) sputtered, sprayed or spotted – Biodot tried this but solution too viscous for available machine	"Line" painted by machine		
9. Outer Coating	Gelatine	Vegetarian equivalent of gelatine - Vege -gel			

Table 7: Design Decisions with selected options highlighted in yellow

4.3.1 Decision 1: Tube Material

The material from which the tube should be made was considered and medical grade extruded polyurethane (PU) of a quality and standard as that of nasogastric tubes in current use was selected. PU was discovered in Germany in 1937 and was first used for a diagnostic catheter in the mid 1960's and is now used extensively in medical devices (Pinchuk 1994). PU comes in a wide range of chemical compositions which combine hard and soft segments bound together by a urethane function. The hard segments give mechanical strength and the soft segments elasticity and flexibility as well as making the material more hydrophilic and bio-stable (Pinchuk 1994).

Some companies (including Pennine) manufacture nasogastric tubes made of medical grade polyvinyl chloride (PVC) but these tubes tend to be used for shorter duration (less than 7 days) (Pennine Healthcare 2014). Materials used in medical devices need to be chemically inert but concerns about the leaching of additives and plasticers have been well documented (Hill, Shaw & Wu 2003, Jenke 2006). Whilst PVC is now considered safe for short term use, the design requirement for a tube that could remain *in situ* for up to 30 days, suggested that PU was the preferred material. Polyurethane can also be produced in a more flexible form than PVC although the PVC Pennine feeding tubes are of a similar shore hardness to PU tubes at shore hardness A80 (Pennine Healthcare 2014).

Silicone rubber was also considered as a possible material but it was suggested by the manufacturer that this material would be more expensive and there is some evidence that it does not perform as well in medical catheters (Cohen et al. 2011). Silicone rubber is a rubber-like material composed of the polymer silicone which contains silicon together with carbon, hydrogen, and oxygen. Silicone rubbers are widely used in industry and the ease of manufacturing and shaping means that it can be found in a wide variety of products, including: cooking and food storage products; clothing and footwear; electronics; medical devices and implants; and in home repair and hardware with products such as silicone sealants (Kreitner 2010).

4.3.2 Decision 2: Incorporation of the conducting wires

The method of incorporating the conducting wires into the tube was considered. In the previous iteration (discussed in chapter 3) the 2 conducting wires had been hand-painted on the external surface of the tubes and initially a method of printing the wires onto the external surface of the tubes was considered for this second iteration. The application of solutions or liquids through printing processes has been used for hundreds of years in order to replicate information on paper in large volumes and at relatively low cost. The adaptation of graphic printing processes to the development of functional devices has been explored by a range of scientific and technology research groups and such methods are now frequently used to apply chemical or biological substances in liquid form to a range of materials. Consideration was given to possible commercial methods of printing technologies, including screen printing, pad printing and printed electronic inkjet. For a full discussion of the range and relative benefits of these printing techniques see Sirringhaus et al. (2006).

Pad printing or tampography was considered most appropriate as it is used for printing on otherwise difficult to print on products in many industries including medical devices. Pad printing is a process that transfers images onto objects using an indirect offset (gravure) printing process. The image is transferred from the stereotype via a silicone pad onto a substrate. The technique is used in the production of sports equipment and toys and also used to deposit functional materials such as conductive inks, adhesives, dyes and lubricants. The exploration of pad printing resulted in contact with CI Medical Ltd (15 Commerce Way, Norton, Massachusettes, USA). CI Medical is the premiere pad printer for the medical device and diagnostic industry specialising in providing complex, permanent markings to meet the exacting standards of the medical device industry. This company has developed innovative medical device pad printing techniques through partnerships with major medical device manufacturers enabling them to offer quality, permanent medical printing services to the medical device community. However discussion with the company (David Young personal communication) revealed that the resistance of the printed wire would vary according to compression or tension and therefore this type of “wire” would not

be suitable for a tube that would be bent through the nasopharynx and which required stable resistance.

It was therefore agreed that the wires of LINGT iteration 2 would need to be manufactured within the walls of the tubes. A tube design which incorporated 3 lumens, one central feeding lumen and 2 side lumens for the wires was suggested by the manufacturers, Arrotek Medical Ltd. This was not considered ideal, because the internal diameter of the tube would be reduced to accommodate the additional lumens reducing the available space for fluid to pass through the tube. If the internal diameter was retained the additional lumens would increase the external diameter making the tube larger and therefore less comfortable for the patient. However, as this iteration would not be used on patients, this was considered a useful design to establish whether the tube would work in samples of tissue and tubes of external diameter 2.7mm French Guage (Fr) 8 were ordered from Arrotek Medical Ltd. Nasogastric tubes are manufactured in a range of sizes from Fr 5 (1.67 mm) for feeding premature babies to Fr 22(7.3mm) used for draining adult stomachs. The size for the prototypes was a pragmatic decision based on the premise that it would be easier to scale up the design so larger guage tubes could be manufactured in a similar way if required.

4.3.3 Decision 3: Wire Materials

Selecting the material from which the wires were to be manufactured was difficult as financial considerations as well as functionality (eg. conductivity and flexibility) had to be balanced. Ideal conductors are precious metals including gold and platinum (TibTech Innovations 2012) but their cost would make the nasogastric tubes prohibitively expensive The price of one gramme of 10 carat gold on 14 January 2014 was given as £10.24 and silver as £0.40 (Gold rate 24 2014). Whilst copper is also an excellent conductor the degradation of copper wire in the stomach environment and risks associated with the absorption of copper (World Health Organisation 2004) meant that this metal was not a viable option for the conducting wires. Other options had to be considered.

Titanium and surgical stainless steel were identified as possible materials for the conductive wires. Titanium is a strong, corrosion resistant transition metal

discovered in Cornwall in 1791 and used in a range of industries including the manufacture of medical prostheses, orthopaedic and dental implants, dental instruments and sporting goods (Ehrenberg 1958). Titanium is as strong as many steels but 45% lighter (Barksdale 1968) which made it a suitable consideration for the wires. However its low electrical conductivity was a concern. Surgical stainless steel is a marketing term for the type and grade of stainless steel used in surgical implants and instruments. Stainless steel is frequently used in medical applications because it is easy to clean and sterilise, strong, and corrosion-resistant (Black 2006). Twenty prototype tubes were manufactured initially, 10 with titanium and 10 with medical grade stainless steel single core wires of 0.25 mm diameter for evaluation in the laboratory.

4.3.4 Decision 4: Wire Diameter

A pragmatic decision regarding the diameter of the wire had to be made by the manufacturers. In this prototype the wires were fed by hand down the side lumens of the tube. Previous laboratory experiments had demonstrated that wires of diameter 0.1mm were suitable in terms of resistance and conductivity however this wire was not sufficiently rigid to be fed down the side lumens. It was therefore agreed that a thicker wire could be used for iteration 2 but subsequent iterations using finer wires of 0.1 mm diameter would be necessary for use on patients.

The effect of the wire on the stiffness of the tube was disappointing as the prototype tubes appeared very stiff on handling compared to nasogastric tubes in current use. Formal assessment was not conducted at this stage but it could be seen that the tubes retained their shape if bent demonstrating a lack of flexibility that would not be suitable for use on human subjects. This issue was addressed in subsequent iterations by reducing the diameter of the wire.

4.3.5 Decision 5: Electrode Position

The conducting wires required connecting to the electrodes situated at the distal (internal) tip of the tubes. Two possible options for connecting the electrodes to the conducting wires were evaluated. The two designs (Figures 11 - 14) were evaluated in the laboratory; both utilising tubes with 3 lumens.

In the first option holes were made between the external surface of the tube and the lumens containing wires in order to expose wire. The exposed wire was connected to metal rings (marker bands) that formed the electrodes. In the prototype tubes these bands were made of gold as the manufacturers could source pre- made gold bands of the required size. These bands were swaged onto the tube and pressure fitted in place. The holes over which the rings were fitted were 10 mm apart along the length of the tube so that the rings were clearly separated. See Figures 11 and 12.

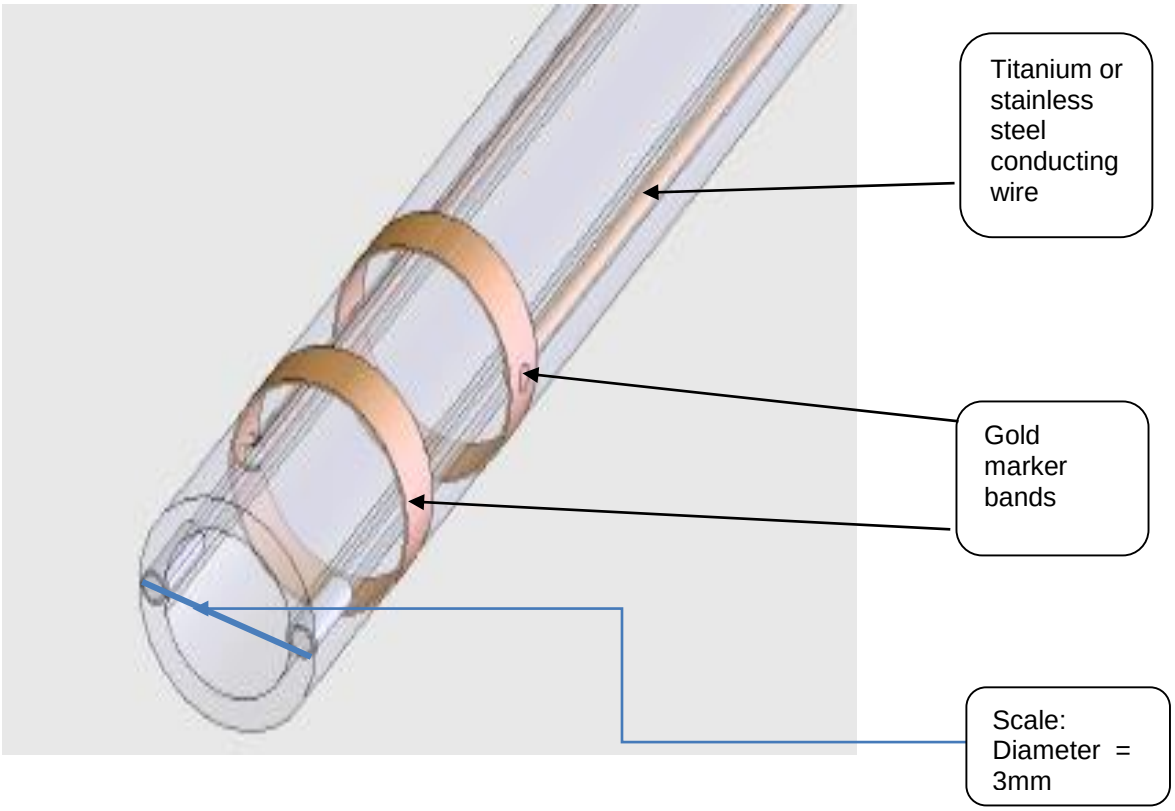


Figure 11: Design option 1 with electrodes formed by gold marker bands

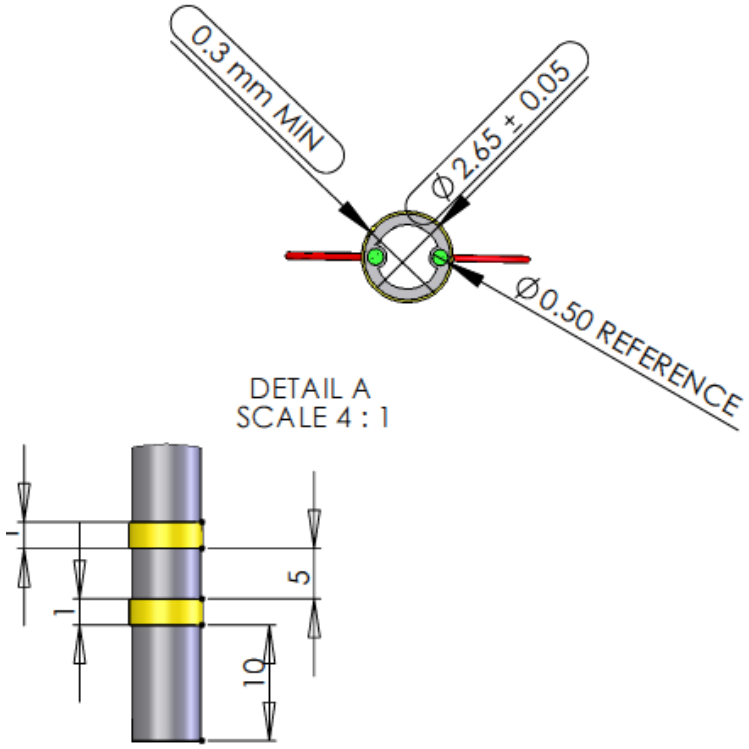


Figure 12: Two dimensional drawing of design 1 with electrodes formed by gold marker bands

In the second design (Figures 13 and 14) the conducting wires were externalised from the tube via a skive hole from the outer surface of the tube to the lumen containing the wire. A 7mm length of wire was externalised to provide the electrode surface. The end of the wire was channelled back into the lumen it was externalised from using a further skive hole. This size of electrode (7mm) was selected in order to balance the need for the electrode to be as small as possible in order to fit on the tip of a nasogastric tube but be sufficiently large to generate detectable and measurable current.

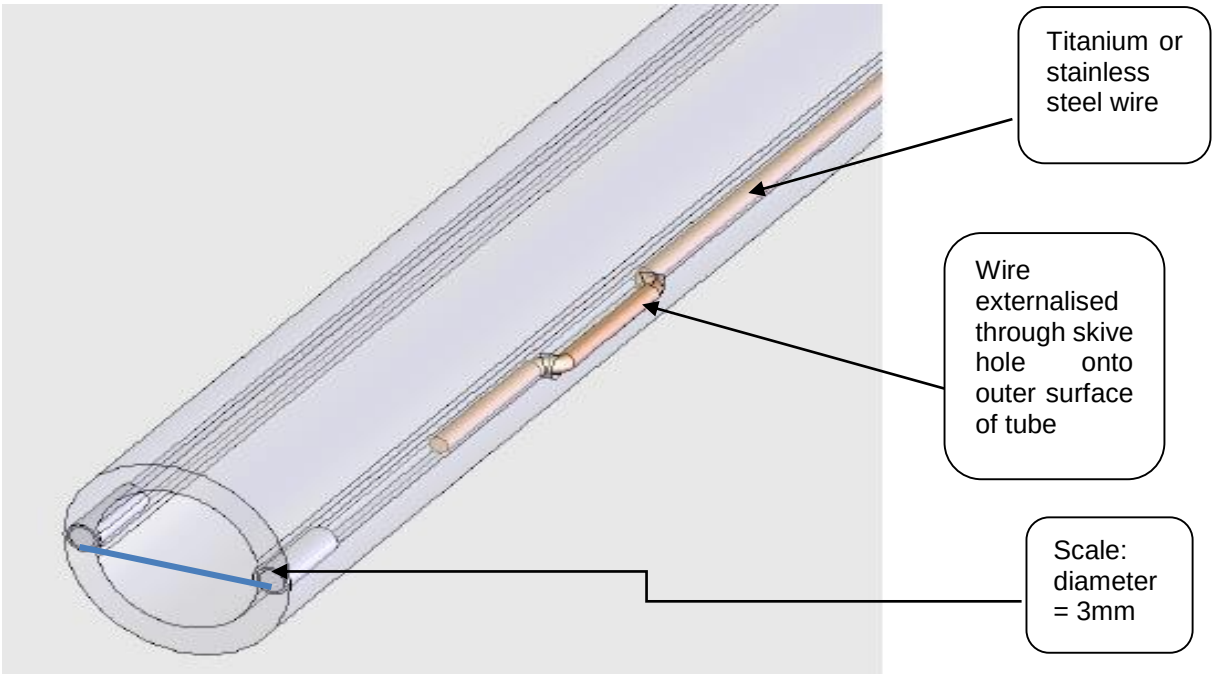


Figure 13: Design 2 with electrodes formed by externalising 7mm of wire through skive holes

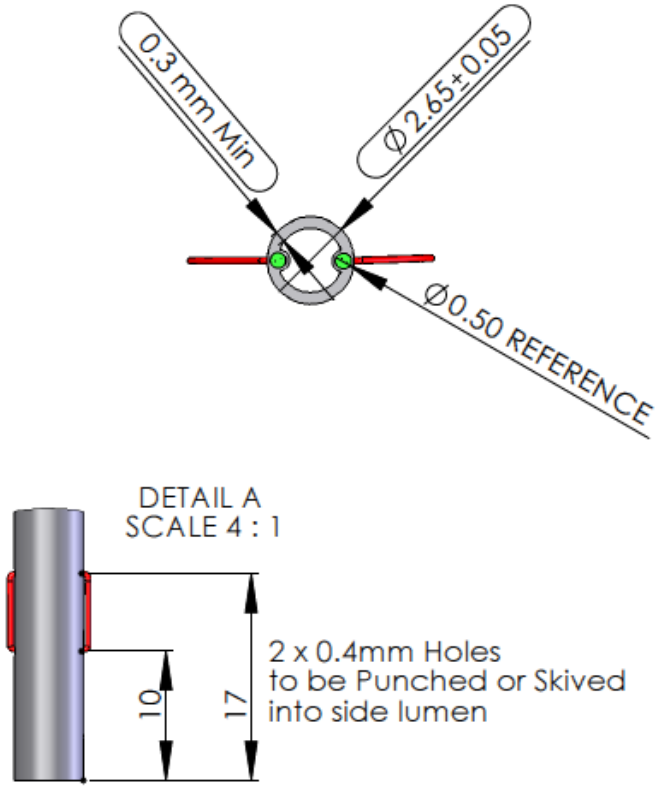


Figure 14: Two dimensional drawing of design 2 with electrodes formed from externalised wire

4.3.6 Decision 6: Electrode Material

In the case of both designs, one electrode was the working electrode and the other acted as a reference electrode. The electrode material was either gold (design 1) or the same as the wire, that is titanium or stainless steel (design 2). Evaluation of both designs took place during April – September 2012 involving laboratory experiments conducted by the Post-Doctoral Research Associate (PDRA) and evaluation of the ease of application of the redox species vitamin K_1 (see below) and reference electrode (silver silver chloride). It was therefore recommended to the project team at the Quarterly Review Meeting in July 2012 that future development focus on design 2 as the preferred option due to cost (the gold marker bands were priced at £3 each) and easier and more uniform application of the electrode material. Therefore an additional 20 tubes of design 2 were ordered from Arrotek Medical Ltd with medical grade stainless steel (10) and titanium (10) wires.

4.3.7 Decision 7: Application of Vitamin K1 to working electrode

The working electrode was coated with 360 µl of 1 mM vitamin K_1 dissolved in ethanol, which was air-dried. This amount and concentration was based on previous studies conducted prior to the start of this project and advice from the electrochemist with reference to previous published work on the immobilisation of redox droplets (Banks et al. 2003). The vitamin K_1 was applied using a micro spotting machine (Deerac Fluidics™ Low Volume Pipetting System NS101, Figures 15 and 16) that allows precise control of volumes used and can apply a precise highly controlled amount of vitamin K_1 in microdroplets of a given volume (300nl per spot) over a specified length of fine wire (6 mm) thus enabling simple reproduction of identical tubes for experimental testing and verification. The preparation of the electrodes was conducted by the PDRA according to a standard protocol (Appendix 6).

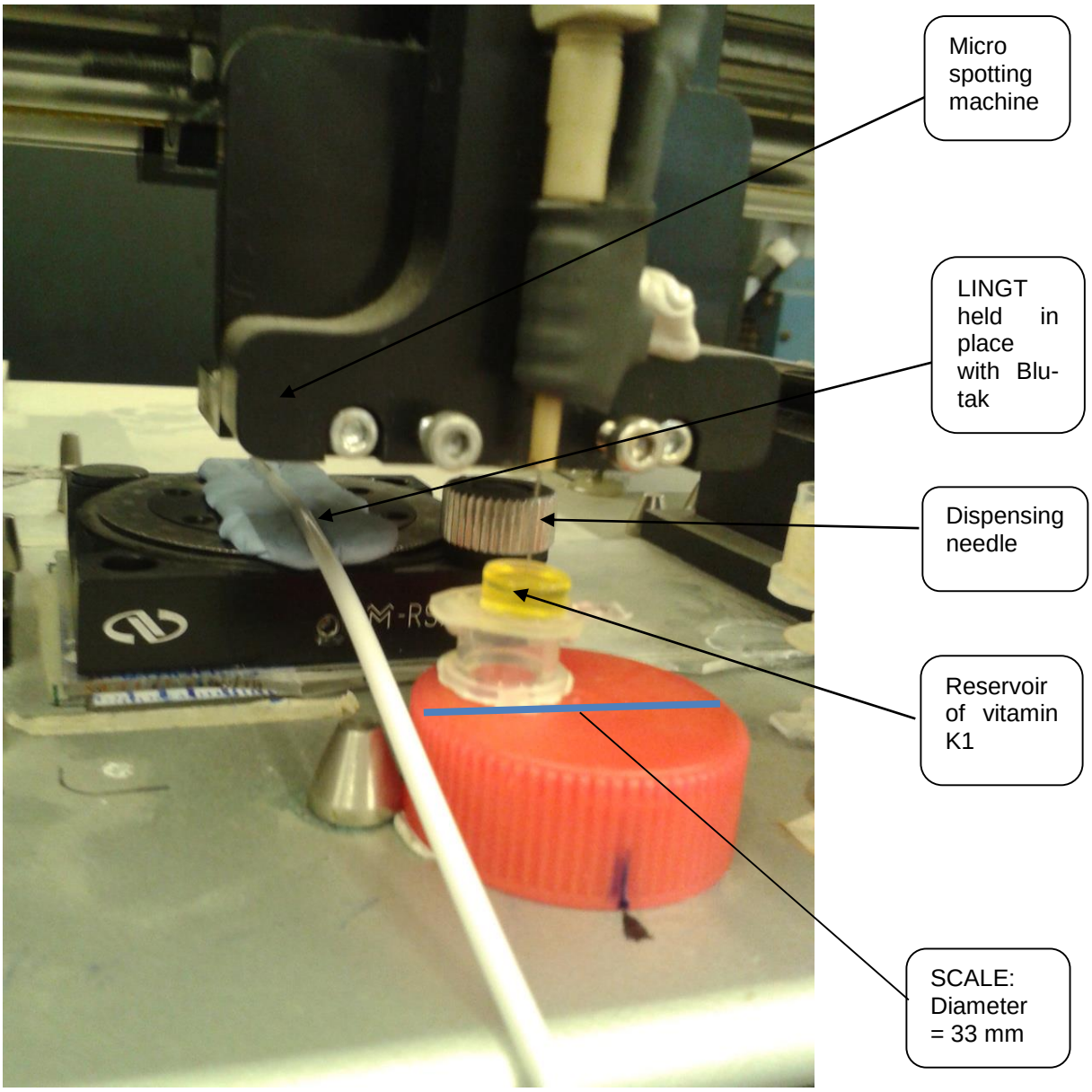


Figure 15: LINGT iteration 2 in place for application of vitamin K1 by microspotting machine

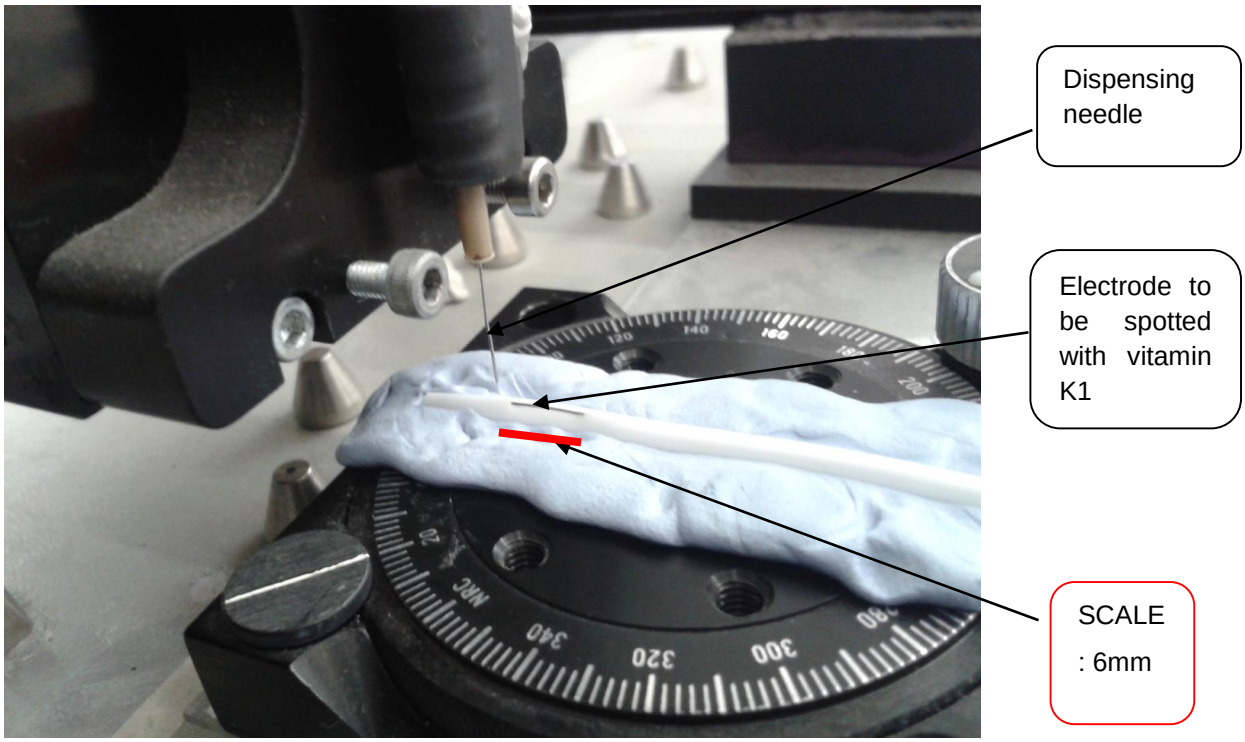


Figure 16: Dispensing needle applying micro spots of vitamin K1 to electrode surface

4.3.8 Decision 8: Application of Ag/AgCl to reference electrode

The reference electrode was coated with medical grade silver-silver chloride ink supplied by creative materials supply code 117-23 (Creative Materials Inc, 141 Middlesex Road, Tyngsboro, MA, USA). This paint was applied by hand using a fine (3mm) short, flat ended, Winsor and Newton, Winton hogs' hair brush suitable for precision painting oil based inks.

4.3.9 Decision 9: Outer Coating

An outer coating for the electrodes was desired in order to provide a physical protective layer for the electrode materials to prevent them from being removed during insertion of the nasogastric tube. This outer coating would also make the tip of the tube smoother and therefore enable easier and more comfortable passage of the tube for patients. There was the additional consideration that digestion of the coating would enhance the electrochemical reaction in the stomach. Earlier experiments prior to the commencement of this project and published papers (Ionescu, Cosnier & Marks 2006) suggested that gelatine enhanced the signal generated and through its digestion in gastric fluid revealed

fresh vitamin K_1. The function of the gelatine coating was therefore to "shield" parts of the electrode from the stomach environment, the idea being that as time passes, given that the immobilised vitamin K_1 may be digested, there is a requirement to provide a "fresh" source of this redox species. This would be achieved via the hydrolysis of the gelatine so that new immobilised vitamin K_1 is "uncovered", thereby allowing the device to retain long-term use.

Gelatine was identified as an appropriate gastrically degradable coating for a biosensor (Ionescu, Cosnier & Marks 2006) and recipes for different types of gelatine were explored (Gelatin Manufacturers Institute of America 2012). Concerns about the acceptability of animal derived products for certain groups in the population (Sattar et al. 2004) led to the decision to use a soft, non-animal derived alternative to gelatine, suitable for vegetarians.

The tips of half of the tubes were coated in a layer of commercially available vegetarian gelatine Vege-Gel™ (Dr. August Oetker Nahrungsmittel KG, Lutterstrasse 14, 33617 Bielefeld, Germany). This was prepared according to the manufacturer's instructions and applied to the last 5 cm of the distal end of the tube covering both of the electrodes. This outer gel coating was applied to the electrodes in two different amounts; one droplet and five droplets.

Ten tubes with titanium wires and 10 with stainless steel wires were prepared, half coated with Vege-Gel and half uncoated, for testing in laboratory and clinical experiments as described in Table 8.

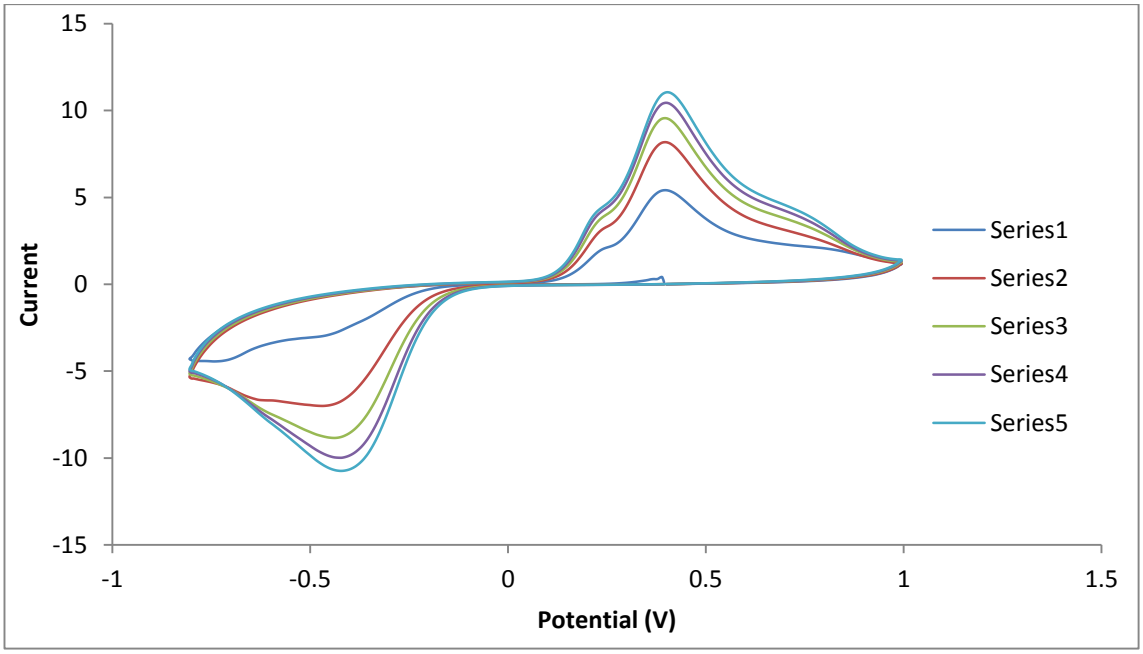
Design 2	**Wire material**	
	Surgical Stainless Steel	Titanium
Vege-Gel coated	5	5
Not coated	5	5
Total	10 tubes	10 tubes

Table 8: LINGT iteration 2 prototypes prepared

4.4 Laboratory Experiments

The prepared tubes were extensively assessed in the laboratory in different solutions (buffered and un-buffered) at varied pH from 0.5 to 8. They were also assessed in food samples with a range of pH values using the potentiodynamic electrochemical assessment measure, Cyclic Voltammetry (CV) by the PDRA. Artificial gastric juice was prepared according to an established recipe used for pharmaceutical development (Li et al. 1997) and the tubes were also assessed in this solution.

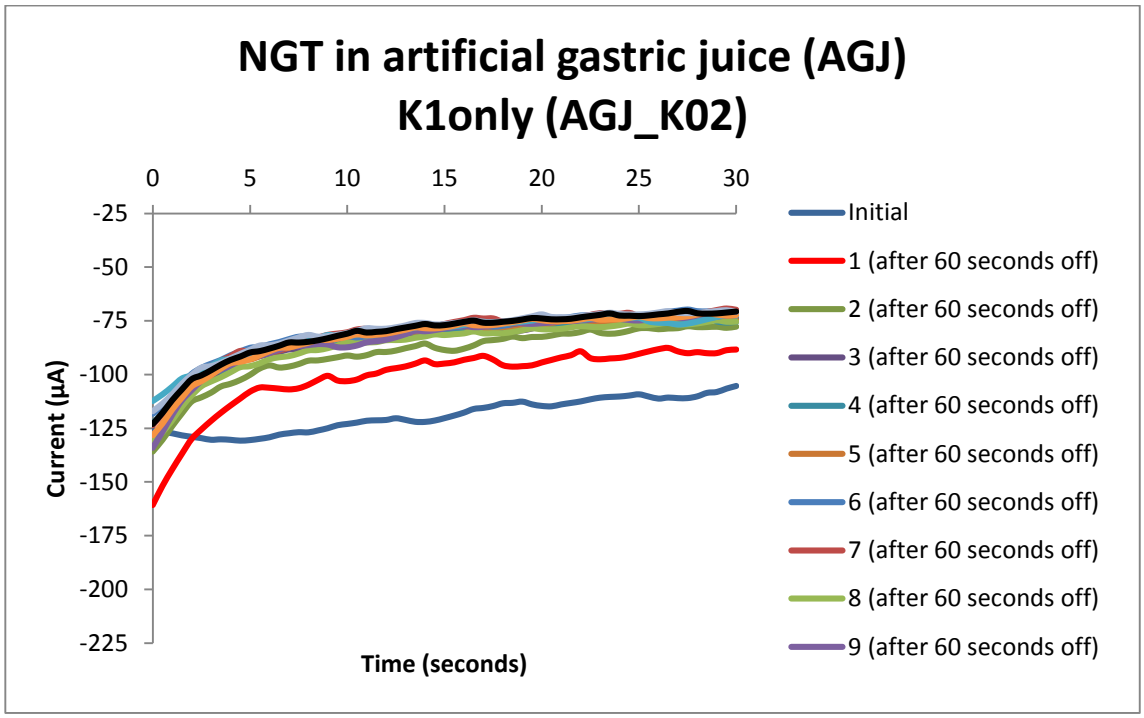
CV is a common electrochemical method used to investigate the initial chemical reactions occuring at an electrode surface. It can be used to determine the oxidation and reduction charactristics of compounds and the potential at which these processes occur (Bard, Faulkner 2001). The current at the working electrode is plotted against the applied voltage to give a cyclic voltammogram trace as shown in Graph 5.



Graph 5: Cyclic Voltammogram of vitamin K_1 coated electrodes in BR buffer solution pH 1

The reversible wave demonstrates the reduction followed by oxidation of the vitamin K_1 with peak reactions in this particular solution occurring at +0.4V and -0.4V. The repeat series of scans demonstrate the stability of the electrode over time.

The PDRA tested the tubes with the voltage being turned on and off. In practice it is envisaged that the indicator box will be connected to the end of the tube, turned on and once correct placement has been verified the indicator box will be turned off and detached from the tube to enable feeding to take place. It will not be re-attached until the next time placement needs to be verified ie at the time of the next feed. It was therefore important to explore the effect of turning the indicator box on and off and assess how quickly the current reached the expected value. Graph 6 shows the effect of turning the indicator box off and on.



Graph 6: LINGT iteration 2 in artificial gastric juice pH 3.5

These experiments were conducted by the PDRA so are not presented in detail as part of this thesis. The experiments suggested that stainless steel was likely to be the preferred wire material as results were more consistent and so 20 tubes were prepared for clinical evaluation in resected stomach tissue, 15 with stainless steel wires and 5 with titanium wires.

4.5 Clinical Experiments in Freshly Resected Human Stomach Tissue

4.5.1 Ethical considerations

A favourable opinion to conduct the study was granted by Leeds West NHS Research Ethics Committee on 23 February 2011 (Appendix 7) with an extension

granted in February 2012. NHS Research and Development approval was granted for the NHS Hospital on 31 July 2012 and management permission for the Private Hospital granted on 24 July 2012. Faculty of Health and Social Care Research Ethics approval was also granted.

All patients gave informed consent for their removed tissue to be used. As their surgery would not be altered by the research their participation only involved giving consent but a key concern was to ensure that the patients' surgery was conducted and continued as required by their condition and that the researchers caused minimal disruption to procedures in the operating theatre.

4.5.2 Methods

Patients undergoing bariatric surgery for the management of obesity at two local hospitals were identified as possible sources of stomach tissue to test the manufactured prototypes of the LINGT. Bariatric surgery involves reducing the capacity of the stomach by creating a small gastric pouch and bypassing a portion of the small intestine. The most common surgical procedure, the Roux-en-Y gastric bypass, involves stapling the upper stomach into a 30ml pouch and creating an outlet which connects to a lower part of the small intestine as shown in Figure 17 (Maggard et al. 2005). This procedure is often performed laparoscopically and generates weight loss by reducing gastric capacity, producing mild malabsorption and hormonal changes (Maggard et al. 2005). In some patients it is necessary to remove part or all of the stomach tissue during this procedure and it is this surplus, but healthy tissue, that was used to evaluate the nasogastric tubes. Discussions with local surgeons identified that small pockets of stomach tissue were often excised during this type of surgery and these would contain sufficient gastric fluid on which to test the prototype tubes.

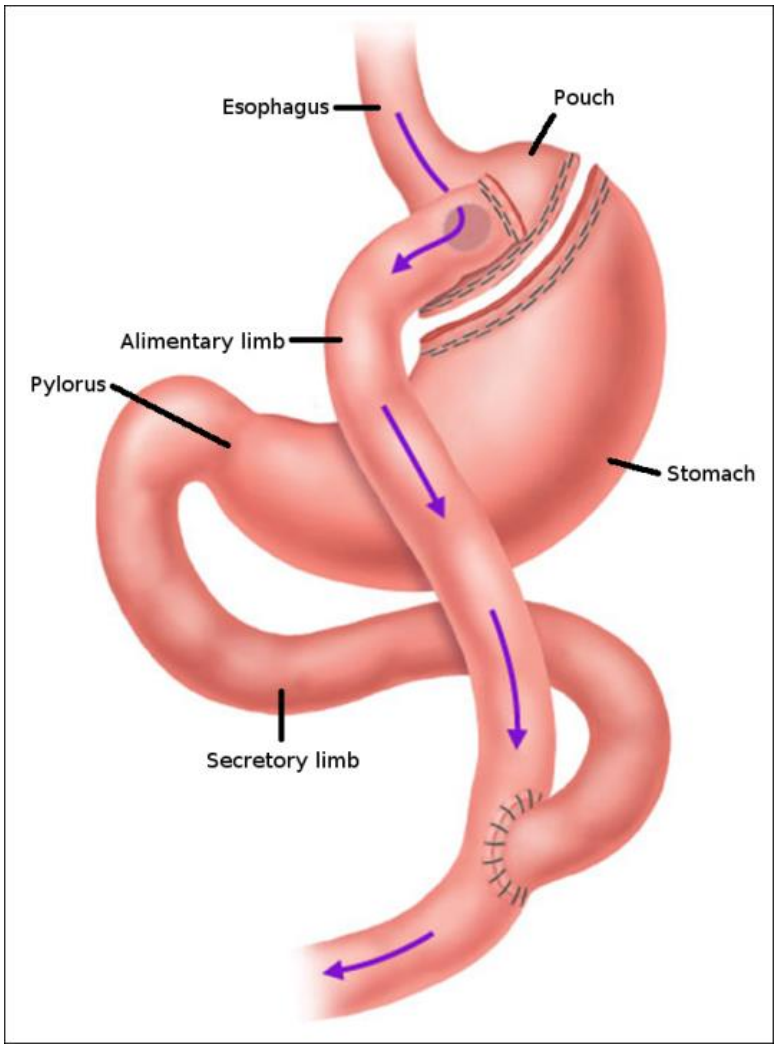


Figure 17: Roux-en-Y gastric bypass showing separation of small pouch of stomach from the main body and anastamosis of secretory limb

Although this procedure is an accepted and established method of managing clinically severe obesity (Wittgrove, Clark 2000) the number of such operations conducted in NHS hospitals has reduced in recent years and so patients were also recruited from the local private hospital.

The experiments on resected human stomach tissue was chosen, rather than animal testing, as the use of animal models could not be justified in this instance. The vast majority of drugs are tested on animal models before human patients are exposed to them but this is only considered to be justified if there is clear patient benefit, no alternative exists and suffering is minimised (Perel et al. 2006). The alternative of resected stomach tissue was readily available and the removed stomach tissue was to be disposed of as clinical waste. There is also concern regarding the discordance between animal and human studies which may be due

to bias or to the failure of animal models to mimic clinical disease adequately (Perel et al. 2006) and so it was considered that the results from resected human gastric tissue would be more applicable to future studies on *in vivo* human stomachs.

Suitable patients listed for bariatric surgery were identified by the consultant surgeon for inclusion in the study. Patients were recruited into the study according to the protocol (Appendix 8) between 14 October 2012 and 30 January 2013. Thirteen patients were recruited at the NHS hospital and six patients at the private hospital giving a total of 19 patients.

The Research Governance Framework (Department of Health 2005) and Good Clinical Practice Guidelines (National Institute for Health Research 2011) were followed

> *"Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible."*

(International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use 1996)ICH Guideline For Good Clinical Practice E6(R1) (1996)

The author, who was the Principal Investigator (PI), had undertaken GCP training in March 2012 and followed the requirements of the standard. She visited the patients on the ward or in clinic to explain the study and give them the information sheet (Appendix 9). She then returned the following day to seek informed consent. Each patient was given a unique research number (RS001-RS019) and only this number appeared on the data collection sheets and no other identifying information was included. Case Report forms were completed for all patients and signed by the PI (Appendix 10). Case Report Forms were stored in a locked cabinet in a locked office in the University of Hull according to the University of Hull Data Management Policy and GCP guidelines. Electronic versions were

stored on a password protected University of Hull centralised computer system (i.e. not an office computer hard drive). No patient details, except age within 5 year bands was recorded. Investigator Site Files were created for both sites and consent forms stored in a locked cabinet in a locked office at University of Hull. All patients gave consent for their General Practitioners (GP) to be informed and the REC approved GP letter was sent to all patient GP's as soon as possible after their surgery (Appendix 11).

Small amounts of stomach tissue removed in the course of bariatric surgery were immediately assessed in theatre after removal by the author and PDRA. The samples obtained were generally small pockets of tissue approximately 2 inches square. Once the surgeon had removed the tissue and given it to the researchers the patient's surgery continued uninterrupted. A prepared LINGT was inserted into the stomach tissue and held in place by the author to ensure that it remained in contact with the gastric fluid. Two samples were larger "sleeves" of stomach tissue which gave much higher readings and for longer periods of time. The external end was initially connected to the prototype indicator box and recordings taken every 30 seconds. However after the first 4 samples it was agreed that it would be useful to obtain more detailed information including cyclic voltammograms and so a potentiostat was used for patients RS006 –RS019.

The majority of tubes had stainless steel wires but 5 with titanium wires were prepared for comparison and 2 of each type of tube were prepared with a gelatine coating. Table 9 gives details of the tubes used for the clinical evaluation studies. Each tube was given a unique identifying number and was prepared in an identical manner. The tubes were used only once and then disposed of in clinical waste. This was due to concerns regarding infection control and a need to ensure that each tube was prepared in exactly the same way with no contamination. It was not considered appropriate to attempt to reuse the tubes as they were heavily contaminated with blood and gastric fluid after the experiments. Each patient tissue sample was only used for one tube.

	20 Prototype Tubes (design 1) for experiments in resected stomach tissue			
	15 tubes with surgical stainless steel wires		5 tubes with titanium wires	
	13 without Vege-Gel	2 with Vege-Gel	3 without Vege-Gel	2 with Vege-Gel
Fixed PD of +0.64 V	RS001 RS002			
Varied PD	RS009 RS010 RS011 RS012 RS014 RS015 RS017 RS019	RS013 RS016	RS003 RS007 RS008	
Not used as no patient tissue removed	RS004 RS005 RS006			RS018 RS020
RS001 – RS019 patient research code numbers PD= potential difference				

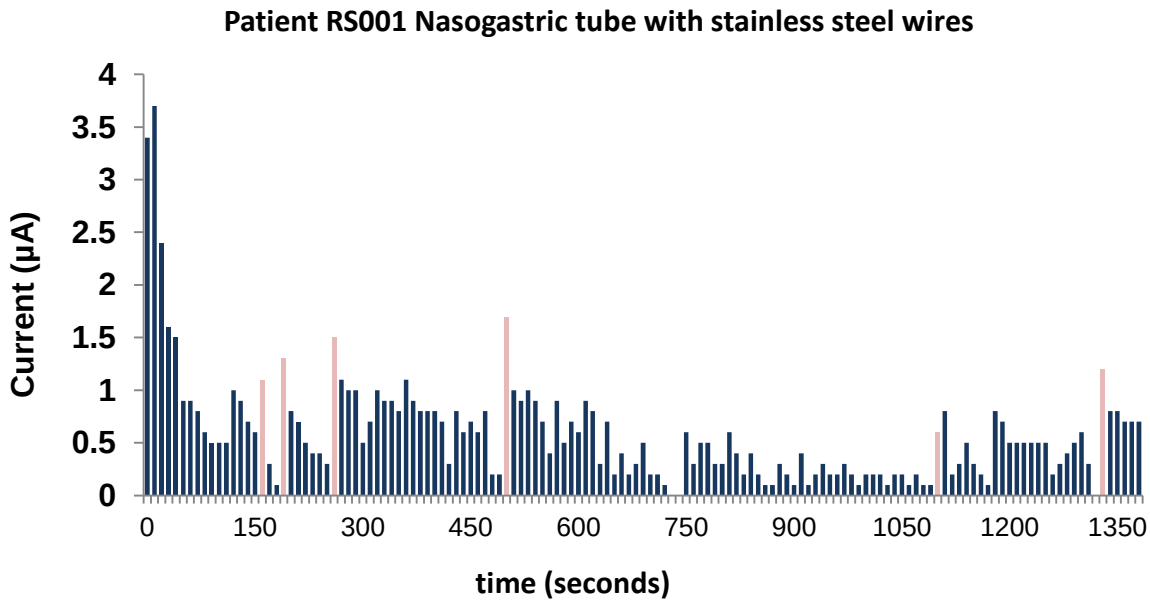
Table 9: Tubes prepared and used

The author and PDRA conducted the assessments within 30 minutes in a room adjacent to the operating theatre in order to minimise any disruption to theatre staff. No patient tissue or fluid was removed from the operating environment. On completion of the assessments the gastric specimen was disposed of in the normal way.

4.5.3 Results

The aim had been for a sample size of 20 patients and 19 were recruited. Four patients (RS004, RS005, RS006 and RS018) did not have tissue removed and so could not be included in the study. Current readings were obtained from stomach tissue removed from 15 patients and analysed.

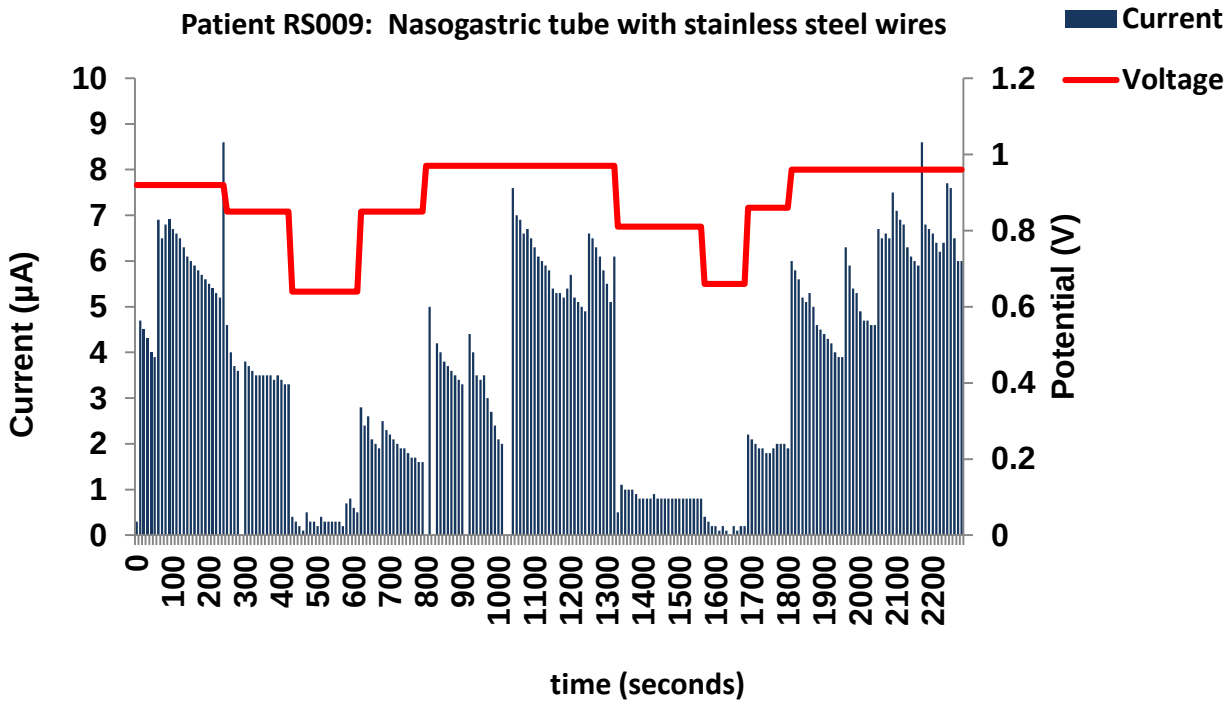
Amperometry is based on the principle that a specific substance oxidises or reduces at metal surfaces, at a specific potential, that is characteristic of that chemical species. An appropriate potential is held constant between the working and reference electrode to generate a diffusion limiting current. A potential difference of +0.64 Volts had been used with iteration 1 (discussed in chapter 3) and this was used for the first 2 patients (RS001 and RS002) with iteration 2. A tube with stainless steel wires was used for these first two patients and the PD was set at 0.64V. Graph 5 shows the current generated at this fixed potential difference. The red bars indicate when the tube was repositioned and the gaps indicate when the tube was removed (intentionally or inadvertantly) at 750 and 1350 seconds. After an initial current of 3.5 microamps the current stabilised at readings between 0.1 and 1.5 microamps.



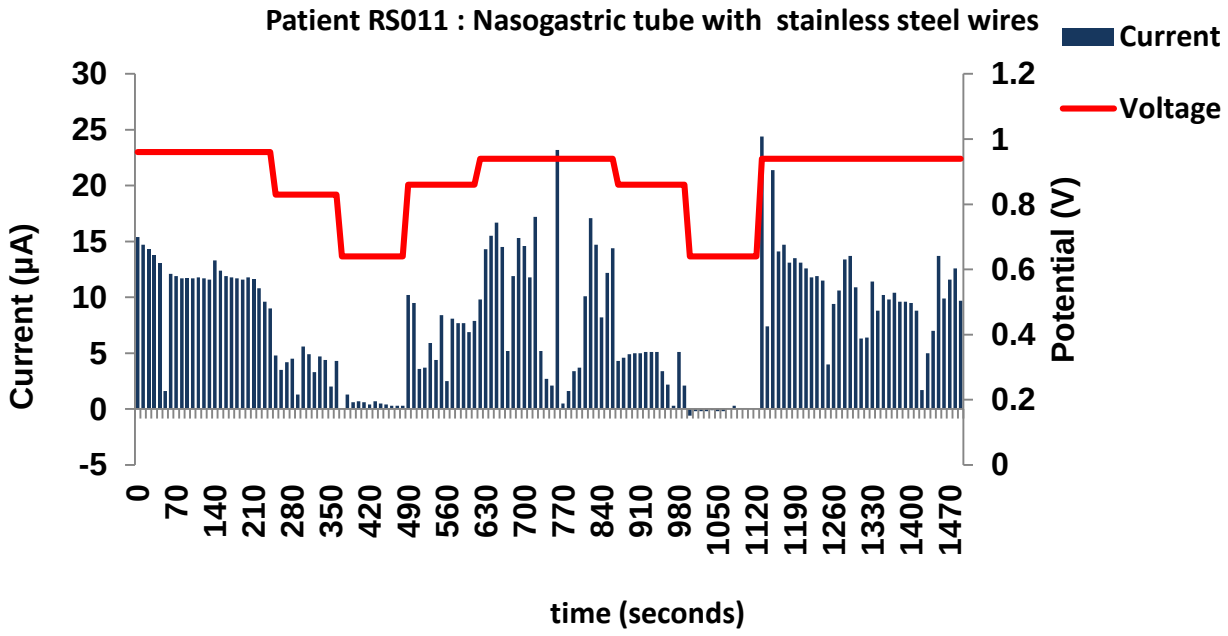
Graph 7: Current generated by nasogastric tube with stainless steel wires in gastric tissue for 24 minutes at fixed potential difference of +0.64v

Similar very low current readings were obtained with patient RS002 with a PD of +0.64V and the PDRA suggested varying the potential difference based on the results of her experiments in buffer solution. The current generated in phosphate buffer solutions of different pH values and at varying potential differences showed that the clearest distinction between acidic and basic pH's was obtained with a PD of 0.7V or 0.8V and so it was agreed that future experiments would vary the potential difference by stepping it down and then up again in order to evaluate the impact of different PD on the current generated. This procedure was carried out with the next 13 patients and Graphs 6, 7 and 8 are illustrative of the effect of the change in PD on the current generated. The potential difference was set on the indicator box and readings were recorded every 30 seconds for upto 30 minutes. A potentiostat was used in addition to provide varied potential difference and run Cyclic Voltammograms to give greater information for samples RS006-RS019. The tubes were repositioned at set intervals and the current increased as the electrodes came into contact with more gastric fluid. In all cases when the tube was removed from the tissue the current dropped immediately to zero.

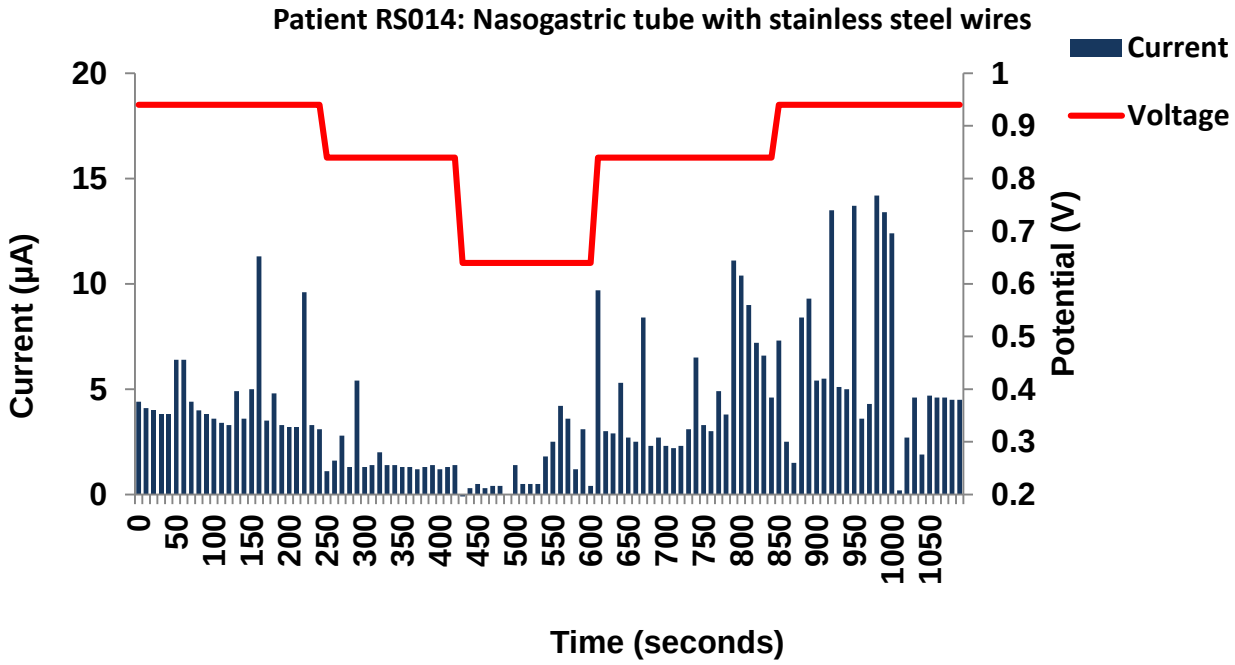
All of the tubes generated a signal (current) when placed in stomach tissue. However the range of current generated varied both between samples and in the same sample over time. The following Graphs give examples of readings obtained from tubes with stainless steel wires (Graphs 6 - 9) with varied PD.



Graph 8: Current generated by nasogastric tube with stainless steel wires inserted into gastric tissue for 30 minutes and PD varied between 0.64v to 0.97v



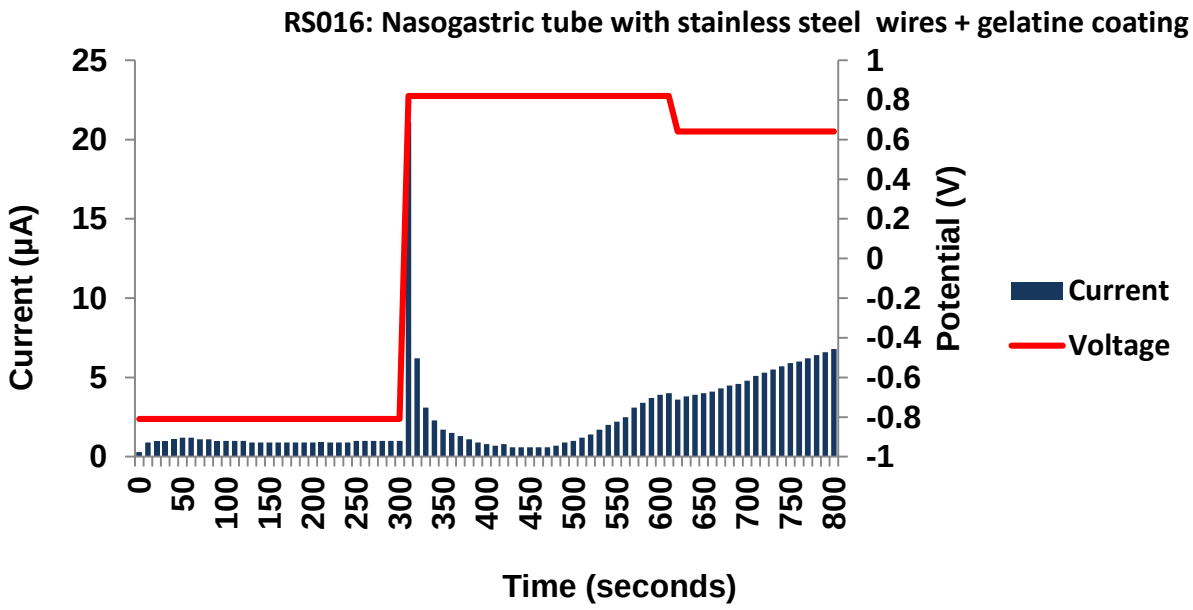
Graph 9: Current generated by nasogastric tube with stainless steel wires inserted into gastric tissue for 24 minutes and PD varied between 0.9v and 0.64v



Graph 10: Current generated by nasogastric tube with stainless steel wires inserted into gastric tissue for 17 minutes and PD varied between 0.94v and 0.64v

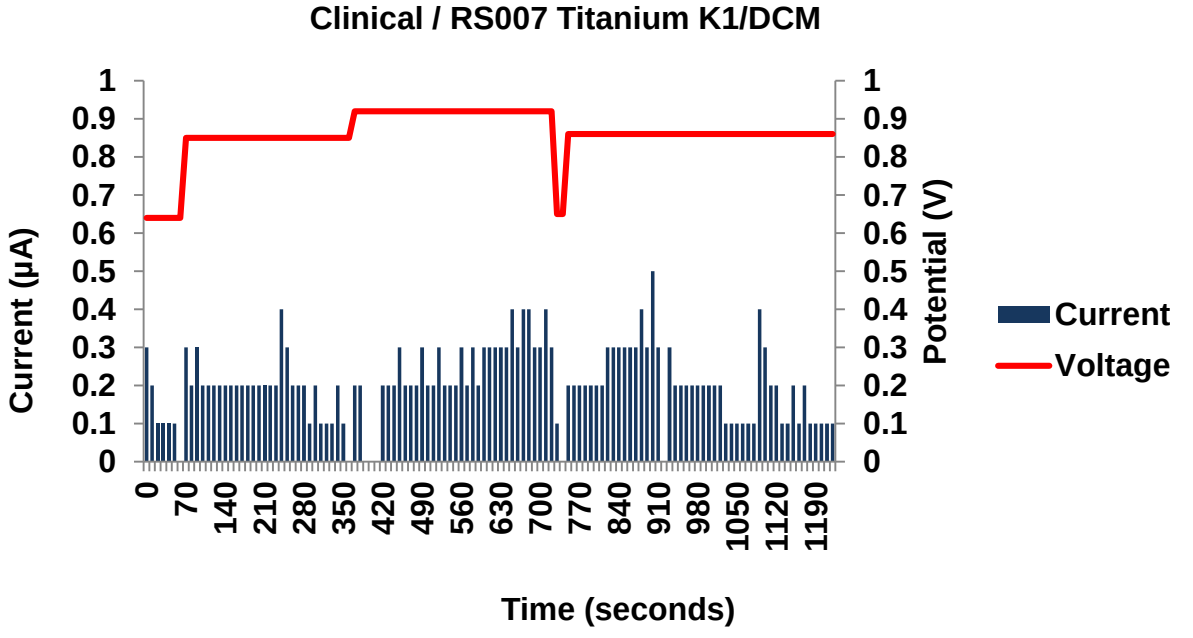
Eight tubes with stainless steel wires were tested in this way with varied positive potential difference and all responded in a similar fashion. It was clear that the system worked and that the sensor was responding to the change in PD; as the current varied when the PD varied but at 0.64V the current generated was relatively low. The indicator box alone was used for the first 5 patients but, as this could only generate positive PD, a potentiostat was used for the remaining patients and negative PD tested in some cases.

Tubes with stainless steel wires coated in gelatine were also tested in a similar fashion and an example of the results presented in Graph 9. The gelatine coating appeared to reduce the signal rather than enhance it as had been hoped and there was a delay in the response.



Graph 11: Current generated by nasogastric tube with stainless steel wires coated in Vege-gel inserted into gastric tissue for 13 minutes and PD varied between -0.8v and +0.8v

The titanium wires did not provide a consistent response when the PD was varied. Graph 10 gives an illustration of the very low response achieved with titanium wires.



Graph 12: Current generated by nasogastric tube with titanium wires inserted into gastric tissue for 30 minutes and PD varied between 0.64 V and 0.9 V

4.5.4 Discussion

Whilst it was clear that the system worked, the variation in the size of tissue samples obtained and the amount of gastric fluid within those samples made it difficult to make comparisons and draw appropriate conclusions. It had been hoped that gastric tissue samples would provide a close proxy for real life insertions into the stomach. However, even though the tissue was freshly resected, some of the samples were very small (approximately 1 inch square) pouches of tissue with minimal gastric fluid and others were large sleeves of stomach tissue containing several millilitres of gastric fluid. It was therefore decided to obtain samples of human gastric fluid to test in the laboratory under controlled conditions. The tubes would also be tested in sputum for comparison.

The gelatine coating did not appear to enhance the signal as was expected and discussions with Richard Reece-Jones (Toxicologist), Professor Vesselin Paunov at University of Hull and the project team were conducted in order to evaluate the benefits and risks of using the outer gelatine coating. Initial laboratory studies reported earlier used both commercially available gelatine and vege- gel.

Table 10 summarises the requirements and outcomes of the discussion. The problems of greatest concern were the response time of the electrode and the adherence of the outer coating to the underlying tube material (polyurethane). Alternative outer coatings were considered such as porous sponge, foam or mesh which could be wrapped around the electrode tip. However discussions with manufacturers of nasogastric tubes suggested that this was not a viable option due to risk of dislodgement in the gastrointestinal or respiratory tract. Hence it was decided not to use any outer coating for the next iteration of the tube.

Proposed requirements:	Outcome from discussions:
• Non-animal derived material • Easily obtainable • Non-toxic and biocompatible • High purity for medical application • Synthesis at room temperature • Non-complex handling properties	There is a large range of materials available which would be of sufficient purity/medical grade. Overall, these requirements are not perceived as a problem.
• Permeable to gastric fluid	Gels/Hydrogels can be made permeable to gastric fluid. However it would be challenging to get a short electrochemical response time.
• Chemically stable in acidic conditions	Compromises have to be made, which could be achieved to an acceptable level.
• Mechanical integrity sufficient to be passed in and out of stomach	The mechanical properties of gels/hydrogels are in general not considered to be good. However, there are options to improve these properties to a certain level.
• Adherence to polyurethane tubes	This was considered as the biggest problem as gels/hydrogels tend not to adhere well to polyurethane. However, the surface of polyurethane could be modified to achieve adherence – there is a large amount of literature available (for example polyacrylate could be used).

Table 10: Summary of considerations for outer coating

4.6 Clinical Experiments in Samples of Human Gastric Fluid and Sputum

The objective of this phase of the project was to establish that, when the tip of a prepared NGT was placed in human bodily fluid, specifically gastric fluid or pulmonary secretions, the reaction between the tip of the tube and the fluid can be detected and measured by the indicator box and/or potentiostat attached to the other end of the tube. Comparison of current measurements obtained in gastric fluid and those obtained in fluid from the lungs formed the basis for calibration of the external indicator box.

4.6.1 Methods

Ethical approval was granted by South Berkshire NHS Research Ethics Committee (Appendix 12). Initially one local hospital was to be used but in order to access sufficient samples an additional hospital was added and a Site Specific Form completed.

Fluid is routinely removed from patients' stomachs before upper gastrointestinal surgery and post operatively to prevent vomiting and discomfort if the gastrointestinal tract is not functioning adequately. This fluid is measured and then immediately disposed of as clinical waste. This gastric fluid was removed and measured by ward staff in the normal way and the author collected fluid samples from 7 post-operative patients on the surgical ward of the local hospital and took them to the onsite laboratory where they were stored in an identified fridge designated for biological samples. The samples were then used for laboratory tests of the LINGT before being disposed of as clinical waste. An additional 14 samples were sent in Safeboxes^{TM} (supplied by Royal Mail) from the second hospital using secure postal delivery system.

Patients with respiratory problems often produce excessive sputum which they cough into sputum pots which are then disposed of as clinical waste. Three samples of sputum were collected before disposal and, as with the gastric fluid samples, taken to the onsite laboratory and used for laboratory tests of the LINGT before being disposed of as clinical waste.

In line with Good Clinical Practice patients were given information sheets (Appendix 13) and informed consent was requested even though their treatment

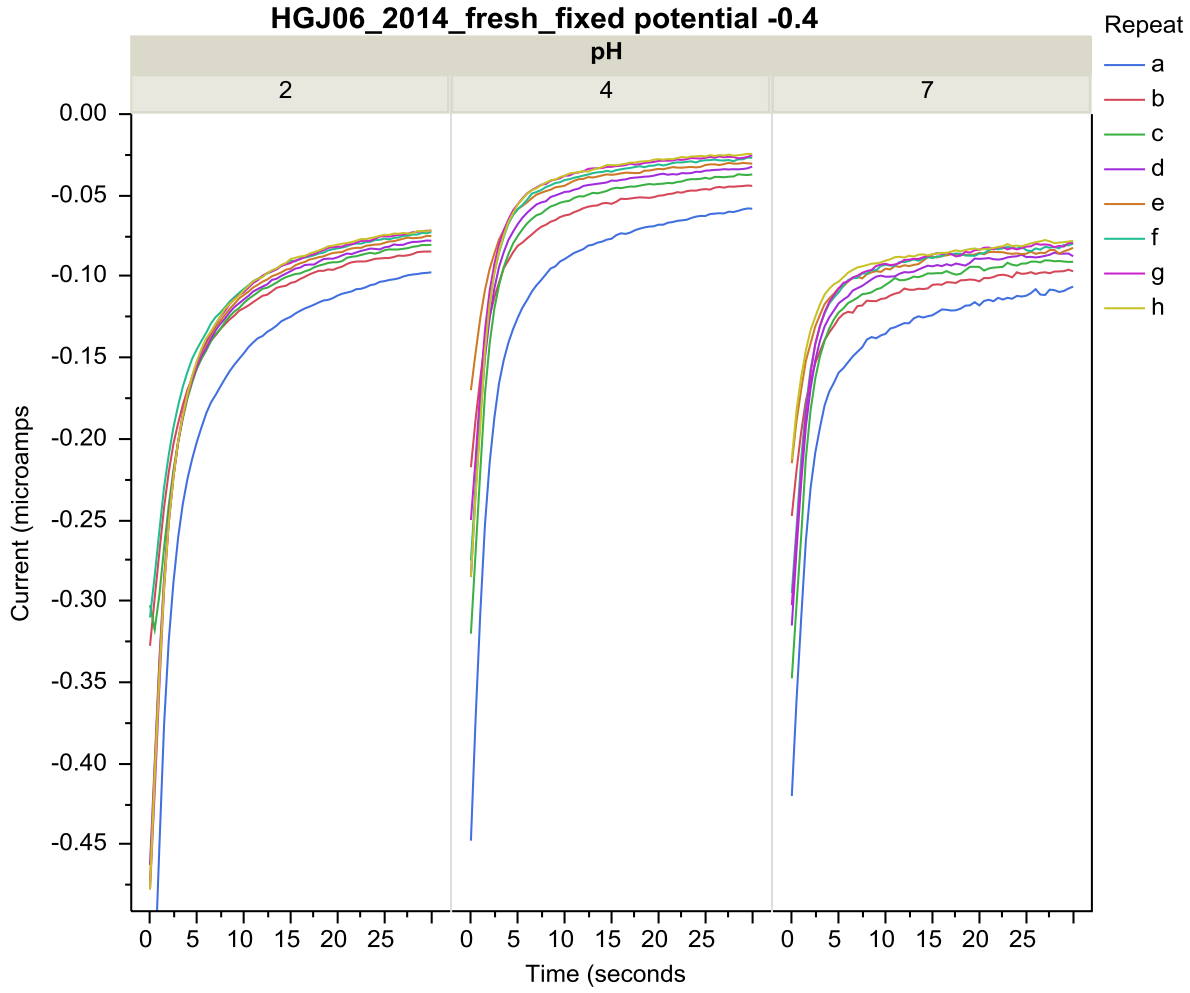
was not affected in any way by participation in the study. They did not receive any intervention for purposes of research and no personal information was collected from or about them. No additional fluid was removed for the research study and no diagnostic tests were performed on the fluid as part of the research. If fluid was required for pathological investigation this sample was collected by ward staff prior to the author being given the remaining fluid. Only fluid destined for clinical waste was used for research purposes. Case Report Forms were completed for all patients participating and stored in accordance with GCP Guidelines (Department of Health 2005). Letters were sent to the patients' General Practitioners following written consent.

The electrochemical response of 20 LINGT, prepared in an identical manner in accordance with documented work instructions (Appendix 6), was assessed in 17 fresh samples of human gastric fluid and 3 samples of human sputum. The sample fluid was used as received for the first measurement and then the pH of each sample was altered with 0.1M hydrochloric acid or antacid (milk of magnesia) to obtain pH values of 1, 4 and 7. The experiment was conducted by the PDRA in Class II biological safety cabinet Biological Safety Cabinet at 37^0C, the pH was measured using a pH indicator strips.

4.6. 2 Results

Initially the first 10 LINGT were assessed using amperometry as in sections 3.4, 3.5 and 4.5. These experiments found the following:

- discrete differences in current readings of sputum samples were observed at pH1 in comparison to pH 4 and 6
- current readings of sputum samples obtained at pH 4 and 6 did not show significant differences in relation to each other
- most current readings of gastric juice samples showed no differences at pH 4 in relation to pH 6
- current readings taken from gastric juice samples (pH 0.5 to 2) showed differences in current readings compared to pH 3/4, however not to those obtained at pH 6
- the transition occurred at pH of ~2.2



Graph 13: Current generated by nasogastric tube inserted into fresh human gastric fluid

These results (example shown in Graph 13) were disappointing as the threshold for change needed to be at pH5 with a clear difference between currents generated at acidic and basic pH. Whilst there was a shift in the level of current between pH2 and pH4, the values returned to similar levels at pH7.

It is essential that the system can distinguish between pH values in the stomach (less than or equal to pH 5.5) and pH values in the respiratory tract, oesophagus or duodenum. The critical route forward was to increase the transition range. To accomplish that, a tenfold increase in Vitamin K_1 (10mM instead of 1mM) concentration was agreed to increase the current output. Further human gastric fluid samples were assessed for electrochemical response with 10 fully prepared nasogastric tubes microspotted with 10mM K_1 instead of 1mM.

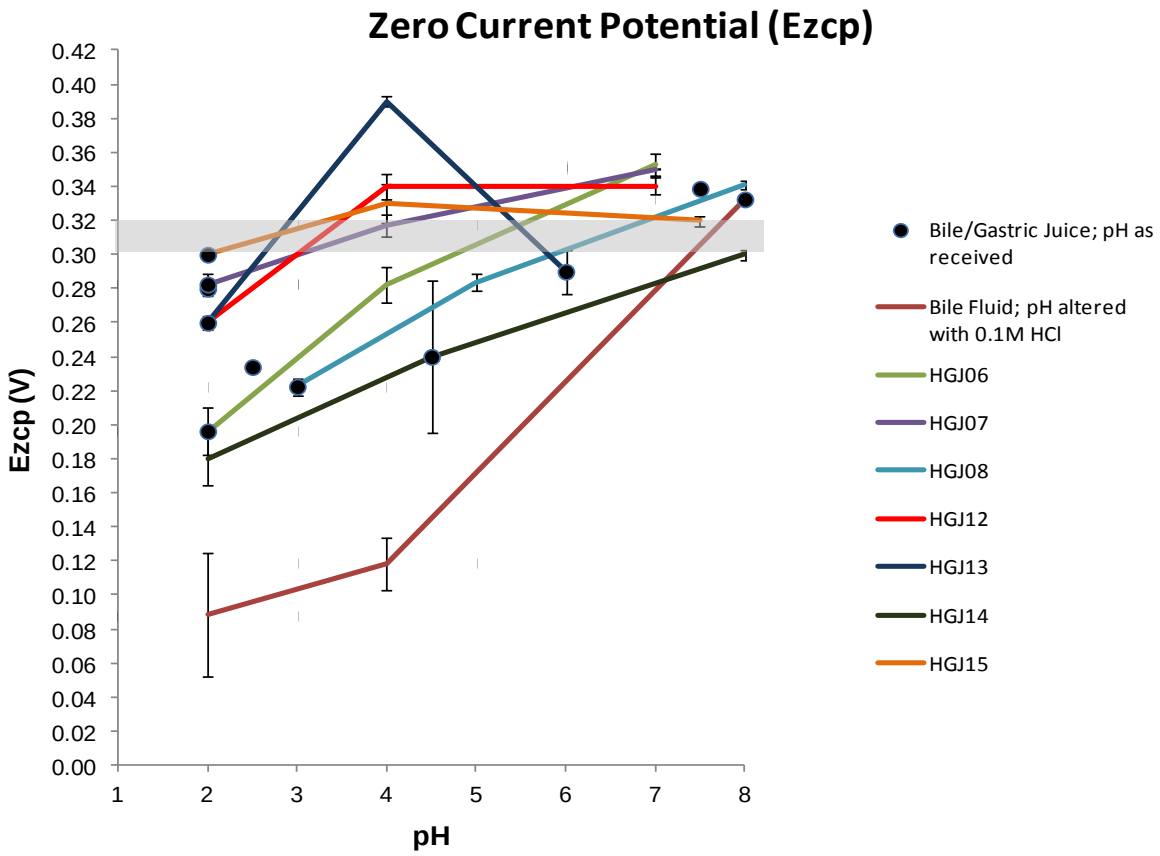
The amperometric evaluation with the gastric fluid samples as received showed some unexpected results. The average current generated by 1mM K_1 coated electrodes in fresh gastric fluid (readings taken from sample as received) showed the lowest reading at pH2 and higher readings at pH 3-4. The 10mM Vit K_1 coated electrodes however generated the lowest current reading at pH4 and the highest reading at pH2 – in a near reversed behaviour.

These amperometric studies with fresh gastric fluid samples showed that all samples with 1mM vitamin K_1 exhibited current readings with increasing pH but there were not clear and distinct differences at varied pH. However, two out of four of the nasogastric tubes with 10mM concentration of vitamin K_1 showed distinct (and desirable) readings according to varied pH.

These experiments suggested that, whilst the prepared nasogastric tubes were in full working order; it was possible that the sample liquid was causing some unexplained electrochemical behaviour due to individual patient differences. Further experiments were therefore conducted in order to optimise the signal strength and enhance the reliability of the system.

The PDRA suggested that, rather than using amperometry, the zero current potential ($E_{zcp)}$ should be used. This is a relatively new method which measures the potential (V) at which the current value reaches zero, and has been successfully used to monitor acid-base properties (Wu et al. 2013). The E_{zcp} is recorded using Linear Sweep Voltammetry (LSV) which is a method in which the current at a working electrode is measured whilst the potential between the working electrode and the reference electrode is swept linearly in time. The experimental setup for LSV utilised a potentiostat with a two electrode configuration; a reference electrode to which the auxiliary electrode lead of the potentiostat was connected and a working electrode connected to the working electrode lead. The linear sweep was set to run from +0.4V to -0.4V with a scan rate of 0.1 V/s; Estep 0.005V. This method produced stable and repeatable readings with a clear distinction between pH levels. Gastric fluid samples were evaluated as received and then the pH was adjusted with 0.1M Sodium Hydroxide to raise the pH and hydrochloric acid to lower the pH. In this way 9 samples of gastric fluid produced 27 readings.

Graph 14 shows the range of E_{zcp} in samples as received and with altered pH.



Graph 14: Zero current potential of 9 samples of gastric fluid demonstrating clear differences between acidic and basic pH

Zero current potential using LSV was obtained within the time frame of 1-4 seconds and was therefore quicker than the previous method of amperometry which took over 60 seconds to stabilise. The results illustrated in Graph 14 show that any value below +0.3V (E_{zcp}) is considered to be pH 5 or less and any value above +0.34V is considered to be pH 6 or over. The values in between are displayed in grey; which is ±0.02V. This makes the detection range for the LINGT to measure pH5 or less and so verify stomach placement at E_{zcp} up to +0.32V ±0.02.

4.6.3 Discussion

The clinical experiments in human gastric fluid and sputum enabled closer examination of the functioning of the system in biological samples. Assessment of the electro-chemical reaction was explored initially with amperometry and

refined with E_{zcp} which proved to be a better assessment of pH than amperometry. The initial tests using amperometry demonstrated that the system worked, but E_{zcp} gave a clearer distinction between pH values in the required range and this measurement was used to calibrate the final indicator box. It was not possible to fully characterise the biological samples and individual patient differences in condition and medication will have influenced the results.

The results were discussed with a statistician to determine the number of samples which will be required to give 95% confidence levels to the range of E_{zcp} associated with pH values lower than pH 5. He conducted calculations using the formula

$$\left[1+\frac{1}{n}+\frac{(x_0-\bar{x})^2}{\sum(x_i-\bar{x})^2}\right]\times\sigma^2$$

where n is the sample size, $\bar{x}$ is the sample mean E_{zcp}, $\sum(x_i-\bar{x})^2$ is the sum of squares of the E_{zcp} observations about their mean and σ^2 the error variance (Rawlings, Pantula & Dickey 1998) equation (1.35).

Following these calculations he recommended testing another 40-50 samples and such experiments are planned as part of the final evaluation of the system when full characterisation of the samples will be undertaken. However a pragmatic decision had to be made in order to progress the project and further electrochemical evaluation was not considered appropriate at this stage.

4.7 Conclusion

This chapter has considered the design of the manufactured prototype of LINGT iteration 2 and the experimental tests conducted on 60 such tubes in the laboratory and with clinical samples. The design options for the tube were considered and the decisions made explained. The design of LINGT iteration 2 has been optimised through an iterative process of laboratory experiments with buffer solutions and artificial gastric fluid and clinical experiments with resected stomach tissue, human gastric fluid and sputum. It has been demonstrated that LINGT iteration 2 can generate an electrical signal when in gastric fluid which is

distinct from that generated at other pH values. A design with stainless steel wires and no gelatin coating has been identified as the most appropriate. This forms the basis for the design freeze of LINGT iteration 3, the final manufactured prototype, which is discussed in chapter 7 following consideration of the commercial and quality management issues and user involvement in the next chapters.

Chapter 5: Regulatory Approval and Commercialisation

5.1 Introduction

The UK Government and health charities spend over £2 billion a year on research, which has produced many new and improved ways of delivering healthcare. However in order to develop a concept or idea through to a marketable medical device there are a great number of procedures and processes to be adopted and challenges to be met. Not least of these is the process of gaining regulatory approval. Regulatory approval for a medical device may be defined as the processes for gaining market authorisation within a given jurisdiction (Henshall et al. 2011) which involves evaluation of the device prior to it being made available to purchase. Such processes are essential for the protection of patients and even with these systems in place there remains concern about the introduction and adoption of certain medical and surgical devices before full evidence of safety and effectiveness is available (Ross et al. 2010).

There are concerns that current regulatory systems are too lax which have led to proposals to raise the level of this pre-market evaluation (Dhruva, Bero & Redberg 2009). On the other side of the argument there is anxiety that regulatory approval processes are daunting and a heavy burden on academic researchers (Arbit, Paller 2006) and may delay or even prevent the translation of basic science discoveries into novel therapies and devices (Stack, Harrington 2011). This tension between protecting patients from unsafe or ineffective medical devices whilst enabling them to benefit quickly and efficiently from new technologies and innovations is a difficult challenge to meet and a consistent approach that balances the pace of medical device development with sufficient safety data relevant to clinical practice is lacking (Krucoff et al. 2012). This chapter critically considers the current regulatory system in Europe with some discussion of that in the United States of America (USA) and discusses the procedures undertaken to gain regulatory approval for the Location Indicating Nasogastric Tube (LINGT).

Regulatory approval is only the first stage in getting a product used by healthcare professionals. The next stage is ensuring adoption by healthcare providers and

this is essential if benefit to patients and financial reward to companies is to be achieved. A key issue for companies manufacturing innovative medical devices is getting healthcare providers to adopt such devices. Even if there is clear evidence of significant patient benefits barriers to adoption may prevent its use and integrating new devices into health delivery can be a difficult transition (Dymond et al. 2012). Unfortunately services often fail to introduce new technologies and the reasons for such failure are rarely clear (Henshall et al. 2011). Being able to negotiate through the technology adoption process is vital and support is now provided through the Health Technologies Adoption Programme (National Institute for Health and Care Excellence (NICE) 2013). The processes for determining which interventions will be provided and paid for in a particular healthcare system is referred to as coverage. Health Technology Assessment (HTA) refers to the collection and analysis of information to enable those responsible for coverage decisions to make scientifically sound and transparent decisions (Henshall et al. 2011).

This chapter focuses on the process of gaining regulatory approval for the LINGT and the challenges of finding a suitable commercial partner to manufacture the device. Whilst the aim of developing the device was always to enable as many patients as possible to benefit from it through HTA and coverage these aspects will only be discussed with regard to their impact on commercialisation. Detailed consideration of HTA and coverage will be undertaken by the final commercial partner when marketing the device and are beyond the scope of this PhD thesis.

5.2 Regulatory Approval

Virtually all developed countries have regulatory systems for the approval and monitoring of medicines and medical devices in order to protect the public by ensuring that all products used in healthcare meet specified standards of safety and performance (Henshall et al. 2011). In Europe regulation is through the three European Directives; the Medical Devices Directive 93/42/EEC, the Active Implantable Medical Devices Directive (90/385/EEC) and the *In Vitro* Diagnostic Medical Devices Directive (98/79/EC) (The Council of the European Communities

1993). Each European Union (EU) state is responsible for overseeing this legislation.

Regulation of medical devices has been in existence for over fifty years in the UK. The Scientific and Technical Branch (STB) was established in the late 1960s to improve the quality and safety of medical equipment alongside the Department of Health. During the 1980s, the STB became part of the NHS Procurement Directorate and was later divided into the NHS Supplies Authority and the Medical Devices Directorate (MDD). The MDD became the Medical Devices Agency in 1994 before joining the Medicines Control Agency (MCA) in 2003 to become the Medicines and Healthcare Products Regulatory Agency (MHRA) (MHRA 2013).

5.2.1 Classification of Medical Devices

Medical devices are classified in Europe and the USA based on the risk they pose to patients with class III devices posing the greatest risk in both jurisdictions. In USA there are three regulatory classes defined by legislation, class I being low risk (for example stethoscopes), class II are medium risk (for example endoscopes) and class III are perceived to be high risk (for example pacemakers) (Maisel 2004).

In Europe medical devices are divided into four classes:
Class I - generally regarded as low risk
Class IIa - generally regarded as medium risk
Class IIb - generally regarded as medium risk
Class III - generally regarded as high risk

(MHRA 2013)

Classification determines the procedures required to demonstrate conformity and depends upon a series of factors, including:

- how long the device is intended to be in continuous use
- whether or not the device is invasive or surgically invasive,
- whether the device is implantable or active
- whether or not the device contains a substance, which in its own right is considered to be a medicinal substance and has action ancillary to that of the device.

The major difference between class IIa and class IIb devices is concerned with the length of time in the body. Annex IV of the Medical Devices Directive details the rules governing the classification of devices with rule 5 relating to invasive devices with respect to body orifices (The European Commision 1993). The LINGT was classified as a IIa medical device by the author with advice from an Independent External Consultant, Professor David Young (DY) as it is intended for short term use (less than 28 days). Devices intended for long term use (over 28 days) are classed as IIb. The appropriate classification form completed as part of the regulatory assessment (Appendix 14).

5.2.2 European Regulatory Approval

Article 14 of the Medical Devices Directive 93/42/EEC stipulates that it is a legal requirement that manufacturers (or their authorised representatives) placing certain types of medical device on the EU market, provide specific information to a competent authority (in the UK the MHRA) through registration. Registration is a self-declaration process whereby manufacturers and their authorised representatives determine that their product falls within the definition of 'medical device' or '*in vitro* diagnostic medical device', and that they have classified them as falling within Regulation 19/44 of the Medical Devices Regulations (SI 2002 No. 618) taking into account the intended purpose(s) and mode(s) of action. For the very lowest risk devices, such as unmedicated bandages registration with the MHRA may be all that is required but for the majority of devices an independent, certification body called a Notified Body must verify the manufacturer's claims about the device to ensure that it meets all the requirements for Conformeté Européenne (CE) marking.

Medical devices cannot be marketed in Europe without carrying a CE mark. This mark is applied by the manufacturer to demonstrate that the device meets the relevant regulatory requirements and, when used as intended, works properly and is acceptably safe (MHRA 2012). There are currently 74 Notified Bodies, who can verify these claims designated for 25 European countries with 6 in the UK (Heneghan et al. 2011). The MHRA is responsible for appointing UK Notified Bodies and regularly audits them to ensure that they perform to appropriate standards. Under European legislation Notified Bodies assess whether applications for medical devices meet the required standard by reviewing

materials and documents supplied to them by the manufacturer. The manufacturer selects which Notified Body to apply to and once this premarket evaluation is carried out the device can be sold in the entire European market. Notified bodies are not supposed to offer a consultancy service on how to receive certification but there is some evidence that this may be occurring in a few European countries (Cohen 2012).

The European regulatory system has come under criticism as not all Notified Bodies work to the same level of approval and Competent Authorities, such as the MHRA, are aware that companies can select a less stringent Notified Body for a particular device (Tinkler 2009, Cohen, Billingsley 2011) A further criticism is that, unlike in the USA evaluation of clinical efficacy is not part of the EU regulatory system for medical devices, as verification only focuses on safety and performance (Hulstaert et al. 2012). This leads to different requirements for clinical trials and devices receiving approval in Europe years before such approval is granted in the USA resulting in earlier market introduction in Europe than USA (Hulstaert et al. 2012). However a positive risk benefit profile for patients is required in Europe (see section 5.5 Risk Management) and is part of the regulatory approvals system. Europe's efficient decentralised approval system which results in early market introduction is viewed as crucial by the world's medical device manufacturers as it enables them to launch their products in a timely manner and prove to investors that their products serve patients well and are financially viable (Woods 2013, Beyond Compliance 2014).

In spite of EU regulatory approval resulting in earlier market introduction of medical devices it does not guarantee that a product will be recommended by HTA bodies or approved by coverage bodies and there are many products that have regulatory approval but have not been adopted by healthcare systems (Henshall et al. 2011). This is in part because HTA and coverage bodies require further evidence of clinical benefit than that needed for regulatory approval in the EU and post marketing data collection is becoming increasingly important.

UK government agencies involved in healthcare, including the National Patient Safety Agency (NPSA) and the National Institute for Health and Clinical Excellence (NICE) work with the MHRA to protect the UK public. It is recognised that no healthcare is completely without risk but these agencies work to ensure

that UK healthcare, including the use of medical devices, is as safe as possible. There is growing recognition that whilst the CE mark identifies compliance more is needed in order to monitor risk and constantly evaluate the performance and efficacy of medical devices and the safest, best and most successful systems are those that always go beyond merely complying to the bare minimum that regulations require (Beyond Compliance 2014). Evidence of effectiveness is frequently sought for coverage decisions but HTA agencies are often faced with a lack of high level clinical evidence when assessing the value of high risk medical devices when they come onto the European market (Hulstaert et al. 2012).

5.2.3 The Medicines and Healthcare Products Regulatory Agency (MHRA)

In the UK the MHRA is the recognised Competent Authority which implements the European Medical Device Directives (MDD). The MHRA regulates a wide range of medicinal products including medicines and medical devices and blood and therapeutic products and services derived from tissue engineering (MHRA 2013). The MHRA is one of the leading regulatory authorities for medicines and medical devices worldwide and works closely with the European regulator, the European Medicines Agency (EMEA) and also collaborates with other international regulators, such as the Food and Drug Administration (FDA) in the USA. International collaboration between pharmaceutical regulators is well established but international co-ordination of regulatory approval for medical devices is less developed and there is variation in the classification and in the processes of assessment and approval of medical devices in different countries (Henshall et al. 2011)

The Committee on the Safety of Devices is an independent body of experts which advises the MHRA. As well as monitoring the approval of new devices the MHRA has the power to withdraw a product from the market, and in the case of medicines, to suspend production. The MHRA can also prosecute a manufacturer or distributor if the law has been broken. The MHRA issues Field Safety Notices on behalf of manufacturers when a device needs to be recalled for technical or clinical reasons and Medical Device Alerts to communicate safety information to device end users in health and social care.

5.2.4 Evaluation of the European Regulatory System

A five year study from January 2006 – Dec 2010 of all Field Safety Notices and Medical Device Alerts found that there was a 1,220% increase in Field Safety Notices during the period, from 62 in 2006 to 757 in 2010, and 447 Medical Device Alerts issued in the same period, 44% of which were judged as causing serious adverse health consequences or death (Heneghan et al. 2011). The dramatic rise in the number of devices recalled during the period is a cause for concern as is the fact that the study authors struggled to gain access to the clinical data or premarket approval data for the recalled devices. Manufacturers and Notified Bodies in the UK were unable to provide premarket clinical data for 192 recalled medical devices as unlike pharmaceutical regulation no summaries are publicly available for independent review (Heneghan et al. 2011).

Such exposure of flaws in the European regulatory system has caused concern amongst politicians, healthcare staff and the public. Clinical data provided for a CE mark are held by the company or the Notified Body and are not available to a public body such as MHRA (Heneghan et al. 2011). Similar problems have been found in Belgium and the Netherlands leading to severe criticism of the European regulatory system where it is believed that confidentiality overrules transparency (Hulstaert et al. 2012). As well as the high profile scandal of Poly Implant Prosthese (PIP) breast implants (Heneghan 2012) an undercover investigation run jointly by the BMJ and the Daily Telegraph resulted in a Slovakian Notified Body allowing a fake hip with dangerous design flaws to proceed to certification (Cohen 2012). The undercover investigation revealed a trail of deception and exposed a severely flawed regulatory system in Europe that is poorly regulated and influenced by financial incentives that put the interests of manufacturers before those of patients (Cohen 2012). The role and actions of specific Notified Bodies were particularly criticised.

Since these concerns came to light regarding hip and knee implants the MHRA has joined the British Orthopaedic Association in setting up a group named “Beyond Compliance” to support the safe and stepwise introduction of new or modified implants such as joint replacements. Data about patients who receive these implants and their recovery following surgery is collected by the Beyond Compliance Advisory Group and made available to surgeons using the implant,

to the manufacturer, and to independent assessors to monitor the implant's performance (Beyond Compliance 2014). In addition, from May 2011, all clinical investigations of implantable medical devices and class III devices are entered onto a non public database and most Competent Authorities, including MHRA, review this documentation although those in some European member states have opted for a passive permission route ie no review (Hulstaert et al. 2012).

A report published by the FDA in May 2012 on unsafe and ineffective devices approved in the EU that were not approved in the US was severely criticised by the European Medical Technology Industry Association, Eucomed, who claim that it is inaccurate and conclusions placed out of context. They claim that the report is politically motivated as it contains so many factual errors (European Medical Technology Industry (Eucomed) 2012b).

Such criticisms of the European regulatory system resulted in the European Commission submitting a proposal for the revision of the EU Medical Devices Directives (MDD) in September 2012. A year later the European Parliament's Environment (ENVI) Committee voted for much-needed measures to improve Europe's notified body system, increase the transparency and traceability of medical devices, introduce unannounced site visits and provide for better stakeholder involvement" according to a press release from Eucomed. It has been suggested that this system represents a more serious threat to medical device innovation than the controversial medical device tax currently being debated in the United States, according to an editorial in Medlatest (Woods 2013). The European Parliament are currently in the negotiation phase with Council (comprised of representatives from the 28 EU Member States), which carries equal weight in the MDD decision-making process. The Parliament and Council must reach a compromise to agree on the joint final text of the MDD.

5.2.5 Regulation in USA

As discussed earlier the premarket regulations of the FDA and Europe are different with the European system being based on demonstration of safety and performance and the system in the USA based on safety and efficacy/effectiveness. In Europe HTA is a continuous process that operates after

regulatory approval where as in the US HTA is part of the regulatory approvals process.

The Centre for Devices and Radiological Health (CDRH) is the part of the FDA responsible for the regulation and monitoring of medical devices in the USA. Most devices are given approval by the FDA to be marketed because they have substantial equivalence to a predicate device, but if the FDA disagrees with such a claim then clinical research studies must be performed to provide data to support a premarket notification 510(k) or premarket approval application (CDRH-Center for Devices and Radiological Health 2014). In an attempt to lessen the burden of regulation and harmonise the process across countries the FDA uses accepted consensus standards in the pre- market review of medical devices although there are situations when this is not possible (Maisel 2004).

Although regulatory approval in USA takes longer and requires more clinical data there is still evidence that the regulatory system is sub optimal resulting in many device recalls and serious adverse events. Concern in the US has lead to increased compliance scrutiny from the FDA (Arbit, Paller 2006) as well as from the MHRA in UK (Cohen 2012). Analysis of the FDA's list of medical devices recalled for life threatening or very serious hazards between 2005 and 2009 revealed that only 21 of the 113 devices recalled had gone through the more rigorous premarket approval process, 80 had gone through the 510(k) process and 8 had been considered exempt from FDA approval (Zuckerman, Brown & Nissen 2011). This finding that the majority of medical devices recalled because of serious safety concerns (78%) had been through the less stringent 510(k) process or no FDA review at all suggest that there is a need to reform the FDA regulatory approvals system to ensure a more rigorous review of medical devices (Zuckerman, Brown & Nissen 2011). Such reviews and the similar ones in Europe discussed above are leading to a risk averse culture amongst those developing new and innovative medical devices which may impede further important innovation (Krucoff et al. 2012).

5.3 Facilitating Regulatory Approval

The financial pressures brought by the rise in research and development expenses have been a concern to medical device manufacturers and other biotechnology firms for some years (Valdes, McGuire 2004). Rising research costs are suggested as being one of a number of barriers to device innovation alongside concerns about the predictability of regulatory processes (Krucoff et al. 2012). The requirement to satisfy rigorous regulatory systems of approval when developing new medical devices can be extremely onerous for academic and clinical researchers. Finding ways to enable detailed evaluation of new devices through novel and improved methods in order to accelerate the development and marketing of new devices is challenging (Erdman, Keefe & Schiestl 2013). As discussed in section 5.2.4 there are problems with the current regulatory systems but in addition there are issues with existing evaluation methods of bench top testing, usually followed by animal experiments and then human studies. Alternative approaches using data-driven and simulation based medical device design and manufacture and computational modelling have been suggested in order to improve innovation and also the regulatory approval of medical devices (Erdman, Keefe & Schiestl 2013).

The aim of regulatory science is the optimal introduction into society of new products of science such as newly discovered substances, new scientific tools and technologies as well as knowledge and information (Sakuma 2013). In the USA Regulatory Science is defined as

> *"The science of developing new tools, standards and approaches to assess the safety, efficacy, quality and performance of all FDA- regulated Products"*

(CDRH-Center for Devices and Radiological Health 2014)

Organisations in a number of countries have introduced various strategies in order to support academic and clinical researchers through the required regulatory processes and obligations in the hope that additional clinical research will be undertaken. For example the University of Minnesota Academic Health Centre developed a programme specifically to assist faculty members with investigational new drug applications and investigational device exemption

applications to the FDA and found that through the programme issues that might have put the university at risk were identified (Arbit, Paller 2006). A number of graduate schools in Japan have also developed educational programmes in regulatory sciences in collaboration with the Japanese regulatory agency, Pharmaceuticals and Medical Devices Agency (PDMA) (Sakuma 2013). In the UK such courses are run by a number of organisations including British Standards Institute (BSI) but these are expensive and academics need to include funding for such courses in grant applications if they are to develop medical devices that can be approved for use in patients.

In addition in the UK the MHRA has been working with professional education and training bodies to raise awareness of the importance of regulation and safe use of products in medical training and continuing professional development programmes. An accreditation scheme is being developed with the medical Royal Colleges to grant the equivalent of a 'driving licence' for the safe use of particular pieces of equipment for different specialties (MHRA 2012).

Understanding of Regulatory Science for the LINGT project was developed through reading the medical devices literature and regulatory frameworks and through discussions with the external consultant, Professor David Young. It was agreed that members of the team would need specific training and attend appropriate BSI courses in order to take on specific roles in the project team. The PDRA attended the appropriate BSI training course in order to be the Controlling Manager for the system and the Commercial Development Officer attached to the project attended the auditor's course in order to establish a system of internal audits.

5.4 British Standard for Medical Devices - Quality Management System

In order to meet the regulatory requirements for eventual CE marking medical devices have to be developed under an appropriate Quality Management System (QMS). The International Organisation for Standardisation (ISO) is a worldwide organisation of national standard bodies which prepares International Standards through the work of its technical committees. The ISO sets out internationally recognised quality management principles in the generic standard ISO 9001.

This provides the steps necessary to adopt a quality management system for any organisation to help them ensure that they meet the needs and expectations of customers and other interested parties. The British Standard BS EN ISO 13485: 2012 Medical Devices – Quality Management Systems – Requirements for Regulatory Purposes is the UK implementation of international standard EN ISO 13485 which is also approved by the European Committee for Standardisation (CEN) and is based on ISO 9001 being the recognised QMS for medical devices.

The main objective of international standard (BS EN ISO 13485:2012) is to "facilitate harmonised medical device regulatory requirements for quality management systems" (p1) and is used by external parties, including Notified Bodies, to assess the organisations ability to meet regulatory requirements required for CE marking. The standard specifies

> *"the requirements for a quality management system that can be used by an organisation for the design and development, production, installation and servicing of medical devices and the design, development and provision of related services"*

BS EN ISO 13485:2003 pp v

These requirements are complementary to technical requirements for products. The international standard takes a process approach to quality management and does not require uniformity in the structure or documentation of the QMS. However it is essential that all members of an organisation apply the processes involved and are committed to the ethos of the QMS. The standard sets out general requirements of the organisation which include:

- Identifying the processes needed for the QMS and its application
- Determining the sequence and interaction of these processes
- Determining the criteria and methods of ensuring that the operation and control of these processes are effective
- Ensuring the availability of resources and information necessary for the operation and monitoring of processes
- Monitoring, measuring and analysing these processes
- Implementing actions to achieve planned results and maintaining effectiveness of these processes

Thus the development of the LINGT had to be carried out under this Quality Management System ISO 13485. The decision to follow the appropriate QMS was a strategic one because the ultimate aim of the project was to have a marketable product by the completion date. It was therefore imperative that such a system be established as soon as possible to reflect what was being done rather than try to impose a QMS later on. It was important to ensure that the QMS was understood and followed by all members of the team. Although the standard is written for organisations of any size there were challenges encountered when applying it to such a small organisation of a project team of 6 people. The standard discusses management responsibility and commitment which in effect had to be the whole team with the PDRA taking the role of the management representative and controlling manager.

An external consultant (DY) was employed to advise the team on the setting up of the system and helped to draft the initial documentation. Figure 18 shows the hierarchy of documentation required for a BS EN 13485:2012 compliant QMS.

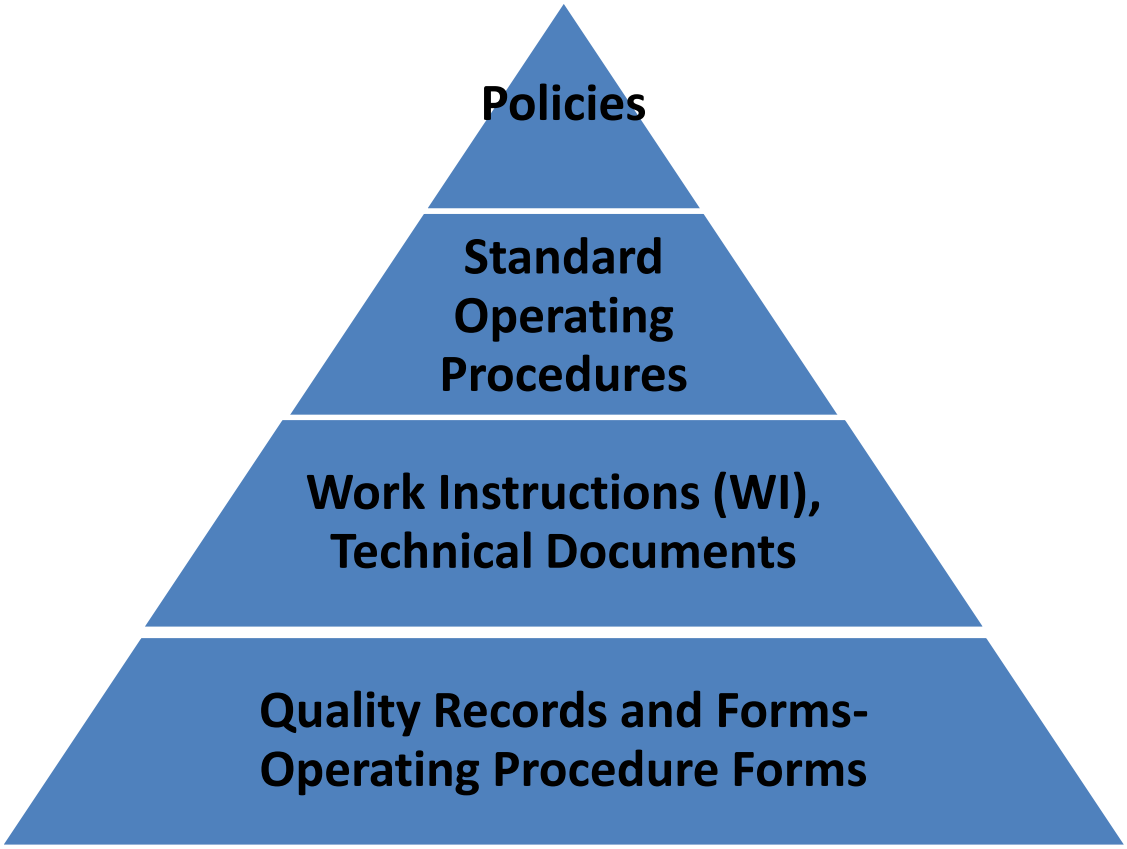


Figure 18: Documentation for Quality Management System compliant with ISO 13485:2012

Whilst the standard does not require a specific format for documentation it does set out general requirements for that documentation which are:

- Statements of the quality policy and quality objectives
- A quality manual
- Documented procedures required by the standard,
- Documents needed by the organisation to ensure the effective planning, operation and control of its processes, including Standard Operating Procedures and Work Instructions
- Records required by the standard, including Design Decision records
- Any other documents required by national or regional regulations

These are discussed in detail below.

5.4.1, Quality Policy and Objectives and Quality Manual

The author wrote a statement of the Quality Policy and Objectives (Appendix 15) in July 2012 and presented them to the team for approval at the Quarterly Review

Meeting. They were approved and subsequently displayed on the wall of the project office. Regular reviews of the Quality Policy and objectives were undertaken at Quality Management Committee meetings to ensure that they continued to reflect the reality of the project. The Quality Manual was initially drafted by the external consultant and then edited by the author and issued in draft form to the project team. After this the PDRA, as controlling manager, conducted further edits of the Quality Manual in August 2013 and April 2014 to ensure that it fully reflected the current procedures of the QMS.

5.4.2 Documented procedures

The QMS had to operate within the University of Hull where the project team were employed and which has its own range of policies and procedures. These policies and procedures, such as the Purchasing Procedure and Lone Working Procedure, were incorporated into the QMS and referenced appropriately. Other policies such as the Quality Management Policy were written specifically for the project to ensure that it met the requirements of ISO13485:2012.

5.4.3 Standard Operating Procedures

Twenty seven standard operating procedures (SOP's) were written to ensure that the project operated under a controlled and regulated system that could be verified and audited. The SOP's were written specifically for the project but had to incorporate already established and monitored University of Hull procedures such as the procedure for purchasing materials and services. A full list of SOPs is included in Appendix 16.

5.4.4 Work Instructions

Details of how specific procedures were carried out were documented in work instructions (WI) which explained exactly what to do. This is crucial in ensuring that the same methods are used each and every time a particular procedure is carried out. An example of the WI for the preparation of the electrodes is included in Appendix 6.

5.4.5 Operating Procedure Forms

Forty-six Operating Procedure Forms (OPFs) were written to standardise the documentation of all documents connected to the project from agendas and

minutes to purchase order forms. The OPF's were created as template forms and then filled in as the project developed and information became available. Key documents such as the Project Initiation Form and Project Team Formation form became part of the Design History File. A full list of OPF's is in Appendix 17.

5.4.6 Design and Development

The ISO standard states that the organisation shall plan and control the design and development of the product by determining design and development stages and the review, verification, validation and design transfer activities appropriate at each of these stages. It also states that the organisation must determine the responsibilities and authorities for design and development.

Design and development inputs were identified, reviewed and approved at regular (fortnightly) meetings and records of outputs were maintained. Design and Development review was conducted formally at the Quarterly Review Meetings at which all team members were present. All design and development decisions were recorded on the relevant OPFs and kept in the Design History File.

5.4.7 Device Master Record

The Device Master Record (DMR) contains all records and data relating the development of the LINGT. It is in fact a shelf in the research office containing all the minutes from meetings, work books, results and data, indeed every document generated in relation to the LINGT. All documents were stored by the author and organised into appropriate files by the Controlling Manager and administrator. The files are organised into subject folders and information stored within them in chronological order. The DMR is in essence a diary of the development of the LINGT.

5.4.8 Design History File

Regulatory authorities require a documented design history of the medical device often referred to as the Design History File (DHF). This file must contain the entire history of the design of the device and any accessories, labelling, packaging and manufacturing processes. It serves as a long term record for the company of how the device was developed, the design decisions made and the

rationale for those decisions. There must be evidence that the design followed a Design and Development Plan and design reviews, design validation and verification activities were undertaken. These activities must be verified through the inclusion of or reference to sufficient documents including verification results and any other data which demonstrates compliance with design requirements (Shenton 2011).

From the start of the project team meetings were held every 2 weeks to discuss the design of the LINGT and verification activities required to demonstrate effectiveness of the design were planned. These activities were in the form of planned experiments by the PDRA and documented in meeting minutes and action plans. The DHF was compiled by the Controlling Manager under the guidance of the external consultant and referred to the vast amount of data collected on the development and performance of the LINGT. Design control procedures were also included ensuring that any changes to the design were reviewed, authorised and tested with regard to risk management, biocompatibility, sterilisation, shelf life and functionality (Shenton 2011).

5.4.9 Control of Documents

A key aspect of running a QMS is the control of documents to ensure that all documents are reviewed and approved by the appropriate personnel, that they are updated and re-approved as necessary and that changes and revision status of documents are identified so that only current versions of approved documents are used. A SOP was written for the control of documents (SOP 1) and this was followed by the project team to ensure that all of the documents relating to the project were approved by the author as project leader and by the controlling manager, circulated to all the team and stored correctly. Once approved master documents were stored so that only the controlling manager, or her deputy, had access to them but official copies were available to the project team in hard copy in the project office and electronically on a shared area of the University computer server. Any proposed changes or revisions to a document had to follow a strict procedure so that such changes or revisions were approved and then the master document changed by the controlling manager and official copies made available to the project team. It was also essential that superseded and obsolete

documents were identified as such and stored securely so that they could not be used inadvertently but they remained available for future reference if required.

5.5 Risk Management

In order for a device to be CE marked the manufacturer must demonstrate that the device complies with the relevant legislation and essential requirements (The Council of the European Communities 1993) . Clinical data are usually required to demonstrate this compliance and such clinical data must be generated from a specifically designed clinical investigation of the medical device. The clinical investigation plan for the LINGT is discussed in section 5.6 but in order to demonstrate that prototype medical devices are safe for the planned clinical investigation it is essential to demonstrate that a proper Risk Assessment has been conducted and that there is a Risk Mitigation Strategy in place.

Risk management for medical devices is regulated by the British Standard for the UK implementation of EN ISO 14971:2009 “Medical Devices – Application of risk management to medical devices” (BSI, 2009). This standard was developed using established principles of risk management and gives manufacturers a framework within which experience, insight and judgement are applied systematically to manage the risk associated with the use of medical devices. The processes for managing risks to the patient are the main focus of the standard but risks to the operator, other persons, other equipment and the environment are also considered.

Risks associated with the LINGT were managed according to guidelines of the harmonised standard EN 14971: 2009, and within the framework of a certified ISO 13485:2012 quality management system. The risk management process can be broken down in the following activities: risk analysis, risk evaluation, risk control, evaluation of overall residual risk acceptability, risk management report, and production and post-production information. The latter two aspects, production and post production information, are beyond the scope of this PhD study as they are to be undertaken by the final manufacturer and so are not discussed.

European medical devices directives (90/385/EEC, 93/42/EEC and 98/79/EC) require that in selecting the most appropriate solutions for the design and construction of medical devices conformity to safety principles must be maintained. Account must be taken of the generally acknowledged state of the art, and manufacturers must apply the following principles in the following order:

1. Eliminate or reduce risks as far as possible – safe design and construction
2. Where appropriate take adequate protection measures in relation to risks that cannot be eliminated
3. Inform users of the residual risks due to any shortcomings of the protection measures adopted.

The perception of risk is subjective and influenced by many factors including cultural, educational and socio-economic background as well as the health status of the patient. The use of a medical device for a particular treatment of a specific patient requires balance of risks and benefits. The use of conventional nasogastric tubes is a frequent and commonly practised procedure but, as discussed in chapter 2, the current procedure carries serious inherent risks which must be balanced with the benefit of the use of this device. Most of the risks are associated with feeding but some are also associated with use for decompression of the gastrointestinal tract. The development of the entire LINGT project was conceived as a risk containment and mitigation response to the risk issues intrinsic to the use of current nasogastric tubes and the known limitations of prior risk containment strategies associated with them. The harm associated with current tubes is considered to be entirely preventable. In 2009 “misplaced nasogastric tubes not detected prior to feeding” was confirmed by the Department of Health as being a “never event” and this problem remains on the 2013/2014 list of “Never Events” and must be reported to the NPSA and publicly (NHS England Patient Safety Domain Team 2013). Never events are serious avoidable events that cause patients harm and should never happen because there are guidelines in place to ensure that they are avoided.

5.5.1 Risk Assessment

The risks associated with the LINGT were assessed and analysed by the author and verified by the Quality Management Committee of the LINGT Project Team

in accordance with the organisation's risk management procedure and with the European harmonised standard EN ISO 14971: 2009 Medical devices. The Quality Management Committee comprised the author and project leader, Barbara Elliott (BE), the Controlling Manager Dr Monika Schoenleber (MS), Commercial Development Officer, Dr Robert Singh (RS), External consultant, Professor David Young (DY), and Prof J MacFie (JM), Professor of Surgery/Consultant Surgeon, Academic Surgical Unit, Castle Hill Hospital, Hull.

The LINGT was classified according to Annex-IX of the MDD to be a Class-IIa device and therefore of medium risk. Annex C of EN ISO14971:2007 lists the questions that should be used to identify medical device characteristics that can impact on safety. Through answering these questions (Appendix 18) the author identified the main risks with the LINGT that required mitigation to be:-

1. the clinical risk of toxicity of the components of the LINGT tube,
2. the mechanical risk of detachment of any component
3. the technical risk of battery failure
4. the clinical risk of cross infection

Analysis of the risks associated with the identified hazards of the LINGT was conducted using an Failure Mode and Effect Analysis (FMEA) approach involving identification of hazard cause, effect and control measures to reduce the (Shebl, Franklin & Barber 2009). It is accepted that the concept of risk has two components the probability of the occurrence of harm, termed frequency and the consequences of that harm, that is the severity of the harm. Severity means the magnitude of the outcome, from death at the worst extreme, to procedural delay as the minimal impact. The British Standard EN ISO 14971:2009 "Medical Devices – Application of risk management to medical devices" (BSI, 2009) states that wherever possible manufacturers should provide quantitative categorisation of risk probability if sufficient data are available but recognise that often manufacturers may need to provide a qualitative description. Table 11 is adapted from the example of semi-quantitative probability levels given in annex D of the standard (BSI 2009, pp 38) and was the one used for the LINGT.

Likelihood of Occurrence			Score
Improbable	<1 in 1,000,000	10^{-6}	1
Remote	<1 in 100,000	10^{-5}	2
Occasional	<1 in 10,000	10^{-4}	3
Probable	<1 in 1,000	10^{-3}	4
Frequent	<1 in 100	10^{-2}	5

Table 11: Frequency of Occurrence

In order to categorise the severity of harm it is suggested that manufacturers use descriptors appropriate for the medical device (BSI 2009) and examples of descriptors are provided in the standard annex D. Table 12 is adapted from the example and was used to score the severity potential hazards for the LINGT.

Severity of Harm	Score	Severity of Harm
Negligible	Cosmetic defect of product; Inconvenience or temporary discomfort.	1
Marginal/Minor	Mechanical failure with little or no loss of function; Results in temporary injury or impairment not requiring professional medical intervention; Restricted patient activity or function; Mild transient pain	2
Serious	Mechanical failure leading to impairment or function; Severe loss of patient activity or function; Moderate pain; Results in injury or impairment requiring professional medical intervention.	3
Critical	Results in permanent impairment or life-threatening injury	4
Catastrophic	Results in death	5

Table 12: Quantitative Estimate of Severity of Harm

Quantitative values were assigned for severity of harm (of the effect of the hazard) and for probability of occurrence (of the hazard), in accordance with Annex D of EN ISO 14971: 2009 and the LINGT Risk Management Plan and SOP

5. Additionally, relevant information from pre-production experience with the LINGT was incorporated into the risk analysis, through consideration of process validations data, first article inspection and quality records.

Risk Index Numbers (RINs) are calculated by multiplying the numerical expressions for the severity of risk by that for frequency of occurrence of that risk. They are used to generate a numerical quantification of risk. As shown in Table 13 RINs less than 3 were considered as “acceptable” against a possible maximum score of 9. For RINs above 3, risk reduction measures were considered. The possible outcomes of these considerations were that either one or more risk reduction measures bring the RIN down below 3 or although some risk reduction is possible, the RIN remains above 3. Should it not be possible to reduce the RIN below 3, then the risk is reduced to a level as low as reasonably practicable (ALARP) and the risk and benefit is compared. If the risk is outweighed by the benefit then the risk may be accepted; if not then the design is abandoned. An acceptable Risk Index Number, is less than 3 while the “as low as reasonably practicable” (ALARP) range is between 3 and 9. Higher than 9 is an unacceptable level of risk. All RINs for the LINGT were calculated by the author with discussion with professional members of the User Advisory Group and were then reviewed by the Risk Management Team and decisions made regarding the actions to be taken to reduce these risks.

Risk Index Number	Acceptability
<3	Acceptable
3 - 9	As low as reasonably practicable (ALARP)
>9	Unacceptable

Table 13: Risk Index Scoring System

Risk Priority Numbers were calculated by multiplying the RIN by the likelihood of detection of a problem by an end user on a scale of 1 to 5. The scale adopted by the LINGT Project Team is shown in Table 14 and Risk Priority Numbers (RPNs) were calculated by the author to determine the order of priority for mitigating the risks of the LINGT.

Likelihood of detection	Score
Frequently	1
Reasonably likely	2
Occasionally	3
Remote chance	4
Extremely unlikely	5

Table 14: Risk Detection Scoring System

The Risk Priority Number estimate is the product of the Severity, Frequency of Occurrence and Frequency of Detection: S x O x D with a possible range of 1 to 125 and the Risk is summarised in Table 15 below.

Criticality Grade	Qualitative	Quantitative	Action
Grade 1	**Low**	**1-20**	No action required **Current Controls** adequate
Grade 2	**Medium**	**21-44**	Action required within a planned schedule
Grade 3	**High**	**45-125**	Immediate action required

Table 15: Risk Priority Number Scoring System

In risk assessments, often only scores that fall into the Medium or High (21-125) RPN require remedial action, but with the LINGT all risks were considered and actions taken to reduce them if at all possible. Details of the risks identified and the scores attributed to them can be found in the Failure Mode and Effect Analysis Table in Appendix 19. A Risk Management Report was written by the author and circulated to the project team and was part of the evidence presented to the Notified Body for certification of the QMS.

5.5.2 Risk Mitigation Measures

Risk mitigation measures were put in place that remove or reduce to an acceptable level the identified risks. They included measures accepted by the medical device industry for reducing risk such as design specifications and design verification and validation activities, in addition the provision of a toxicological assessment of the components of the LINGT, specific instructions for the user and a practical method of cleaning the device prior to each instance of the administration of an enteral feed or medication were devised and written. The

control measures that are proposed to mitigate and reduce risks will be verified by two methods. First is an analysis of the control measure on the basis of previous information and existing experience. This may include bench top measurements as well. The second method is by collating information through the clinical investigation of this system.

5.5.3 Residual Risks

Despite the mitigation measures implemented there remained residual risks of the tube being wrongly inserted into the lungs, cross infection, patient injury and musculoskeletal injury arising from manual handling of bulk quantities of the product. The user must be warned and made aware of these risks through warning statements in the Instructions For Use (IFU) and appropriate labels on the device and/or the packaging. In current clinical practice, the minor harms or injuries identified for the LINGT are acceptable in return for the benefits of reliable and known correct location which overcomes the risks and problems of conventional nasogastric tubes. It is recognised that nasogastric feeding will never be completely without risk until there is a completely reliable method of placement verification (Yardley, Donaldson 2010).

5.5.4 Risk Management Activities

Table 16 shows a summary of risk management activities which were carried out as part of the risk management process for the LINGT. It gives an indication of the activities for each development phase of the project referred to as phases I - V. Assignment of responsibilities and authorities are also indicated for the personnel involved in the risk management of the device.

Legend: BE-Barbara Elliott, Project Leader; **JG-** Prof John Greenman, Lead Scientist; **JW –** Dr Jay Wadhawan, Chief Electrochemist; **RS-**Dr Rob Singh, Commercial Development Officer**; MS-**Dr Monika Schoenlebr, PDRA, Controlling Manager**; DY-**Prof David Young, External Consultant.			
PHASE I: OPPORTUNITY AND RISK ANALYSIS (FEASIBILITY STUDY + PROJECT PLAN)			
Activity	**Actual date of completion**	**Responsibility/ Document prepared by**	**Review and approval by**
Early risk assessment	15 December 2005	BE, LS, JW, JG Literature review and application for YC funds	BE, LS, JW, JG
Initial assessment of regulatory and clinical pathway by in-house staff and external consultant DY	June 2009	BE, RS, DY, JW, JG Application for NIHR funding and Gantt chart	BE, RS, DY, JW, JG, JM, LS
PHASE II: FORMULATION/CONCEPT (DESIGN INPUT)			
Activity	**Actual date of completion**	**Responsibility/ Document prepared by**	**Review and approval by**
Initial design risk analysis and FMEA for LINGT	19 October 2011	BE, RS, MS, DY Annex C questions and minutes of meeting	Minutes sent to JM and LS. Email responses received Nov 2011
Initial design risk analysis and FMEA for indicator box	19 October 2011	BE, RS, MS, DY Annex C questions and minutes of meeting	Minutes sent to JM and LS. Email responses received Nov 2011
Revised design risk analysis and FMEA for LINGT (review)	July 2012	DY	BE,MS,RS,JM Discussed with lay and professional user groups
Revised design risk analysis and FMEA for Indicator box (review)	July 2012	DY	BE,MS,RS,JM Discussed with lay and professional user groups Aug 2012 (minutes in User group file)
First issue of risk analysis and FMEA for LINGT(after first design review meeting)	Oct 2012	DY draft of QMS documents and first draft of FMEA	DY,MS,RS,JM Discussed with lay and professional user groups March 2013
First issue of risk management report (after first design review meeting)	March 2014	BE	MS, JM,JG,JW,DY
PHASE III DESIGN VERIFICATION AND DESIGN OUTPUT PHASE			
Review of control measures following design verification activities/results (Part of second design review meeting)	Dec 2010 October 2013	JMSL BE, MS, DY revised FMEA, toxicology reports and design verification	BE,JM,MS,RE,CAS, TAP, JMG and JMSL
Second issue of risk management report	To be done	To be identified/confirmed	BE, MS, DY, EMT Member

Table 16: Risk Management Activities

5.6 Clinical Investigation in the UK

Clinical investigation of a new medical device is essential and guidance is provided by MHRA as follows:

> *"a clinical investigation of a non-CE-marked device must be designed to establish that the performance claimed by the manufacturer can be adequately demonstrated, and that the device is judged to be safe to use on patients taking into account any risks associated with the use of the device when weighed against the expected benefits"*

Clinical investigations of medical devices – guidance for manufacturers November 2013 page 3

Whilst double blind, randomised controlled trials are the recommended gold standard for many medical products, particularly drugs, such trials may be impractical or unethical when evaluating medical devices (Li, Yue 2008). For most medical devices "blinding" is difficult if not impossible and the use of a placebo device cannot be justified if the procedure is invasive or unpleasant. This was certainly true of the LINGT. The very nature of the device, using an indicator box to demonstrate correct placement rather than testing gastric aspirate with pH indicator strips, meant that those using the LINGT would be clearly aware of the situation. An evaluation study was devised whereby the LINGT would be used for gastric decompression in patients undergoing gastro-intestinal surgery and compared with conventional ryles tubes normally used for this purpose.

The number of patients required for clinical investigation of new medical devices prior to CE marking, often referred to as feasibility or performance trials, varies but is suggested to be generally less than 100 (Hulstaert et al. 2012). In order to conduct a clinical investigation of the LINGT, prototype tubes suitable for use in humans had to be manufactured, packaged and sterilised. A company to perform these processes had to be identified and the clinical investigation plan written. Ethical approval for this clinical investigation had to be obtained and MHRA notice of no objection given. Whilst it is beyond the scope of this thesis to conduct and discuss the clinical investigation of the device (due to be conducted in Sept 2015) the selection and contracting of a company to manufacture the prototypes is

discussed in section 5.8. The performance trials were planned in accordance with ISO 13485:2012 QMS principles and the risks assessed and managed according to ISO 14971. The Clinical Investigation Plan for these trialsis discussed further in chapter 7.

5.7 Intellectual Property

Any innovative activity generates novel or previously undescribed outputs known as Intellectual Property (IP) which is owned, can be bought, sold or licensed and must be adequately protected (Dymond et al. 2012). Owners of IP have legally protected rights (IPR) to exert monopoly control over its exploitation and to prevent others gaining from it, referred to as “infringement”.

An IP review was conducted at the start of the project to explore whether anyone else had had a similar idea for solving the problem of placement verification of nasogastric tubes. A patent attorney was employed to conduct a patent search in order to determine the “freedom to operate” which is the evidence that the LINGT development would not infringe any other IP. Two possibly problematic patents were identified but on detailed consideration it was verified that their IP was completely different to that incorporated into the LINGT.

Dymond et al (2012) explain that patents apply to inventions which embody a new idea capable of being made or used by industry and which involve a non obvious inventive step. Advice was sought from the Knowledge Exchange at the University of Hull regarding the need to protect the invention of the LINGT and a patent was written and filed as in Figure 19 (Wadhawan et al. 2007). The Patent Cooperation Treaty (PCT) is an international agreement with over 145 Contracting States which enables inventors to seek patent protection in a wide range of countries simultaneously. One single “international” patent is filed rather than several national or regional patents. The granting of the patents remains with each national or regional patent offices and so, as has happened with the LINGT, patents can be granted by different offices at different times (World Intellectual Property Organisation (WIPO) 2014).

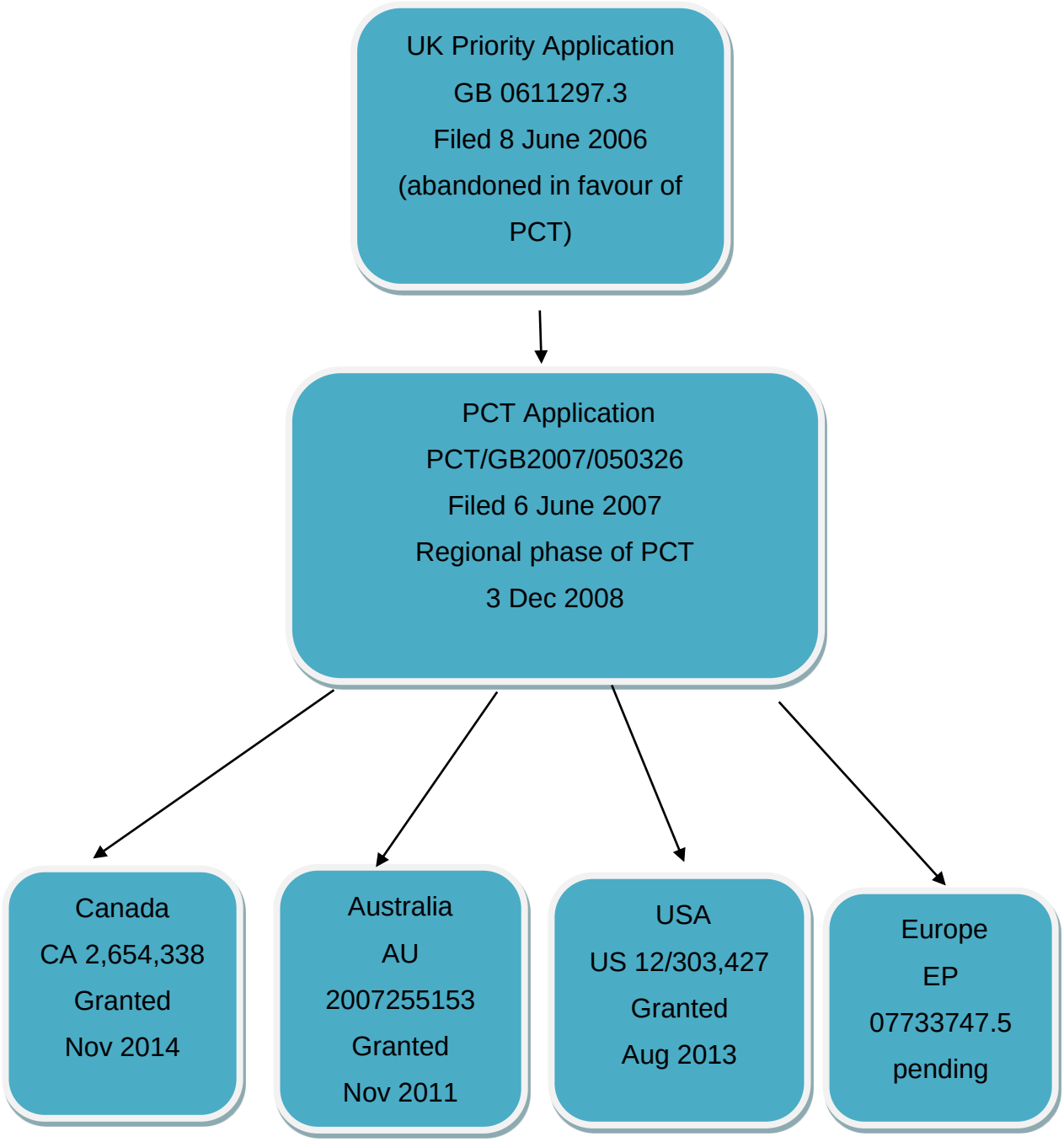


Figure 19: Patent Prosecution of LINGT

The Patent Act (1977) states that the employer owns any IP created by employees in the course of their normal work. The University of Hull has an IP policy whose terms and conditions the LINGT team agreed to when signing their contracts of employment. This policy states that IP is shared between the University and the inventors.

5.8 Commercialisation

5.8.1 Market and Clinical Need

The stages in the innovation pathway from concept to adoption are described by Dymond, Long et al (2012) who suggest that market context is as important for medical devices as clinical need and that this should be addressed early in the project. The University of Hull Knowledge Exchange supported the author in arranging a market survey which was commissioned in 2007 and conducted by Cion Ltd, an independent company to identify the market context for the proposed new tube. The market survey identified UK nasogastric tube suppliers including Medicina, Vygon, Merck, Viasys, Pennine Healthcare, Fresenius Kabi, Kendall/Tyco Healthcare, Unomedical and Nestlé most of whom operated internationally. Low cost PVC nasogastric tubes used for less than 10 days, as they become brittle after this, costing on average. £0.30 to manufacture, were identified as well as tubes used for slightly longer term costing on average £1 and polyurethane (PU) tubes suitable for use up to 4-6 weeks costing £4 - £10 or even more. Higher value PU tubes are favoured in Europe due to concerns over the phthalate plasticisers used in poly vinyl chloride (PVC). Similar products are available globally; all share risks of misplacement and detection.

The market survey was repeated in 2013 and discovered that a number of UK nasogastric tube suppliers had either changed name or no longer supplied such tubes to the NHS. New suppliers including Intervene Ltd and GBUK Enteral Ltd were identified. A Freedom of Information Act request 3476 was filed with the NHS Business Services Authority in April 2013 and answered on 15th May. Although the person filing this request is not known the information provided is publicly available and was accessed by the external consultant advising the project. The response from the NHS revealed that the top 5 brands of nasogastric tubes over financial years 2011 and 2012 were as follows:- GBUK Enteral, Corpak MedSystems Ltd, Intervene Ltd, Medicina Ltd and Vygon (UK).

The market place need was also evident from NPSA alerts and guidance and Never Events Framework presented in sections 2.9 and 2.10. It is clear from the risks associated with current methods of verifying correct placement discussed in sections 2.9 and 2.10 that there is an urgent need for a safe, effective, bedside

method for detecting the position of nasogastric tubes and all of the manufacturers contacted were aware of this.

The benefits of LINGT could be justified on safety grounds alone but they were also reinforced by belief that use would lead to significant cost savings from reduced morbidity and shorter procedure (staff) times. Current annual UK usage of nasogastric tubes is estimated to be 275,000 (Yardley, Donaldson 2010). However discussions with individual hospitals, British Association of Enteral Nutrition, NHS Purchasing and Supply Chain and 3 large nasogastric tube manufacturers suggest that this may be considerably higher. Including Europe and USA usage is estimated at 69 – 154m nasogastric tubes per annum worth £60 – 120m although figures often conflict. Sales of the tubes are often combined with oral nutrition supplements and so obtaining precise figures is not possible. This situation was confirmed by the UK Head of Marketing for a leading international healthcare company that manufactures nasogastric tubes who indicated that they alone sold in the range of £5-10 million of nasogastric tubes in the UK per annum (personal communication).

Although there will be additional materials and process costs with LINGT compared with normal nasogastric tubes in current use, it is envisaged that in commercial production, any additional increase in price would be offset by the reduction in risk associated with use of the LINGT, including reduced risk of litigation. The additional components are low-cost and the LINGT is being designed with a view to reducing the manufacturing process costs. The commercialised LINGT will significantly affect clinical practice with increased reliability and de-skilling enabling more lay carers to be taught the procedure facilitating earlier discharge and increased home care. Reduced anxiety and time savings are persuasive benefits and new medical devices offering such a profile have a good history of success (Burns 2007).

5.8.2 Commercial Partners for LINGT Iteration 1

It is not advisable for clinicians or academics to approach commercial companies direct but rather work through their employer's R&D department or Technology Transfer office (Dymond et al. 2012). This was done through the Commercial Development Officer (RS) who was part of the project team. Industrial partners

depend on innovation and want to develop strong relationships with clinicians and customers and to make it easy to share ideas. However it is important that IP is protected and no discussions or meetings took place until a Non Disclosure Agreement (NDA) was in place. The solicitor's office provided the University of Hull standard NDA for all discussions with companies whether these were held by telephone or face to face.

A company had to be found for whom the innovation fitted within their plan of work. A number of companies were interested in the concept but were not prepared to divert resources to product development at the cost of other initiatives. Dymond, Long et al (2012) list 5 questions that companies ask when deciding whether to invest time and effort in a new device:

1. Does the product work?
2. Is it measurably different from and better than what is currently available?
3. Can it be proved clinically?
4. Can it be manufactured and sold profitably?
5. Will anybody in the market place buy it?

pp 433

In addition industry values product ideas if they are novel and compelling, the IP has been appropriately protected, worldwide regulatory approval has been gained, first human use has been performed, methods of company reimbursement exist, clinical proof of safety and efficacy are evident, manufacturing has been established, demand for product verified and sales achieved (Dymond et al. 2012).

A market survey of current manufacturers of nasogastric tubes was commissioned from Cion Consulting in 2007 and initial contact with companies commenced. A Danish manufacturer UnoMedical were sufficiently interested to send 2 members of staff to Hull to view the hand-made prototypes and results of experiments conducted with these. However, although the IP had been protected, these hand painted prototypes were very basic and there was considerable developmental work still to be done. The company did not believe that they could divert resources to such an untested product at this time which prompted application for funding from NIHR to provide the evidence of clinical

effectiveness and manufacturing feasibility required by companies in order to take on the manufacture of the LINGT. In effect the financial risks associated with such a novel design of a nasogastric tube had to be removed before a company would consider licensing the product.

5.8.3 Commercial Partners for LINGT Iteration 2

The search for a suitable manufacturer was reinstated as soon as the project was awarded NIHR funding as it was clear that the hand-made prototypes prepared by the author and discussed in chapter 3 could not be used on patients. Initially a search was made for a manufacturer of prototype medical devices. The plan set out in the project Gantt chart (Appendix 20) and approved by the funders was to undertake clinical evaluation of manufactured prototypes and then, with this data available, approach manufacturers of nasogastric tubes to offer licencing options to manufacture the CE marked device. However this did not prove to be possible as discussed below and an alternative strategy had to be adopted.

The author presented the project to a meeting of Business Angels in July 2010 and following this was contacted by a Business Angel who gave her the contact details of a local company who manufactured single use surgical instruments. However this company was unable to manufacture the LINGT, as they did not have their own manufacturing capabilities, but they did suggest an Irish manufacturer of prototype medical devices, Arrotek Medical Ltd. This company is certified to ISO 13485 to manufacture medical devices and telephone discussions between the Managing Director and Technical Director of this company and the author clarified that they were able to do the work. A contract was agreed and signed and the company supplied two alternative designs for the second iteration of LINGT. The laboratory and clinical evaluation of these prototypes is presented in chapter 4.

Whilst these prototypes were useful for demonstrating that the sensors worked and the system was viable for detecting placement in the stomach they had a number of limitations for use in human clinical trials discussed in chapter 4. The biggest drawback was the impact of the three lumen design on the internal or external diameter of the tube. The design involved either reducing the internal diameter making it difficult to insert feeds or withdraw fluid from the stomach or

increasing the external diameter of the tube making the tube more uncomfortable for the patient. A way of incorporating the conducting wires into the walls of the tube known as co-extrusion had to be found.

5.8.4 Commercial Partners for LINGT Iteration 3

Discussions were held with a the Product Development Manager and Research and Development Department of a German company who already manufactured tubes with co-extruded wires for other types of medical devices. Initial discussions were very promising and a design meeting was held with their chief design engineer. Dymond, Long et al (2012) suggests that strong synergy between the innovation and something already manufactured by the company is compelling motive for a company to take on a new product. This company already manufactured a nasogastric tube with co-extruded wires for a completely different purpose and it was hoped that the synergy between the two tubes would encourage them to take on the manufacture of the LINGT product. However it may be that the products were considered to be too alike by the company and as their main focus of work and own R&D was mainly involved in neurosurgical devices they did not consider it worth diverting resources to manufacture the LINGT. Although the company submitted a proposal it included impossible penalty clauses of a fine of £100,000 if sales targets of the finished device were not reached.

Contact was made with a number of manufacturers who produced prototype medical devices in UK, Europe and USA. Whilst many seemed interested it soon became apparent that they were not able to fulfil all of the requirements of the project. The process of contacting companies, establishing a dialogue with the appropriate company representatives, setting up NDAs and negotiating the project requirements took 2-3 months for each company. A list of companies and progress made was presented at every project meeting in order to keep the team informed. It was clear that all companies recognised the clinical need to develop a failsafe, easy method of verifying nasogastric tube placement and they were aware of the limitations of current methods.

The inability to find a suitable prototype manufacturer was discussed with the funders at NIHR. An application for a one year no cost extension was made and

this was agreed in August 2013 setting a new project completion date of July 2015. Lack of success with manufacturers of medical device prototypes resulted in a complete re-evaluation of the companies contacted and approaches made. In August 2013 it was agreed that rather than looking for a prototype manufacturer the team should explore the possibility of a manufacturer of current nasogastric tubes taking on the production of the LINGT prototypes with a view to licensing the product once clinical evaluation had taken place. This was a departure from the original plan and in effect brought forward some of the licensing discussions but it appeared to be the only viable option.

Contact was made with the Managing Directors (MD) of the three main suppliers of nasogastric tubes to the NHS, namely Medicina, Enteral UK and Intervene. None of the companies manufacture in the UK, an issue that had been encountered with prototype manufacturers also, two manufacturing in China and the other in France. The author and Commercial Development Officer visited the Head Offices of these companies to discuss the design specification of the nasogastric tubes and offer them an opportunity to develop the final prototype of the LINGT and manufacture a relatively small number of these for clinical evaluation. It was hoped that the option of licensing the final product would be an incentive to engage in this development work at a cost that was affordable within the project budget. The visits also enabled a better assessment of the companies' manufacturing capabilities and willingness to engage with the development work. Dymond, Long et al (2012) suggest that potential commercial partners expect a fully documented device development record including engineering workbooks, patent protection and all discussions must be covered by confidentiality agreements. Patent protection had commenced in 2007 and as the LINGT project had been established with the aim of having a fully certified QMS to ISO 13485 standard the documents for the device development were well established and the PDRA had maintained detailed lab books of all work undertaken.

The following issues are considered important when companies are deciding whether to proceed with a particular device:

1. technological soundness of the project,
2. internal resources to support the development,

3. likely risk and cost and time needed to develop a marketable product
4. strategic fit with the company's business plan
5. market size, applicable segments, competition and the need for market development
6. probability of adoption by health service delivery systems and of reimbursement
7. regulatory requirements

Dymond, Long et al (2012) pp 434

The technological soundness of the project could be demonstrated by the vast range of bench top and clinical studies conducted and the large amount of data available. Resources internal to the company were not required for the development as the project funds covered the manufacture of the prototypes including the purchase of any additional equipment required. Risks for the company in manufacturing the prototypes were therefore minimal as funding was available. It is suggested that for smaller companies who do not have their own R&D departments external funding can be very attractive. The LINGT had a good strategic fit with the business plans of all 3 companies who had a clear understanding of the need for a device that could verify correct placement easily and safely. They agreed that the current market could tolerate a small increase in cost for improved safety but profit margins were tight and competition fierce (personal communication). Decisions regarding licensing would require further consideration once results from clinical evaluation were available but potential losses to the company at this stage were thought to be acceptable. However the investment of time to develop and manufacture the prototypes was required and time spent on the LINGT would be lost to other potential projects so concerns about this were discussed. Information about the market size and the need for market development were presented in the User Requirement Specification (URS) prepared for the companies (Appendix 26). However this was largely known to them as they already sold products in the nasogastric tube market.

The likelihood of adoption of a new nasogastric tube was discussed and all 3 companies had strategies in place and contacts with procurement officers to encourage uptake of the LINGT once CE marked. NHS England has commissioned NICE to take over the work of the NHS Technology Adoption

Centre through the Health Technologies Adoption Programme (HTAP). HTAP will provide a more systematic approach to the adoption by the NHS of new technologies that improve the care given to patients and will facilitate the adoption of selected health technologies across the NHS (National Institute for Health and Care Excellence (NICE) 2013). It is envisaged that once the LINGT is ready for adoption across the NHS this organisation will be contacted for support and advice.

5.8.5 Competitive Products

Whilst undertaking the review of possible prototype manufacturers the author encountered a rival device, the NG Pod created by Westco Ltd. This device had already been approved for a CE mark and as such was further along the commercialisation pathway than the LINGT. However compelling evidence is required for the uptake of new technologies and this device had not been tested on patients and so the company was struggling to get health service providers to use the device. The company had chosen a very different route to the LINGT seeking private investment rather the public funding. Two meetings were held with the company Managing Director (MD) to determine whether there was any possibility of joint working however this did not materialise and whilst the devices were very different in terms of operation they both sought to solve the same problem and so were in direct competition. As discussion with manufacturers of nasogastric tubes developed it became clear that there were a number of reservations about this device and the company went into administration in April 2014 (Hodgson 2014). This demonstrated a key advantage of the LINGT to be support from NIHR in terms of funding.

5.8.6 Commercial production of the Indicator Box

The prototype indicator box in Figure 8, page 81 was designed and produced as a simple potentiostat by staff in the Chemistry Department, University of Hull. This was sufficient for the laboratory and clinical studies undertaken as part of this PhD project but a more user friendly device that met the ISO standards for electrical devices had to be manufactured for the planned clinical evaluation studies with patients.

A small electronics company, Image to Implant, was identified and contracted to undertake this work and they manufactured 5 prototype Indicator Boxes for use in the clinical studies. Meetings were held with the company MD and design engineer to agree the design of the Indicator Box and feedback from the User Network discussed in the chapter 6 was used to inform these decisions.

5.9 Summary

This chapter has considered the complex regulatory and commercial procedures involved in developing a medical device. These are as important to successful development of a new device as establishing the clinical need for such a device and demonstrating the scientific background and data to support its feasibility discussed in previous chapters.

Figure 20 gives a visual representation of the steps involved in developing a new medical device discussed in this chapter from the initial idea, through development of the idea to commercialisation and CE marking. The steps are not purely sequential but must be conducted alongside each other in order to make progress and ensure that the development is conducted in such a way as to ensure quality and regulatory compliance. This PhD project has conducted all but the final stages of this process and the plans for the manufacture of the final device and clinical investigation are discussed in chapter 7.

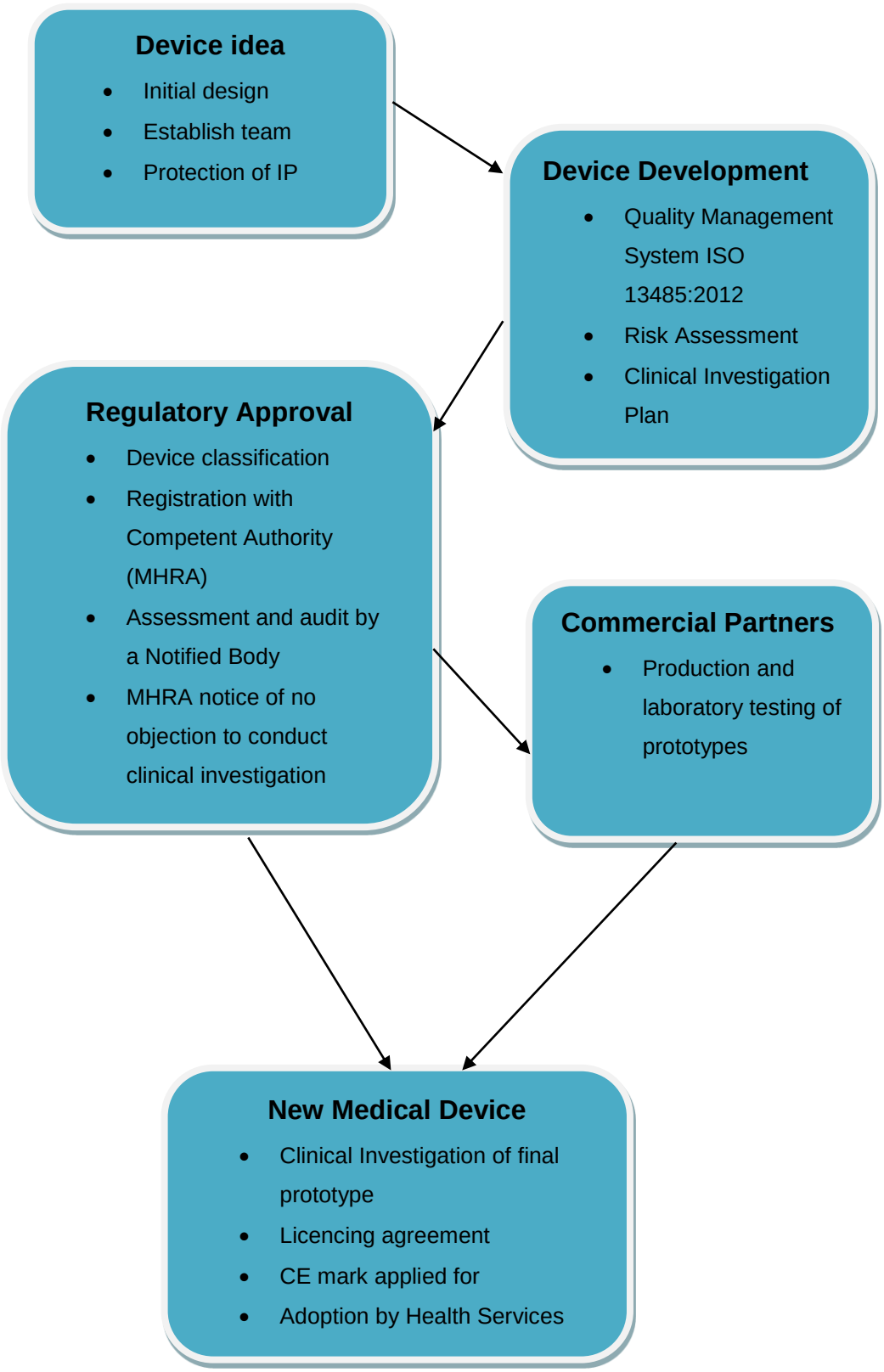


Figure 20: Regulatory and commercialisation process for developing a new medical device

Chapter 6: The Development of a User Network

6.1 Introduction

Discussions with professional and lay users of nasogastric tubes identified the unmet clinical need for a safe, reliable bedside method of detecting the placement of feeding tubes. The views of users of nasogastric tubes have therefore been the foundation for this research and it was essential that they continued to influence the study. The range of practitioners who use nasogastric tubes is extensive and includes parents and carers as well as health professionals. Thus it is essential that any new device and placement detection method can be taught to lay carers for use in the home as well as to nurses and doctors for use in hospital wards, intensive care units and theatres. The involvement of representatives of these groups of users is considered essential in developing a new device and this chapter considers the theoretical concepts of user engagement and explores the practical issues of this involvement as experienced in this project. It has been suggested that case studies reflecting the full range of user involvement in research, including the failures as well as the successes, are essential in order to increase knowledge of this aspect of research (Buckle et al. 2006).

Clinical researchers are in a privileged position of having access to professional and lay users and recipients of medical device interventions unlike manufacturers who are removed from the consumers of their products. Whilst manufacturers may have Advisory Panels for product design they are usually made up of key decision makers who may be influential but are often removed from the actual use of the device or product. It is essential therefore that the information provided by user groups is not lost or misinterpreted by manufacturers and there must be clear methods of communicating user views to those manufacturing the prototypes and final device. This chapter considers how this was achieved and how the views of both professional and lay users were incorporated into the development of the Location Indicating Nasogastric Tube (LINGT). The reality of user involvement in the development of a medical device is explored and lessons for future studies and ways of improving user involvement in research are reviewed.

6.2 Background

6.2.1 Patient and Public Involvement in Health Research

The involvement of users and carers in the planning and delivery of services has been a key focus of health care policy in the United Kingdom (UK) in the late 20th and early 21st centuries (Department of Health 1989, Department Of Health 1994, Department of Health 2000a, Department of Health 2000b, Department of Health 2010, Department of Health 2012, Department of Health 2013). At the same time there has been recognition that users have a crucial role in healthcare research to ensure that their issues, and not just those of interest to clinical and academic professionals, are studied (Hogg 2006, Cavet, Sloper 2005). The involvement of the public is central to health research policy in the majority of developed countries (Boote, Wong & Booth 2012).

The involvement of service users in all aspects of research is now expected by the majority of current funding bodies and regulatory agencies. The National Institute for Health Research (NIHR) and Research Councils have had an increasing focus on Patient and Public Involvement (PPI) in grant applications in the last decade and increasingly require NHS organisations to demonstrate PPI in the research they undertake (National Institute for Health Research 2013). Similar emphasis is placed on the importance of consumers and researchers working in partnership in Australia (Australian Government, National Health and Medical Research Council 2014) and in Canada a framework for Citizen Engagement has been established (Canadian Institutes of Health Research 2014). A Council of Public Representatives advises the Director of the National Institute of Health in the USA on issues concerned with public participaton (National Institutes of Health (NIH) 2013). In Scandinavian welfare states PPI in health care is regulated by laws and guidelines and therefore viewed as citizens' rights (Rise et al. 2013).

In UK the advisory group INVOLVE was established to promote PPI in the NHS, public health and social care research (INVOLVE 2013b). They define the public as

> *"patients and potential patients; people who use health and socal services; informal carers; parents/guardians; disabled people;*

> *members of the public who are potential recipients of health promotion programmes, public health programmes and social service interventions and organisations that represent people who use services"*

And public involvement in research as

> *"doing research "with" or "by" the public rather than "to", "about" or "for" the public"*

(INVOLVE 2014)

The desire for PPI in health research is underpinned by epistemological, moralistic and consequentialist influences (Boote, Baird & Beecroft 2010). The epistemological view that the experiential knowledge and personal insights of patients and carers can be of benefit to researchers has been discussed in the literature (Boote, Wong & Booth 2012). The right of the public to be involved in publicly funded research that may impact on their health or the services they receive provides the moralistic argument for PPI (Boote, Baird & Beecroft 2010) and the belief that PPI improves the quality, relevance and impact of health research provides the consequentialist argument (Thompson et al. 2009). It is claimed that PPI improves the way that research is prioritised, commissioned, undertaken, communicated and used (INVOLVE 2013b)

The benefits of user involvement have been reported (Hanley et al. 2004, Allsop et al. 2010, Barber et al. 2011, Howe et al. 2010). However, support for public involvement in research is not unanimous and there is concern that such involvement may be tokenistic (Ward et al. 2010). There is limited quality evidence of the impact of user involvement in research and information about what strategies work best is lacking (Telford et al. 2002, Smith et al. 2008).

The feasibility of evaluating the impact of public involvement in health and social care research was explored in a mixed methods study by Barber et al (2011). The study included a 2 round Delphi study and the importance of evaluating the impact of PPI was endorsed although the complexities of evaluating a process that is subjective and socially constructed were identified (Barber et al. 2011). Subsequently a systematic review of studies reporting the impact of PPI between 1995 and 2009 identified 66 studies which met the inclusion criteria and data

were extracted and quality assessed using the guidelines of NHS Centre for Reviews and Dissemination and Critical Appraisal Skills Programme (CASP) (Brett et al. 2012). The authors identified a number of positive impacts which enhanced the quality and appropriateness of the research at every stage of the research process as well as some challenging impacts.

In the US a systematic review, environmental scan and manual search of peer reviewed literature using a metanarrative approach identified 202 eligible studies on patient and service user engagement (PSUE) in research (Shippee et al. 2013). This review emphasised the importance of involving patients and service users as early as possible in the research process in order to improve study design and applicability. It was also stressed that users for whom the outcomes of the research are of interest should be included and that there should be a sense of equality between parties (Shippee et al. 2013).

Brett et al (2012) found studies that reported users helping to identify relevant topics for research projects which were grounded in the reality of their day to day lives, prioritising those topics and developing commissioning briefs. It is crucial that users are involved early in identifying appropriate topics for research as examples of researchers' ideas being abandoned, because service users and carers did not believe the ideas worth pursuing, have been published (Boote et al. 2012). Users may also be involved in helping with recruitment and identifying effective ways of accessing participants as well as in undertaking research by ensuring that the user perspective is accounted for in the project design, for example by identifying cultural issues, enabling informed consent to be obtained and adapting academic language (Brett et al. 2012).

A review of papers reporting the underlying principles and standards of public involvment in NHS, public health and social care research was published in October 2013 and concluded that work in this area was moving away from a "one size fits all" model of PPI to a more flexible application of guidance (INVOLVE 2013a). A huge variety of activity was reported with regard to public involvement across a range of studies making it difficult to identify a set of core standards and principles which were described in a number of different ways. However a set of values underpinning the various principles were identified from a range of

documents and listed as respect, support, transparency, responsiveness, diversity and accountability (INVOLVE 2013a).

6.2.2 User Involvement in the Development of Medical Devices

The views of users are essential in the development of medical devices, not only in identifying the need for specific devices, but also in developing the technology and evaluating the final product. Regulatory agencies such as the Food and Drug Administration (FDA) in the USA and the Medicines and Healthcare Products Regulatory Agency (MHRA) in UK require developers to demonstrate that they have considered human factors engineering processes, also known as ergonomics or user centred design, through compliance with recognised standards (Martin, Barnett 2012). Groups promoting service user involvement in the development of medical devices have evolved such as the Multidisciplinary Assessment of Technology Centre for Healthcare (MATCH) an Engineering and Physical Sciences Research Council (EPSRC) funded project to develop methods of user engagement in the medical device technology cycle. It has been claimed that the success or failure of a medical device as well as the quality of the product can be determined by user involvement (Shah, Robinson 2006). It is similarly claimed that in order for a medical device to be "well designed" it must not only be clinically effective and safe but it must also meet the requirements of the people that use it and are treated by it (Martin et al. 2012). This can be a complex process as one particular medical device may be used for different functions with patients with varying conditions, in a range of clinical and non clinical settings and a further complication arises when the person using the device is frequently not the person with purchasing authority (Martin et al. 2012).

Nasogastric tubes are such devices in that they are used with patients of all ages from neonates to the elderly, with a range of medical and surgical conditions. They are used for different purposes, to deliver feed and medications, to decompress the stomach and for investigations, in a variety of settings both in the hospital and community. Clinical practitioners including doctors, nurses and dieticians use nasogastric tubes as well as informal carers such as parents. In some situations patients pass tubes on themselves and use them to deliver feed and medication. Thus there was a clear challenge in ensuring that

representatives from this wide range of users were involved in the study and had the opportunity to share their views.

It is suggested that many researchers are unsure about how to include good PPI in their research (Telford et al. 2002) and the range of contexts and reasons for research make it difficult to be prescriptive about the best approach to the involvement of users in studies (Smith et al. 2008). However there are a number of organisations and resources available to assist in the process. As this project was funded by NIHR, their resources and those produced by INVOLVE were used in the first instance. The author attended a study day on PPI organised by NIHR at the start of the project and the NIHR Director of PPI, Philippa Yeeles, attended a project meeting in July 2012 to discuss this aspect of the project. In addition a literature search was undertaken to inform the process of user involvement, particularly with regard to the development of medical devices and the author continually evaluated the process with the project team and the users involved in the study.

6.3 Literature Search

In order to plan and develop effective user engagement in this project it was important that the experiences of others were considered and lessons from previous studies learned. The Faculty of Health and Social Care at the University of Hull employ a Service User and Carer Advisor and she was an important source of information and contacts. It was also essential to conduct a search of the nursing, medical and technology literature. There is a considerable amount of literature on PPI in the nursing and medical literature but much less focussed on the development of medical devices. Table 17 summarises the search terms used to conduct the literature search.

	Boolean term	search terms
Stage 1		“medical device*”
Stage 2	AND	design or develop* or research or innovat*
Stage 3	AND	user* or patient* or carer* or lay* or public* or consumer* or client*
Stage 4	AND	involve* or participat * or consut* or collaborat* or partner* or experience* or inclusion or opinion* or voice*
Stage 5	NOT	tele*

Table 17: Search terms used for User Involvement

Table 18 indicates the number of papers found in the range of databases searched. These databases were used because they were considered the most appropriate to identify relevant literature with the required focus. Once duplicates had been identified 205 records were inspected and abstracts read to determine the relevance of the papers and 68 papers were identified as relevant and informative for the project and full copies of the papers were accessed.

Database	Number of records found
CINAHL	136
Medline	609
Psych Info	193
Business Source Premier	333

Table 18: Results of literature search

Reference lists of the papers were used to identify key papers and additional literature was identified through the INVOLVE website.

6.4 Users of Medical Devices

The users of medical devices are usually regarded as the health care practitioners using the devices with or on patients rather than the patients themselves (Bridgelel Ram et al. 2005). The working patterns of these clinical users as well as their capabilities and the environment in which the device is to be used require consideration during medical device development (Sharples et

al. 2012). However manufacturers of medical devices have a preference for involving more senior healthcare staff, who they recognise may not actually use the device in practice, as it is believed that they can speak on behalf of more junior staff as well as patients (Money et al. 2011).

Manufacturers prioritise the views of senior health care staff when developing medical devices as they believe that they will be promoting the devices to patients even if the patients will be using the devices themselves (Money et al. 2011). However it is also important to ensure that the views of those who are on the receiving end of the device, that is the patients, are considered as well as lay users who may be required to use a device in non clinical environments such as the home. The difficulties encountered when involving particular types of healthcare users in healthcare decisions are discussed by Shah and Farrow (2008) and the involvement of surrogates considered. Shah and Robinson (2008) define the end user of a medical device as the person who is the ultimate beneficiary of the usage of the medical device and consider that end user surrogates are usually clinicians and formal and informal caregivers (Shah, Robinson 2008).

In this research study one group of end users are neonates who inevitably require surrogate decision makers to act on their behalf and this was achieved by involving their parents and a neonatal community nurse. Parents may be defined as informal carers with regard to medical care i.e. “lay persons who provide care” with formal carers being “the professionals trained to provide care such as nurses” (Shah, Robinson 2008) pp 810). A number of advantages of using surrogates in healthcare decisions on behalf of end users deemed unable or incompetent to act for themselves have been identified by Shah, Farrow et al. (2009). The most important benefit is the representation of the end users’ needs, views, values and interests and ensuring that these views are taken into account in any healthcare decisions (Shah, Farrow & Robinson 2009). However there may be discrepancies in views between end users and their surrogates and failure to predict their preferences accurately. This is particularly challenging with neonates who are unable to verbalise their own views and are dependent on both lay and formal carers as surrogates. Tensions between these surrogates and their own needs may mean that those of the neonate are not accurately reflected.

This is not unique to the development of medical devices and clinicians who work with infants and children have a legal duty to ensure that the best interests of the child are prioritised as stipulated in The Children Act (HM Government 2004). Surrogates representing the views and experiences of minors are expected to ensure that device development takes account of their particular needs and does not cause them harm.

The use of parents and teachers as surrogates for children's opinions on technology development has been documented and it is claimed that the views of the children themselves are often marginalised (Druin 2002). Methods of eliciting the opinions of children are discussed by Weightman, Preston et al. (2010) who present an informative case study of the involvement of children in the design and evaluation of two devices for upper limb rehabilitation in children with cerebral palsy (Weightman et al. 2010). These researchers recruited children with cerebral palsy through their schools or community physiotherapists and invited them to select 3 friends to join them in evaluating the devices. In this way children with cerebral palsy and able bodied children were involved as the researchers were keen not to develop a device viewed as being just for "the disabled". Evaluation sessions took place in the children's schools, providing a familiar environment and a process of interviews, peer tutoring and observation was used to capture the children's responses to the new devices. A child friendly visual Likert scale the "Smileyometer" was used to assess the children's preferences for specific device designs (Weightman et al. 2010). Whilst the methods used had some success in eliciting the views of young users of medical devices the traditional power relationships between adults and children remained an issue and communication with children with disabilities in particular remains a challenge. The authors suggest alternative methods such as co-discovery and participatory design as possible ways of overcoming these issues (Weightman et al. 2010).

Adolescents are a particularly neglected population with regard to medical devices research and have to use devices designed with adult or child user involvement (Lang et al. 2014). This may result in poor compliance with medical equipment that may be inappropriate, inefficient or unpleasant to use by this age group. Effective and ethical strategies for including adolescents are discussed by

Lang et al. (2014). Every effort was made to include children and adolescents in the user advisory group for this PhD study in order to ensure that they had the opportunity to present their own views rather than surrogates presenting their interpretation of those views. However as discussed later this had limited success.

The importance of "Lead Users" in developing and evaluating technology as well as in contributing to the early adoption and acceptance of new products has been described (von Hippel 1986). There is evidence that manufacturers of medical devices seek out the most influential users in terms of purchasing decisions for their user groups (Money et al. 2011) and this may be the case with some lead users. Lead users of nasogastric tubes may be considered to be those who use them the most such as Nutrition Specialist Nurses, neonatal nurses, anaesthetists and those who purchase the devices on behalf of the NHS. It was considered essential to have representatives from all of these groups involved in the project and to engage them from the beginning to ensure that they were involved in the early stages of the product development. However the views of less influential users in terms of purchasing were equally important for this project.

6.5 Benefits of User Involvement

The benefits of user engagement in the development of medical devices are that the likelihood of producing devices that are safe, usable, clinically effective and appropriate to cultural context are increased (Bridgelal Ram, Grocott & Weir 2008). A systematic review of the literature by Shah and Robinson (2007) identified the major benefits of user involvement in the development of medical devices to be access to user ideas and perspectives, improvement in design, user interface, functionality, usability and quality of medical devices. Shah and Robinson (2007) suggest that communication and collaboration between users and manufacturers needs to be direct as it enhances the quality of products, their functionality, design, effectiveness and the adoption of medical device technologies. It is also suggested that development costs can be reduced by user involvement and in many cases it determines product success of failure

(Shah 2011). As well as meeting the requirements of regulatory bodies such as the MHRA user involvement can lead to the development of successful products with resultant higher sales and profits (Shah 2007). Without user involvement medical devices may be developed with inherent safety issues and potential operator errors because the needs and abilities of the users have not been considered.

In order to maximise their effect, user involvement should not just be in the final evaluation of a product, rather users should be involved in every stage of the development process (Shah and Robinson, 2007). There is evidence of users generating ideas for new and innovative devices (Conway, McGuiness 1986) as well as identifying problems with current products and suggesting possible solutions to those problems (Shah 2007). In particular it is considered important to involve users in the early stages of product development rather than only in the later stages (Shah 2007). Early participation of users is suggested as a way of avoiding initial problems in other areas of health research such as service development. The NIHR suggest five key stages in the research process for involving patients and public in research: developing the grant application, design and management of the research, undertaking the research, analysis of data and dissemination of research findings (National Institute for Health Research 2013). This project involved PPI in the grant application, design and management of the research and dissemination of the findings as discussed in more detail below.

In spite of the considerable evidence in the literature of the benefits of user involvement in the development of medical devices there is little research into the actual process of involving users (Magnusson, Mathing & Kristensson 2003) and there is limited knowledge regarding which approaches work best, in which contexts and why. Regardless of current policy initiatives their involvement tends to be as passive participants (Bridgelal Ram, Grocott & Weir 2008) so every effort was made to ensure active involvement of users of nasogastric tubes in this research project.

6.6 Barriers to User Involvement

The goal of user involvement in an iterative process of product design is often difficult for companies to achieve because of financial pressures to get products to market, confidentiality issues and accessing vulnerable groups (Bridgelal Ram, Grocott & Weir 2008). For successful user involvement in the development of medical devices there needs to be sufficient resources in terms of time, money and labour available. Whilst Shah and Robinson's (2007) review of the literature found user involvement to be cost effective they also found resource issues in terms of time, money and labour to be crucial and therefore a major barrier to user involvement.

Other barriers are the availability, preparation, training and support, co-operation and characteristics of users (Shah 2007). Some users of medical devices are known to be hard to reach such as the elderly and disabled but the LINGT study found that parents of young children are also a hard to reach group due to commitments to a young family as well as to employers. Clinicians can also have many commitments making it difficult to find time to engage in product development. Shah and Robinson (2006) suggest the use of surrogates in place of hard to reach groups and this has been discussed in relation to neonates but for other users the author tried to find alternative ways of communicating with users rather than replacing them with surrogates.

Barriers to user involvement may involve confidentiality issues particularly in relation to commercially sensitive product development (Shah 2007). This was addressed by ensuring that both lay and professional members of the User Network signed confidentiality agreements at the beginning of their involvement. It is not considered that knowledge and understanding of technology should be a barrier to involvement as manufacturers should not expect users to solve complex technological problems for them rather they will identify and clarify user requirements and experiences (Shah 2007). Although some members of the User Newtwork did have some understanding of the technology and contributed to discussion of this, such knowledge was considered a bonus and was not expected of members of the User Network.

It has been suggested that manufacturers of medical device technology need a cultural shift in attitudes in order to encourage greater user involvement (Craig et al. 1999). In depth interviews with representatives from 11 medical device manufacturers revealed that they believed proactively engaging users in medical device design and development slowed down the process and they preferred a reactive involvement in the form of complaints or feedback on devices already released into the healthcare system (Money et al. 2011). Research into effective ways of engaging users is lacking and interventions that are reliable, robust, fast and cheap have yet to be identified (Shah 2007). The LINGT project had a number of advantages in this area, namely the cost of user involvement had been included in the research budget and such involvement was seen as a key area by the funding body (NIHR), the research team included medical as well as nursing practitioners with good clinical contacts through which to access users and the University of Hull had secured appropriate patent protection.

6.7 User Involvement Strategy

The literature on the involvement of users in the development of medical devices reviewed above stresses the importance of user involvement however detail of the process and reality of involvement is lacking (Martin, Barnett 2012). Therefore a User Involvement Strategy was developed for the LINGT project (Appendix 21) to articulate the detail of the planned involvement of users in the development of the novel nasogastric tube. The strategy incorporated the values of respect, support, transparency, responsiveness, diversity and accountability identified as being key to quality user involvement (Involve 2013, Popay 2013) and documented the commitment and methods that underpin user involvement in the project. The aim of the strategy is to ensure that “users' views are integral to the development of the Location Indicating Nasogastric Tube” (Appendix 21 page 1). This was achieved by:

- Gathering information from lay and professional users about their experiences of using nasogastric tubes to inform the project in terms of: tube and monitor design; risk assessment and patient information

- Ensuring information was collated, analysed and fed into the project and that users were kept aware of this process
- Updating users on project progress
- Committing the project to developing good practice in user involvement
- Monitoring user involvement in the project
- Working with users to evaluate the impact of user involvement in the project
- Involving users in talking and writing about the project after its completion

6.8 Ethical Issues

The joint statement developed by the National Research Ethics Service and INVOLVE provides clarity and guidance on PPI in research and the requirements for ethical review (INVOLVE and The National Research Ethics Service 2009). Members of user-carer groups actively involved in the research process are not research participants (INVOLVE and The National Research Ethics Service 2009) and so ethical approval for their participation is not usually expected. There is a clear differentiation between research participants, who are afforded protection by research governance arrangements including research ethics committees, and the active involvement of the public in the research process. However the literature on user involvement in the design and development of medical devices often describes users testing the device and as such they then become research participants with the required ethical approvals sought. This may inhibit manufacturers in the involvement of users in product development as the necessary approvals processes may appear onerous and time consuming (Shah 2007).

In this PhD project participants were not expected to use the new medical device rather they were required to comment on its development and the research process for its trial and evaluation. Ethical approval was therefore not sought when initially recruiting members. However from the initial meetings participants provided rich descriptions of their experiences and it was believed that the author had a responsibility to share and learn from these experiences. Without appropriate consent it was considered impossible to fully utilise this material in

reports and publications and so following discussions with the Chair of the Faculty's Research Ethics Committee retrospective consent was sought from participants to analyse and use the content of their discussions in this PhD and future publications. All users were happy for their comments and experiences to be shared and used in this way and all signed the consent form.

6.9 Recruitment

The establishment of a User Advisory Group was a key milestone for the project and quarterly meetings of the group were planned on the project Gantt chart. In order to recruit suitable and interested people a one page information sheet (Appendix 22) was prepared giving details of the project in language suitable for a lay person. This was sent to key personnel in local Health Trusts who had contact with patients who use nasogastric tubes such as dieticians, neonatal nurses, community children's nurses and intensive care nurses. The aim of this was twofold: firstly to identify health professionals who might be interested in joining the User Advisory Group and secondly for them to identify patients who might be approached to also participate in the group. The information sheet was also sent to patient organisations through the Faculty Service User and Carer Advisor and to parent support groups. As the project progressed an "Information and Invitation" bulletin was produced (appendix 23) giving more information about the project in a more attractive format including photographs of the team and a baby with a nasogastric tube. This was useful in further publicising the project and was made available through the Faculty User Carer website.

A method of snowballing developed where the identification of one group member lead to new contacts which lead in turn to additional members. Snowballing is a recognised method of recruiting hard to reach participants for research studies (Atkinson 2001, Streeton, Cooke & Campbell 2004).

Recruitment was an ongoing process and continued throughout the project as information about the development of LINGT spread through word of mouth and regular project Bulletins (see Appendix 24). No limit was set to the number of people who could be involved and fourteen members, six health professional members and eight members of the public eventually joined the group. A policy

was adopted of welcoming any user of nasogastric tubes who contacted the LINGT team to join the network as it was considered useful to obtain as many views and experiences as possible. Table 19 gives details of the members of the User network.

Professional Users Total = 6	Lay Users Total = 8
Specialist Nutrition Nurse (adults)	Mothers x 3 of babies fed via nasogastric tube due to prematurity.
Intensive Care Nurse (adults)	Fathers x 2 of babies fed via nasogastric tube due to prematurity.
Advanced gastroenterology dietician	Mother of 3 year old with Downs Syndrome
Children's Community nurse x 2	Young adult given temporary nasogastric tube
Neonatal Community Nurse	55 year old female who had had a nasogastric tube following abdominal surgery

Table 19: Description of members of the User Network

There is evidence in the literature of the challenges of recruiting service users from a range of backgrounds and specific groups are considered "hard to reach" including minority ethnic groups, older people and people with disabilities (Brett et al 2012). As well as children users of nasogastric tubes are often in the latter 2 groups and it was disappointing that only one person who had received a nasogastric tube could be recruited. Involvement in a User Advisory Group was not thought to be as onerous as participation as a research subject however the difficulties in accessing children and adolescents were similar. Contact was made with 3 parents of adolescents who had experience of nasogastric tubes, one because of chemotherapy for treatment of a spinal tumour and 2 for treatment of Crohn's disease. A request was made to involve these young people in the User Advisory Group but, whilst these parents were supportive of the project, they felt that their children were not well enough to participate and did not give permission for them to be approached. Parents acting as "gatekeepers", allowing or denying access to their children, is well documented in research with children and young

people and their actions, usually intended to protect their children, may in fact deny them opportunities for involvement (Kirk 2007).

Adult patients who had experience of nasogastric tubes were approached and one young adult agreed to help with the project.

6.10 Methods of Involvement

Initially it was envisaged that meetings of the User Advisory Group would be held every 3 months involving both professional and lay users of nasogastric tubes. At the first meeting, however, it became apparent that the professional users were concerned about openly discussing the risks associated with nasogastric tubes in front of parents. In addition the parents involved were conscious of being critical of the support they received in front of health professionals. A decision was therefore made to hold separate meetings for professional and lays users and a model of sharing information between each group and the research team was envisaged as shown in Figure 21.

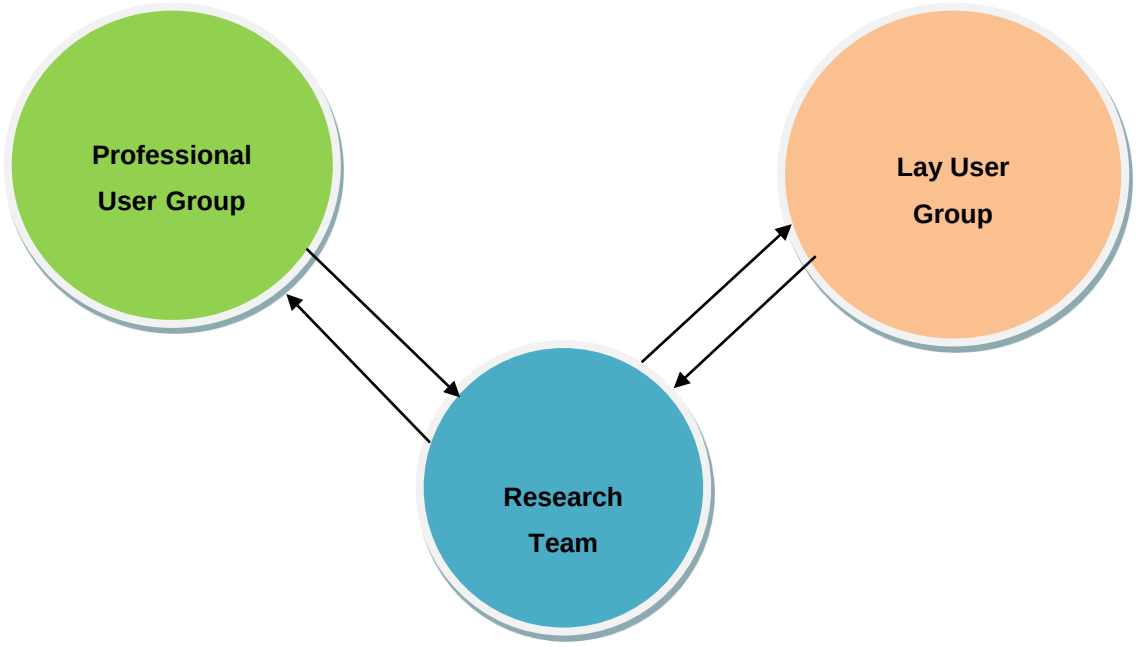


Figure 21: Initial model for information sharing between professional and lay user groups and research team

After the second meetings with the Lay User Group and Professional Use Group held separately, it became apparent that a more flexible approach was required to accommodate the availability of working parents and health care professionals. Whilst parents and professionals were keen to be involved finding suitable dates and times to meet was a challenge. It also became apparent that not all lay users were comfortable meeting in groups and so individual and small group meetings were necessary. Parents of children who had used nasogastric tubes at home were keen to attend meetings but for a range of reasons often had to send apologies. However their willingness to be involved in this study and their enthusiasm for the project meant that they were motivated to identify alternative strategies for involvement. The notion of a "User Advisory Group" soon became obsolete and "User Network" seemed a better description of the range of users involved in the project and the variety of methods of engagement.

Discussion during early meetings and further reflection identified a number of reasons why lay users found it difficult to attend in spite of being offered travel expenses and support costs for child care. Parents are not traditionally viewed as a "hard to reach" group of health service users but for the purposes of this

research the request for them to attend meetings was possibly unreasonable in addition to their coping with jobs and family responsibilities, especially when for some their child still had additional care needs related to feeding. In particular one single mother of a child with Down's syndrome found it very difficult to commit to attending meetings but her interest in the project enabled alternative solutions to be found. Users who suffer from anxiety with regard to group meetings may be difficult to recruit and methods of facilitating their involvement needs to be found (Brett et al. 2012).

The problems of attendance of patients and specialist nurses at research meetings and workshops have been described in the literature (Bridgelel Ram, Grocott & Weir 2007). Nurses are primarily clinicians and may not have the time or flexibility to attend meetings. This however was not the case with this project as the majority of professional users elected to attend regular meetings and found the joint discussions helpful. The support of managers to enable nurses to attend meetings during their working day was invaluable and at a time of severe workforce pressures in the National Health Service it was heartening to have such commitment to a research project.

As well as face to face meetings it was considered important to share information on progress of the project with the User Network in a variety of ways and a flexible approach was required in the ways lay and professional users were involved in line with their preferences. This led to a range of contact summarised in Table 20.

Type of Contact	Frequency of Contact	Total number over 3 years
Meetings with parents in the university	6 monthly	6
Meetings with health professionals in the university	6 monthly	6
Individual meetings with health professionals in their place of work	Annually for 1 member for 2 years Once for 1 member	3
Individual meetings with lay users in their own homes	Annually	2
Telephone conversations with professional and lay users	6 monthly for 1 member	6
Email contact with professional and lay users	At least 6 monthly	36

Table 20: Summary of contact with professional and lay users

It was essential that people approached to be involved in the project were aware that the author could be contacted by telephone, letter or email and that meetings could be held in a variety of venues. They were informed that their views and feedback could be offered at any time outside of meetings. Consideration was given to the accessibility of meeting venues as it was recognised that some lay users might not feel comfortable in the University environment and so a local café with private room was used on one occasion.

For users who preferred to offer their views in writing, consideration was given to the production of a questionnaire, based on the discussions during meetings. Professional users who were often in direct contact with lay users offered to share the discussions and collect feedback when meeting them to deliver care to their child. In this way the network of contact and sharing of information developed and grew as the project progressed as shown in Figure 22. The simple 2 way sharing of information shown in Figure 21 was too simplistic and a complex network of sharing information between individuals and groups developed. It was ensured that all information fed back to the research team.

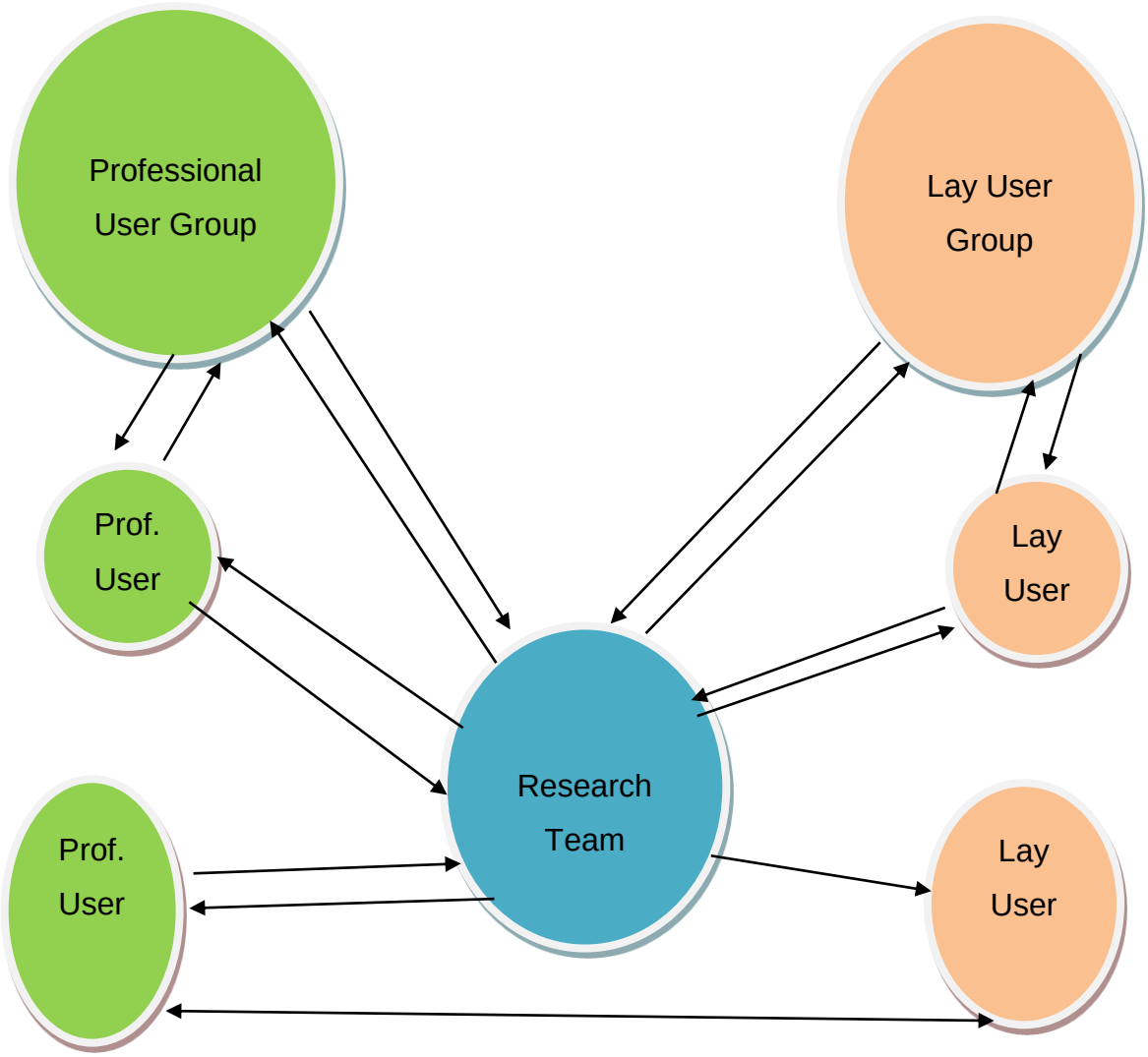


Figure 22: Final model of information sharing between professional and lay users and the research team

In order to ensure the diligent recording, collation, analysis, feedback and monitoring of user involvement appropriate documents were developed and stored securely in the project office. Table 21 summarises the documents generated.

Information Sharing Documents	Information Protection Documents
User information folder	Confidentiality agreement
User Involvement Strategy	Data protection form
User activity tables	Information and consent form regarding the use of anonymised information from meetings
Feedback from meetings Meeting minutes and notes	
Project Bulletins	

Table 21: User Network Documents

An information folder was prepared and given to all members when they joined the User Network. This folder contained all the information about the project and copies of the forms required. The User Involvement Strategy (Appendix 21) was reviewed annually at the June Quarterly Review Meetings (QRM) to ensure that it remained relevant and a User Activity Table (Appendix 25) was presented at every QRM as a summary of user involvement for the 3 month period. Notes from all meetings with users, whether group or individual, were written up immediately following the meeting and shared with participants to confirm their accuracy. Group meetings were presented as minutes.

Communication on progress of the project was facilitated through a Project Bulletin which was sent every 6 months to all members of the User Network as well as team members and other clinicians (for example see appendix 24). An Introduction and Invitation version was written to provide background and detail of the project and this was used when recruiting members to the User Network as well as patients to the clinical evaluation studies to test the new device (Appendix 24). Six monthly Bulletins were issued and formed part of the updating

and feedback process and were a useful way of continuing to communicate with the user carer network in between meetings.

The nature of the project required all members of the User Network to sign a confidentiality agreement in order to demonstrate that the Intellectual Property of the development of the medical device was protected. As it was necessary for personal details of members to be stored in paper and electronic format at the University of Hull it was essential that members signed a Data Protection Form as a record of their agreement to this. All these forms were stored securely in a locked cabinet in the project office and copies given to the members of the User Network.

6.11 Project Stages in which Users were involved

6.11.1 Concept - Clinical need for an improved device

The aim of the first encounter with users whether in a group, on an individual basis or on the telephone, was to explore their experiences of using nasogastric tubes and create a baseline for the development of the new medical device in terms of design and procedure for use as recommended in the literature (Bruseberg, McDonagh-Philp 2001). Involving users in the full cycle of device development from concept through to production increases the probability of producing safe, usable, effective and appropriate devices (Grocott et al. 2013). It was essential that the new device was not only safer but quicker and easier than the current method of detection of placement. Through these discussions insight into the experience of using nasogastric tube feeding was gained which was invaluable in adding information to the development process.

The experiences of people using nasogastric tubes were a continuing reminder of the need for the development of a new way to confirm the correct positioning of the tubes and provided further evidence of the need for an easier and safer method of location detection. The motive of turning this unmet need into a device design solution was the rationale behind the project and remained the key focus throughout, ensuring that the research was problem rather than product led. At the beginning of the project it was anticipated that manufacturers of nasogastric

tubes would already be developing their products to alleviate the current dissatisfaction with detection procedures, but it soon became apparent that this was not the case. Whilst the NPSA regularly issue guidance and alerts regarding the risks of current detection methods there is no obvious route for the public or clinicians to communicate their dissatisfaction with current devices to manufacturers (Brown et al. 2005). Medical device manufacturers tend to design new products based on old ones resulting in the inadequacies of previous devices being repeated (Norman 2002). There is some evidence that new devices developed in the last 7 years to aid correct placement of nasogastric tubes have evolved with input from clinicians, for example the Cortral EMSD (Corpak Medsystems, Chicago, IL,USA) evaluated by Rao, Kallam, et al (2009) and Windle et al (2010). Complex methods of placement verification have also been developed but all of these innovations involve expensive equipment and highly trained personnel and have been developed without any consideration of or input from lay users (see sections 2.7.3, 2.10.10 and 2.10.11).

Most concerns of both lay and professional users were with regard to checking the position of the tube and the key issues identified are discussed below. The uncertainty of the current procedure for verifying tube placement was a concern for all parents in the User Network (n= 6). This related to the uncertainty of what to do if no fluid could be aspirated from the baby's stomach, the lack of clarity of the changes in the pH indicator paper and the lack of consistency in information provided by nursing staff. This is a concern when there are national guidelines issued by NPSA (National Patient Safety Agency 2011a) and local protocols and suggests that uncertainty and related stress experienced and expressed by parents and professionals remains a concern.

The problem of obtaining aspirate is under reported in the literature but parents reported that they had to repeatedly draw back on the syringe to try to aspirate some stomach fluid. Often they were unable to draw any back and they were concerned as to whether damage was being caused to the delicate lining of their baby's stomach. Some parents were taught to put sterile water down the tube and aspirate back in line with current recommendations (NPSA 2011a) but they were concerned about how many times this could be done. One parent was

advised to put a small amount of feed down the tube and then draw back to check the position.

In spite of there being clear protocols and parent information leaflets on the procedure parents reported that the information from nurses varied and they became aware that nurses relied on their experience to judge whether the tube was in the right place as well as official Trust procedures. One parent was concerned because he was told to judge the position of the tube by inserting a certain length of tube, but he could not remember any further advice regarding the verification of placement. Another was advised that the position could be checked by the baby's reaction as they would cough and become cyanosed if the tube had been placed in their lungs. This advice is clearly contrary to current guidelines.

Uncertainty regarding the position of the tube could not be alleviated by X-ray verification of tube position as parents were told that this was unreliable and it might take a while to get an X-ray done. The clinical need for a more certain and reliable method of verifying tube placement was clearly apparent from the experiences of members of the User Network and their enthusiasm to help develop the device was sound evidence of the importance of the issue for them.

In addition parents explained that the potential for early discharge puts pressure on parents to claim that they feel confident in the use of the nasogastric tube when that may not be true. Parents reported that they felt that their babies might be allowed home earlier if they were seen to be doing well with nasogastric feeding and if parents were confident in this procedure. Parents felt there was a need to get out of hospital as soon as possible and one parent reported that they had only changed the tube once before discharge, but had seen it done on a number of occasions.

Whilst it was reassuring to have the need for a new device reinforced by both the professional and lay users the management of their expectations became a challenge during the project. The time-to-market for new healthcare products can be a clear barrier to user involvement in product development as it can result in them becoming cynical and disinterested particularly when there is an urgent need for a better device (Bridgelal Ram, Grocott & Weir 2008). It was necessary

to repeatedly remind members of the group of the timescale of the product development and disappointment in not having a device to try immediately contributed to dissatisfaction in the process of user involvement.

A strategy to manage expectations suggested by (Bridgelal Ram, Grocott & Weir 2008) is to communicate regularly about the progress of the project and completed milestones and this was adopted through a regular, 6 monthly, Project Bulletin as discussed earlier.

6.11.2 Design

User involvement was logged in the user carer activity table, which was reviewed at project meetings held every 2 weeks and Quarterly Review Meeting held every 3 months. The views of the User Network members on the design of the indicator box were crucial in ensuring that the device was “user friendly” and met the needs of lay as well as professional users and could be beneficial in home as well as hospital environments. Table 22 gives a summary of suggestions.

Question	Responses
What needs to be included in the design of the box?	On/off button and screen
	date
	Time – useful to show battery is working
	Low battery indicator
	Needs to be robust
	Simple connector
	Easy connection
	Possibility of losing the box – could nurses carry a spare?
	Must not be able to attach the box to the mains
	Low battery indicator
	Should not be too heavy
	Nothing that might drag
	Enable parent – baby contact while feeding
	Put on table while parent feeding baby
What would be the appropriate size of the box?	Mobile phone size
	Not small and fiddly – larger than mobile phone would be OK
	Mobile phone size to fit in a baby bag
	Experience of using a monitor that fitted into the pocket (not for NGT)
What would be the best design for the indicator	As simple as possible
	Not sounds – hospitals are noisy places
	Should not have to need to interpret the results
	Words, colours, ticks and crosses
	Green for correct, red for stop
	Vibration – like a mobile phone – useful for blind, deaf and those with reading problems
	Sad / smiley face
	More than one method to indicate that the tube is in the right place
	Green tick, red cross
	Buzzer
	Yes/no
Batteries	Batteries might get lost
	Should not be able to use batteries for other devices

Table 22: User Advisory Group views on design of indicator box

6.11.3 Manufacture

The views of the User Network were fed into the Risk Assessment documents and Instructions for Use and also into the design brief and User Requirement Specification Document (Appendix 26) prepared for the potential manufacturing companies for the prototype tubes and indicator box.

6.11.4 Testing

Members of the User Network were not involved in testing the tube directly but they will be shown the prototypes and their opinions sought with regard to the look and feel of the tubes and the ergonomics and ease of use of the indicator box. User evaluation of medical devices is an important part of the development process and has been reported as a means of involving users in device development, for example, manual handling equipment (Pain et al. 1999), but with new devices it is important to distinguish between user evaluation and participation in clinical trials or evaluation studies.

6.11.5 Trials

Professional and lay users helped to develop the information sheets to be used in the clinical trials of the tubes. This ensured that they were easy to read and understand by a range of people. Involving users in improving the wording of information sheets and invitation letters and ensuring that the wording is sensitive has been reported in the literature (Paterson 2004).

6.11.6 Dissemination and Implementation

Involving users in disseminating results is advocated although there can be challenges with this aspect of the research process particularly when publishing in academic journals (Brett et al. 2012). A publication strategy has been discussed with professional and lay users who will be involved in preparing papers for publication.

6.12 Evaluation of User Involvement

Key issues identified in this aspect of the project were the need to be flexible in definition of the term “users” and in the methods of communication with them. Rigid approaches and the notion of a User Group meeting together every few months needed to be abandoned and an understanding of how group members communicate with each other as well as the research team were developed.

User satisfaction with involvement in the project will be assessed by questionnaire and discussion at the end of the project at a final “thank you” meeting. The impact of the User Network on the project will be assessed by reviewing all aspects of user involvement including analysis of user feedback, design decisions and documentation.

The Public Involvement Impact Assessment Framework (PiiAF) was introduced after the commencement of this research but has proved a useful tool in guiding the evaluation of the impact of the User Network and confirming the strategies employed in this project (PiiAF Study Group 2014).

To assess the impact of user involvement in the project a ‘thank you event’ will be held towards the end of the project in June 2015 as a way to ensure final feedback and provide an opportunity to gather views about the ways the project has approached user involvement from the perspectives of those involved. This event will provide an opportunity to invite all members of the User Network to participate in the development of publications and presentations following completion of the project in order to disseminate experiences and expertise of user involvement in the development of a medical device.

6.13 Conclusion

This chapter has examined the reality of involving users of medical devices, be they professional or lay users, in the development of a new medical device and the challenges encountered when trying to facilitate that involvement. A total of

14 users were involved in the project, 8 lay users and 6 professional users. The evidence base for the impact of user involvement in research remains weak particularly with regard to medical device development however the literature available was used to discuss the experiences gained in this study.

Difficulties in promoting and maintaining user involvement in research have been reported and it is suggested that the majority of studies will experience interruptions in user involvement. However this should not be a reason to curtail such involvement and practical suggestions have been made in this chapter for increasing and maintaining user involvement. The need for a standard framework and language for user involvement has been discussed in the literature and it is hoped that this study can add to the available evidence base for developing such a framework.

Chapter 7: Discussion, Conclusions, Limitations and Future Work

7.1 Introduction

This final chapter summarises the research conducted and discusses the limitations and implications for further research. Ongoing work to enable the next stages of the research, ie the manufacture of LINGT iteration 3 and the clinical evaluation of this new device is discussed.

7.2 Discussion

This thesis documents the research undertaken to develop a novel nasogastric tube which can self-indicate its position in the stomach. Chapter 1 considered the importance of translational research in transferring scientific innovations from bench to bedside and chapter 2 discussed the literature and current issues associated with nasogastric tubes and enteral feeding justifying the need for the development of a new medical device.

Chapter 3 explored the initial development of hand painted prototype tubes (LINGT iteration 1) and discussed the results of experimental evaluation of 40 of these tubes with a range of fluids in the laboratory and with freshly resected gastric tissue in clinical settings. LINGT iteration 2 involved prototype tubes manufactured by Arrotek Medical Ltd and the design decisions and experiments with 60 of these tubes are discussed in chapter 4. Experimental work conducted in the laboratory by the PDRA is summarised and detailed discussion of the evaluation in theatre conducted by the author is presented.

Experimental data are not sufficient to develop a medical device ready for introduction to the market and health services and chapter 5 considered the regulatory processes involved and the Quality Management System required, including risk assessments in order to achieve a device that can be used with patients. The involvement of users is crucial, not only in health service research but particularly in the development of a new device that will be used by lay as

well as professional carers. The development of a User Network is explored in chapter 6 and the input of this network evaluated.

7.3 Limitations

LINGT iteration 1 was clearly limited by the nature of the application of the “wires” and sensing materials, vitamin K_1 and silver/silver chloride (Ag/AgCl), by hand painting. In spite of efforts to ensure uniformity of the application of the silver paint and sensing materials, the processes inevitably varied and so it could not be claimed that the 40 tubes produced and tested were of consistent quality. Never the less one third of the tubes generated a current forming the basis for iteration 2. The current generated by LINGT iteration 1 was in the range of 50-200 microamps considerably higher than that generated by LINGT iteration 2 which was in the range of 1- 30 microamps. This is believed to be because of the much smaller amount of vitamin K_1 that could be applied with the application technique used in iteration 2 than with the dipping technique used in iteration 1.

LINGT iteration 2 was manufactured by Arrotek Medical Ltd and thus were of a consistent quality with wires (stainless steel or titanium) integrated into the walls of the tube and a controlled process of applying the sensing materials to ensure the precise application of a specific amount was found. This gave greater confidence that the prototype tubes were of uniform quality and experiments could be conducted with greater confidence. Whilst experiments using buffer solutions and artificial gastric fluid gave consistent results the variation of size and composition of clinical samples including gastric tissue, gastric fluid and sputum, made comparisons difficult and results using amperometry were disappointing. The use of zero current potential proved far more successful in distinguishing between different pH levels in human gastric fluid and this electrochemical test is to be used in the final design of the indicator box.

Review of the relevant literature suggested that the selected sensing materials would not be harmful to patients in the quantities used however a report from a qualified Toxicologist is necessary in order for MHRA to give a notice of no objection for clinical investigation of the new device to take place. This has been commissioned from a registered toxicologist and reports included in Appendix 4.

The development of the User Network discussed in chapter 6 had a number of limitations. The author commenced the project with the aim of establishing a User Advisory Group which would meet at regular 3 monthly intervals and offer advice regarding the design of the device and the project. However a review of the literature on the topic and feedback from initial meetings indicated the limitations of this approach. A more flexible model of a User Network was developed but this was still limited by the people available for and willing to be involved. In particular input from children and adults who had used nasogastric tubes was limited.

7.4 Future Work

7.4.1 Design Freeze and Completion of Prototype Nasogastric Tubes and Indicator Box

At the start of the project it was envisaged that a prototyping company would be found who would manufacture, package and sterilise 300 prototype tubes for clinical evaluation. The inability to find such a company discussed in chapter 5 has resulted in a nasogastric tube company being appointed to manufacture the tubes but this company cannot apply the specific sensing materials required for the system to function. The author has therefore had to arrange for this work to be conducted at the University of Hull requiring the purchase and installation of a class 8 clean room, the selection, purchase and installation of appropriate machines to apply the coatings and contracting a company to undertake this work. This has now been achieved (Figure 23) and the first prototype tubes are due to be coated in the cleanroom in December 2014.

Figure 23: Validated cleanroom with Biodot machines installed for application of sensing materials

Table 22 summarises the companies selected and appointed and the work is planned to take place in the first quarter of 2015 with the sterilised tubes ready for testing in anaesthetised patients in the second quarter of 2015. The final design freeze of the tube was agreed in August 2014 after INTERVENE found that co-extruded wires would not be possible and the designs included in Appendix 27 were used to manufacture LINGT iteration 3.

Company	Role	Completion Date
Connect 2 Cleanrooms	Installation and validation of class 8 clean room	August 2014
Biodot Ltd	Supply and installation of spotting machines to apply vitamin k1 and Ag/AgCl	September 2014
INTERVENE Ltd	Manufacture and supply 300 prototype nasogastric tubes. Package and sterilise once sensor materials applied	January 2015
Technostics Ltd	Apply sensing materials to prototype tubes supplied by INTERVENE using Biodot machines	February 2015
Image to Implant	Manufacture and Supply 5 prototype Indicator Boxes	January 2015
Reece-Jones Consulting	Supply toxicology reports on Vitamin K1 and Ag/AgCl for MHRA	September 2014
SGS	Certify Quality Management System as compliant with ISO 13485:2012	February 2015

Table 23: Summary of companies involved in the future development of LINGT

7.4.2 Clinical Investigation

The route to CE marking discussed in chapter 5 requires that a Clinical Investigation Plan is submitted to MHRA. This is currently being prepared and the required ethical and R&D permisions sought as well as the MHRA notice of no objection.

The primary objective of the clinical investigation is: to verify the performance of the LINGT device (nasogastric tube and indicator box) under normal conditions

of use. This will be a prospective, observational, phase 1 type study. Answers to the following questions will be sought:

- Does the LINGT accurately and reliably indicate the position of its tip in the stomach?
- How easy or difficult is it to introduce the LINGT in adults in comparison with conventional nasogastric tubes?
- Does the external indicator box provide sufficiently detectable visual signal that correct tip location has been achieved in a hospital operating theatre?

Any undesirable side effects will also be assessed. The clinical investigation will be in 2 phases, first a validation study to evaluate the prototype LINGT iteration 3 in 140 anaesthetised patients undergoing abdominal surgery and requiring insertion of a nasogastric tube as part of their routine care. These patients routinely have nasogastric or orogastric tubes passed under direct vision by consultant anaesthetists to ensure gastric decompression. The number of patients required for the study has been calculated with the help of a statistician, Dr Eric Gardiner (Faculty of Health and Social Care, University of Hull) based on the sensitivity and specificity of current procedures and those of the LINGT. Sensitivity is defined as the proportion of correctly placed tubes according to the gold standard that will be recorded as correctly placed by the indicator box and specificity as the proportion of incorrectly placed tubes according to the gold standard that will be recorded as incorrectly placed by the indicator box. The gold standard in this case will be palpation or visualisation of the tube in the stomach by the surgeon.

The required number of measurements needed where the tube is correctly placed needs to be adjusted upwards as some tubes will be inadvertently incorrectly placed. It would be unethical to deliberately insert tubes into the lungs to obtain data from tubes incorrectly placed but it is considered acceptable to halt the insertion short of the stomach with the tip sitting in the oesophagus in order to obtain a reading for tubes incorrectly placed. Table 24 gives the suggested numbers of patients required for the study.

Anticipated Sensitivity	Anticipated Specificity	Minimum acceptable Sensitivity	Minimum acceptable Specificity	Number of tubes correctly placed	Number of tubes wrongly placed
0.9	0.9	0.75	0.8	67	134

Table 24: Summary of number of required participants in clinical evaluation in relation to specificity and sensitivity

The values of sensitivity and specificity reported in Hanna et al (2010), section 7.4 for the 'ph<=5.5' criterion were considered when agreeing the minimum acceptable levels of sensitivity and specificity. The anticipated sensitivity and specificity of the LINGT should be higher than these levels, however without published confidence intervals the published figures were treated with caution by the statistician. Minimal levels of sensitivity and specificity of 75% and 80% respectively were agreed on consideration of the literature and discussion with experts in the field. The anticipated values of 90% for both sensitivity and specificity were agreed on analysis of the available data for the LINGT and the number of participants calculated using published formulae (Pepe 2003).

The study will be conducted in patients listed for abdominal surgery. It is standard anaesthetic practice in this type of surgery for an orogastric or nasogastric tube to be passed immediately following induction of anaesthesia to ensure gastric decompression during surgery. Inserting a gastric tube by an anaesthetist in an anaesthetised patient is safe and accurate because the anaesthetist passes the tube under direct vision directly into the upper oesophagus. In this way the patient is not distressed by having the tube inserted and there is no change to their normal expected care and treatment

Patients listed for abdominal surgery will be identified from the waiting list. The Principal Investigator or research nurse will visit the patients on the ward or in the Outpatient Department at least 24 hours before their surgery to explain the study, answer any questions and leave an information sheet with them. One of them will return the following day to answer any further questions and seek consent.

In this study a prototype LINGT iteration 3 in place of the standard "Ryles" nasogastric tube. They are similar in consistency and identical in size. The most commonly used size of 12 Fr has been manufactured for use in the study. The external end of the LINGT will be attached to an indicator box which will indicate correct position by a light signal. The surgeon will be able to verify that the tip of the tube is positioned inside the stomach by feeling and seeing the tube in place.

If these preliminary in vivo studies confirm the reliability and accuracy of the prototype tube a second efficacy study will be conducted to explore the use of the tube in enteral feeding. The clinical investigation is planned for spring 2015 with each phase of the investigation lasting a period of 22 weeks. The NIHR funded project will therefore be completed in July 2015.

7.4.3 Evaluation of User Network

Whilst patient and public involvement is crucial for high quality health care research there are particular issues encountered when involving users and carers in the development of medical devices. These were discussed in detail in chapter 6 and the development of a flexible User Network described. Whilst the final evaluation of this network will not take place until the end of the project in June 2015 the value of the involvement of lay and professional users is evident throughout the project. Contact with members continues through newsletters and meetings and the continued willingness of members to be involved in the project is testament to the value they place in the research.

Never the less improvements could be made and contact with the support group “Patients on Intravenous and Naso-gastric Nutrition Treatment” (PINNT) has given the author new opportunities for involving the public in her research (PINNT Patients on Intravenous & Nasogastric Nutrition Therapy 2014). Feedback from current members of the User Network will be used with views from this organisation to improve communication and ensure that users continue to be involved in LINGT iteration 3.

7.5 Other Developments

Since the commencement of this research the issues and problems associated with the placement of nasogastric tubes has received increasing attention. In the USA the multiprofessional, interorganisational venture sponsored by the Association of Parenteral and Enteral Nutrition (A.S.P.E.N.) named the New Opportunities for Verification of Enteral Tube Location (NOVEL) project has been established to develop effective and practical solutions to the problem of initial safe placement and continued verification of correct placement of nasogastric tubes in children (Irving et al. 2014). This group is looking at new technologies that will minimise or eliminate the need for frequent x-rays and suggest that this technology should incorporate the following features:

- "*Placement accuracy across a wide range of feeding tube sizes commonly used in children*
- *Allow ongoing verification of the location of the device and its tip with accuracy*
- *Incorporate simple, user friendly, portable technology*
- *Have a reasonable cost with durability for sustainable use*
- *Provide electromagnetic compatibility eg with pacemakers, subcutaneous medication pumps*
- *Not require any change in the pliability and flexibility of the enteral access device"*

(Irving et al. 2014) pp 76

It is very reassuring that the LINGT meets all of these requirements and once clinical evaluation has been completed contact with the NOVEL project will be made.

7.6 Conclusions

This thesis details the development of a new medical device to meet a recognised clinical need. The clinical need is clearly evident from the detailed literature review and discussions with professional and lay members of the User Network. An electrochemical reaction was identified and applied as a sensing mechanism

to a nasogastric tube, initially by hand and then by manufacturing techniques, to produce a nasogastric tube that can self-indicate its position. The design and development of the device was informed by the views of both lay and professional users who collaborated with the author through a User Network. Regulatory approval was enabled through the establishment of a Quality Management System compliant with BS EN ISO 13485:2012 and intellectual property rights protected through international patents.

Further research is required to evaluate the final manufactured LINGT iteration 3 and clinical trials will be conducted with this device in 2015. The design of LINGT iteration 3 has been agreed and manufacturing processes have been set up to ensure that the device is manufactured to the highest standards and meets the regulatory requirements in order to conduct clinical trials.

The author has succeeded therefore in translating the findings from scientific research into a new medical device which will be of benefit to patients. Nurses have a pivotal role in translational research as they are well positioned to identify clinical problems of concern to patients and have an appreciation of how those problems may be answered. Nurses are inevitably innovative in their daily practice through problem solving and applying knowledge from a range of subject disciplines to their work with patients. Given the right opportunities such innovation can be developed and nurses may be instrumental in taking problems from the bedside to the bench, where solutions can be found, and taking those solutions from the bench back to the bedside for the benefit of patients.

Nurses frequently work in collaborative, multi-disciplinary teams and have experience of searching for joint solutions to complex problems. As translational science emerges, as a new area for research and funding opportunities, nurses must be at the forefront using their unique insights, knowledge and skills to ensure that developments in scientific research are applied successfully to real world clinical problems. In the future nurse researchers will be increasingly involved in translational research ensuring that new knowledge is developed for patient benefit.

References

Adam, S. & Batson, S. 1997, "A study of problems associated with the delivery of enteral feed in critically ill patients in five ICUs in the UK", *Intensive Care Medicine,* vol. 23, no. 3, pp. 261-266.

Ahrens, T. & Sona, C. 2003, "Capnography application in acute and critical care", *AACN Clinical Issues,* vol. 14, no. 2, pp. 123-132.

Allen, D.B. 1988, "Postprandial hypoglycemia resulting from nasogastric tube malposition", *Pediatrics,* vol. 81, no. 4, pp. 582-584.

Allsop, J., Holt, R., Levesley, M. & Bhakta, B. 2010, "The engagement of children with disabilities in health-related technology design processes: Identifying methodology", *Disability and Rehabilitation: Assistive Technology,* vol. 5, no. 1, pp. 1-13.

American Academy of Pediatrics Committee on Fetus and Newborn 2003, "Controversies Concerning Vitamin K and the Newborn", *Pediatrics,* vol. 112, pp. 191-193.

American Association of Critical Care Nurses 2010a, *, Practice Alert: Verification of Feeding Tube Placement* [Homepage of American Association of Critical Care Nurses], [Online]. Available: http://www.aacn.org/wd/practice/docs/practicealerts/verification-feeding-tube-placement.pdf?menu=aboutus [2014, 13 June].

American Association of Critical Care Nurses 2010b, *Verification of feeding tube placement: Audit Tool* [Homepage of American Association of Critical Care Nurses], [Online]. Available: http://www.aacn.org/wd/practice/docs/practicealerts/audit-verification-feeding-tube-placement.pdf?menu=aboutus [2014, 13 June].

Anderson, O., Buckle, P. & Hanna, G. 2012, "Ergonomic risk assessment of nasogastric tube placement and implications for design and training", *Work: A Journal of Prevention, Assessment and Rehabilitation,* vol. 41, pp. 4689-4691.

Araimo, , F, Caramia, , R & Meschesi, , E 2011, "Intracranial placement of a nasogastric tube in a non-trauma patient", *HSR Proceedings in Intensive Care & Cardiovascular Anesthesia,* vol. 3, no. 1, pp. 71-71.

Araujo-Preza, C., Melhado, M.E., Gutierrez, F.J., Maniatis, T. & Castellano, M.A. 2002, "Use of capnometry to verify feeding tube placement", *Critical Care Medicine,* vol. 30, no. 10, pp. 2255-2259.

Arbit, H.M. & Paller, M.S. 2006, "A program to provide regulatory support for investigator-initiated clinical research", *Academic Medicine: Journal of the Association of American Medical Colleges,* vol. 81, no. 2, pp. 146-153.

Australian Government, National Health and Medical Research Council 2014, *Draft Statement on Consumer Involvement in Health and Medical Research* [Homepage of Australian Government], [Online]. Available: http://consultations.nhmrc.gov.au/public_consultations/consumer_involvement [2014, 13 August].

Aynsley-Green, A. 1983, "Hormones and postnatal adaptation to enteral nutrition", *Journal of Pediatric Gastroenterology and Nutrition,* vol. 2, no. 3, pp. 418-427.

Bankhead, R., Boullata, J., Brantley, S., Corkins, M., Guenter, P., Krenitsky, J., Lyman, B., Metheny, N.A., Mueller , C., Robbins, S. & Wessel, J. 2009, "Enteral nutrition administration. In: A.S.P.E.N. enteral nutrition practice recommendations.", *JPEN Journal of Parenteral and Enteral Nutrition,* vol. 33, no. 2, pp. 149-158.

Banks, C.E., Davies, T.J., Evans, R.G., Hignett, G., Wain, A.J., Lawrence, N.S., Wadhawan, J.D., Marken, F. & Compton, R.G. 2003, "Electrochemistry of immobilised redox droplets: concepts and applications", *Physical Chemistry Chemical Physics,* vol. 5, no. 19, pp. 4053-4069.

Barber, R., Beresford, P., Boote, J., Cooper, C. & Faulkner, A. 2011, " Evaluating the impact of service user involvement on research: a prospective study", *International Journal of Consumer Studies,* vol. 35, pp. 609-615.

Bard, A.J. & Faulkner , L.R. 2001, *Electrochemical Methods: Fundamentals and Applications,* 2nd edn, Wiley, Chichester.

Barker, H.M. 2004, *Nutrition and Dietetics for Health Care,* 10th edn, Churchill Livingstone, London.

Barksdale, J. 1968, "Titanium. " in *The Encyclopedia of the Chemical Elements.* , ed. C.A. Hampel, Reinhold Book Corporation, New York, pp. 732-738.

Barwing, J., Ambold, M., Linden, N., Quintel, M. & Moerer, O. 2009, "Evaluation of the catheter positioning for neurally adjusted ventilatory assist", *Intensive Care Medicine,* vol. 35, no. 10, pp. 1809-1814.

Baum, E.D., Elden, L.M., Handler, S.D. & Tom, L. 2008, "Management of hypopharyngeal and esophageal perforations in children: three case reports and a review of the literature", *ENT: Ear, Nose & Throat Journal,* vol. 87, no. 1, pp. 44-47.

Beckstrand, J., Ellett, M.L.C. & McDaniel, A. 2007, "Predicting internal distance to the stomach for positioning nasogastric and orogastric feeding tubes in children", *Journal of Advanced Nursing,* vol. 59, no. 3, pp. 274-289.

Berry, S., Orr, M., Schoettker, P., Lacy, J., Davis, C., Warshawsky, K., Nussbaum, M. & Bower, R. 1994, "Intestinal placement of pH-sensing nasointestinal feeding tubes", *JPEN.Journal Of Parenteral And Enteral Nutrition,* vol. 18, no. 1, pp. 67-70.

Beyond Compliance 2014, [Homepage of Beyond Compliance], [Online]. Available: http://www.beyondcompliance.org.uk/ [2014, 03/10].

Black, J. 2006, *Biological performance of materials : fundamentals of biocompatibility,* 4th edn, CRC Taylor & Francis, Boca Raton, Fla.

Boivin, M., Levy, H. & Hayes, J. 2000, "A multicenter, prospective study of the placement of transpyloric feeding tubes with assistance of a magnetic device. The Magnet-Guided Enteral Feeding Tube Study Group", *JPEN.Journal of Parenteral And Enteral Nutrition,* vol. 24, no. 5, pp. 304-307.

Boote, J., Baird, W. & Beecroft, C. 2010, "Public involvement at the design stage of primary health research: a narrative review of case examples", *Health Policy,* vol. 95, no. 1, pp. 10-23.

Boote, J., Wong, R. & Booth, A. 2012, "'Talking the talk or walking the walk?'A bibliometric review of the literature on public involvement in health research published between 1995 and 2009", *Health Expectations,* [Online], . Available from: http://onlinelibrary.wiley.com/doi/10.1111/hex.12007/full. [13 August 2014].

Boote, J.D., Dalgleish, M., Freeman, J., Jones, Z., Miles, M. & Rodgers, H. 2012, ""But is it a question worth asking?" A reflective case study describing how public involvement can lead to researchers? ideas being abandoned", *Health Expectations,* [Online], . Available from: http://onlinelibrary.wiley.com/doi/10.1111/j.1369-7625.2012.00771.x/full. [13 August 2014].

Bourgault, A.M. & Halm, M.A. 2009, "Feeding tube placement in adults: safe verification method for blindly inserted tubes", *American Journal of Critical Care,* vol. 18, no. 1, pp. 73-76.

Bourgault, A., M. 2012, *Adoption of AACN verification of feeding tube placement practice alert by critical care nurses*, Georgia Health Sciences University.

Bourgault, A., M., Heath, J., Hooper, V., Sole, M., Lou, Waller, J., L. & NeSmith, E., G. 2014, "Factors Influencing Critical Care Nurses' Adoption of the Aacn Practice Alert on Verification of Feeding Tube Placement", *American Journal of Critical Care,* vol. 23, no. 2, pp. 134-144.

Boyd, S. 2005, "Aspiration of naso/orogastric tubes", *Infant,* vol. 1, no. 5, pp. 156.

Brett, J., Staniszewska, S., Mockford, C., Herron-Marx, S., Hughes, J., Tysall, C. & Suleman, R. 2012, "Mapping the impact of patient and public involvement on health and social care research: a systematic review", *Health Expectations,* [Online], vol. 15. Available from: http://onlinelibrary.wiley.com/doi/10.1111/j.1369-7625.2012.00795.x/full. [13 August 2014].

Bridgelal Ram, M., Grocott, P.R. & Weir, H.C.M. 2008, "Issues and challenges of involving users in medical device development", *Health Expectations,* vol. 11, no. 1, pp. 63-71.

Bridgelel Ram, M., Browne, N., Grocott, P.R. & Weir, H.C.M. 2005, *, Methodologies to Capture User Perspectives in Medical Device Development: A Survey of the Healthcare Literature. Multidisciplinary Assessment of Technologies Centre for Healthcare (MATCH) Report 2005. Project 3: Deliverable 6* [Homepage of MATCH], [Online]. Available: http://www.match.ac.uk [2014, 14 August].

Bridgelel Ram, M., Grocott, P.R. & Weir, H.C.M. 2007, "Issues and Challenges of Involving Users in Medical Device Development", *Health Expectations,* vol. 11, no. 1, pp. 63-71.

British Association for Parenteral and Enteral Nutrition & Advancing Clinical Nutrition 2010, *Annual BANS Report* [Homepage of BAPEN], [Online]. Available: http://www.bapen.org.uk/pdfs/bans_reports/bans_report_10.pdf [2013, 16 June].

British Society of Gastroenterology 2013, *Guidance for Enteral Feeding* [Homepage of BSG], [Online]. Available: http://www.bsg.org.uk/ [2014, 11 July].

Brown, D.J., Battersby, S., Standen, P., Anderton, N. & Harrison, M. 2005, "Inclusive design for disability: A prototype switch for use in virtual learning environments", *International Journal on Disability and Human Development,* vol. 4, no. 2, pp. 103-119.

Bruseberg, A. & McDonagh-Philp, D. 2001, " New product development by eliciting user experience and aspirations", *International Journal of Human-Computer Studies,* vol. 55, no. 4, pp. 435-452.

Bryman, A. 2008, *Social Research Methods,* 3rd edn, Oxford University Press, Oxford.

Buckle, P., Clarkson, P.J., Coleman, R., Ward, J. & Anderson, J. 2006, "Patient Safety, Systems Design and Ergonomics", *Applied Ergonomics,* vol. 37, pp. 491-500.

Burns, L.R. 2007, "Growth and innovation in medical devices: a conversation with Stryker chairman John Brown", *Health Affairs,* vol. 26, no. 3, pp. w436-44.

Burns, S.M., Carpenter, R. & Truwit, J.D. 2001, "Report on the development of a procedure to prevent placement of feeding tubes into the lungs using end-tidal CO2 measurements", *Critical Care Medicine,* vol. 29, no. 5, pp. 936-939.

Burns, S.M., Carpenter, R., Blevins, C., Bragg, S., Marshall, M., Browne, L., Perkins, M., Bagby, R., Blackstone, K. & Truwit, J.D. 2006, "Detection of inadvertent airway intubation during gastric tube insertion: Capnography versus a colorimetric carbon dioxide detector", *American Journal Of Critical Care,* vol. 15, no. 2, pp. 188-195.

Callard, F., Rose, D. & Wykes, T. 2012, "Close to the bench as well as at the bedside: involving service users in all phases of translational research", *Health Expectations,* vol. 15, no. 4, pp. 389-400.

Canadian Institutes of Health Research 2014, *Citizen Engagement* [Homepage of CIHR], [Online]. Available: http://www.cihr-irsc.gc.ca/e/41592.html [2014, 14 August].

Cannaby, A., Evans, L. & Freeman, A. 2002, "Nursing care of patients with nasogastric feeding tubes", *British Journal of Nursing (BJN),* vol. 11, no. 6, pp. 366.

Castell, D.O. 2000, "Nasogastric tubes permit reflux and aspiration: is there any evidence?" *Annals of Internal Medicine,* vol. 132, no. 7, pp. 594-595.

Catalano, K. 2006, "JCAHO's national patient safety goals 2006", *Journal of Perianesthesia Nursing,* vol. 21, no. 1, pp. 6-11.

Cavet, J. & Sloper, P. 2005, "Children and Young People's Views on Health and Health Services: A Review of the Evidence", *National Children's Bureau: London,* pp. 1-83.

CDRH-Center for Devices and Radiological Health 2014, *, U.S. Food and Drug Administration, Protecting and Promoting Your Health* [Homepage of Food and Drug Administration], [Online]. Available: http://www.fda.gov/MedicalDevices/default.htm [2014, 03/10].

Chandra, R. & Kumar, P. 2010, "Intracranial introduction of a nasogastric tube in a patient with severe craniofacial trauma", *Neurology India,* vol. 58, no. 5, pp. 804-805.

Chau, J.P.C., Lo, S.H.S., Thompson, D.R., Fernandez, R. & Griffiths, R. 2011, "Use of end-tidal carbon dioxide detection to determine correct placement of nasogastric tube: A meta-analysis", *International Journal of Nursing Studies,* vol. 48, no. 4, pp. 513-521.

Chau, J.P., Thompson, D.R., Fernandez, R.S., Griffiths, R. & Lo, H. 2009, "Methods for Determining the Correct Nasogastric Tube Placement after Insertion: A Meta-Analysis", *Joanna Briggs Institute Library of Systematic Reviews,* vol. 7, no. 16, pp. 679-760.

Chellis, M.J., Sanders, S.V., Webster, H., Dean, J.M. & Jackson, D. 1996, "Early enteral feeding in the pediatric intensive care unit", *Journal of Parenteral and Enteral Nutrition,* vol. 20, no. 1, pp. 71-73.

Chen, Y., Wang, L., Chang, Y., Yang, C., Wu, T., Lin, F., Liu, S. & Wei, T. 2014, "Potential Risk of Malposition of Nasogastric Tube Using Nose-Ear-Xiphoid Measurement", *PLoS ONE,* vol. 9, no. 2, pp. 1-7.

Chernoff, R. 2006, "An overview of tube feeding: from ancient times to the future", *Nutrition in Clinical Practice,* vol. 21, no. 4, pp. 408-410.

Chesla, C.A. 2008, "Translational research: Essential contributions from interpretive nursing science", *Research in Nursing & Health,* vol. 31, no. 4, pp. 381-390.

Choonara, I., Scott, A., Haynes, B., Cholerton, S., Breckenridge, A. & Park, B. 1985, "Vitamin K1 metabolism in relation to pharmacodynamic response in anticoagulated patients.", *British journal of clinical pharmacology,* vol. 20, no. 6, pp. 643-648.

Clevenger, F.W. & Rodriguez, D.J. 1995, "Techniques and procedures. Decision-making for enteral feeding administration: the why behind where and how." *Nutrition in Clinical Practice,* vol. 10, no. 3, pp. 104-113.

Clough, P. & Nutbrown, C. 2002, *A student's guide to methodology: justifying enquiry,* Sage, London.

Cohen, A.B., Stavropoulos, S.W., Dagli, M., Mondschein, J.I., Soulen, M.C., Shlansky-Goldberg, R.D., Solomon, J.A., Chittams, J.L. & Trerotola, S.O. 2011, "Silicone and Polyurethane Tunneled Infusion Catheters: A Comparison of Durability and Breakage Rates", *Journal of Vascular and Interventional Radiology,* vol. 22, no. 5, pp. 638-641.

Cohen, D. 2012, "How a fake hip showed up failings in European device regulation", *BMJ,* vol. 345, no. 7880, pp. 19-21.

Cohen, D. & Billingsley, M. 2011, "Europeans are left to their own devices", *BMJ (Clinical research ed.),* vol. 342, pp. d2748.

Cohen, D. 2012, "UK health secretary promises to tighten regulatory procedures for medical devices", *BMJ (Clinical research ed.),* vol. 345, pp. e7192-e7192.

Conway, H.A. & McGuiness, N.W. 1986, "Idea generation in technology-based firms", *Journal of Production and Innovation Management,* vol. 3, pp. 276-291.

Cordero, L., Nankervis, C.A., Coley, B.D. & Giannone, P.J. 2010, "Orogastric Tube placement in extremely low birth weight infants", *Journal of Neonatal-perinatal Medicine,* vol. 2, no. 4, pp. 253-259.

Cornwall Partnership NHS Foundation Trust 2013, *, Paediatric Community Services - Enteral Feeding Policy and Procedures for Children in the Community* [Homepage of Cornwall Partnership NHS Foundation Trust], [Online]. Available: http://www.rcht.nhs.uk/DocumentsLibrary/CornwallFoundationTrust/Policies/Clinical/ClinicalGuidelines/PCS03712Validation.pdf [2014, 14 July].

Covington, A.K., Bates, R.G. & Durst, R.A. 1985, "Definitions of pH scales, standard reference values, measurement of pH, and related terminology", *Pure Applied Chemistry,* vol. 57, no. 3, pp. 531-542.

Craig, J., Russell, C., Patterson, V. & Wootton, R. 1999, "User satisfaction with realtime teleneurology", *Journal of Telemedicine and Telecare,* vol. 5, no. 4, pp. 237-241.

Crocker, K.S., Krey, S.H. & Steffee, W.P. 1981, "Performance evaluation of a new nasogastric feeding tube", *JPEN.Journal of Parenteral and Enteral Nutrition,* vol. 5, no. 1, pp. 80-82.

Crosby, S.S., Apovian, C.M. & Grodin, M.A. 2007, "Hunger strikes, force-feeding, and physicians' responsibilities", *JAMA,* vol. 298, no. 5, pp. 563-566.

Cumming, C. & McFadzean, J. 2005, "A survey of the use of capnography for the confirmation of correct placement of tracheal tubes in pediatric intensive care units in the UK", *Paediatric Anaesthesia,* vol. 15, no. 7, pp. 591-596.

de Boer, J.C., Smit, B.J. & Mainous, R.O. 2009, "Nasogastric tube position and intragastric air collection in a neonatal intensive care population", *Advances in Neonatal Care,* vol. 9, no. 6, pp. 293-298.

De Vaus, D.A. 2001, *Research Design in Social Research,* Sage, London.

Department of Health 2013, *Treating patients and service users with respect, dignity and compassion*, England, London.

Department of Health 2012, *Caring for our future: reforming care and support* [Homepage of DOH], [Online]. Available: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/136422/White-Paper-Caring-for-our-future-reforming-care-and-support-PDF-1580K.pdf [2013, 16 June].

Department of Health 2010, *Equity and excellence: Liberating the NHS*, [Online], Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/213823/dh_117794.pdf. [9 October 2013].

Department of Health 2005, *Research Governance Framework for Health and Social Care -second edition* [Homepage of Department of Health], [Online]. Available:

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/139565/dh_4122427.pdf [2014, February 10].

Department of Health 2000a, *Research: Who's Learning? Consumers in NHS Conference Report* HMSO, London, January.

Department of Health 2000b, *Working Partnerships: Consumers in NHS 3rd annual report*, HMSO, London.

Department Of Health 1994, *The Health of the Nation: Key area Handbook, Mental Illness*, 2nd edn, HMSO, London.

Department of Health 1989, *Caring for People: Community Care in the Next Decade and Beyond*, HMSO, London.

Dhruva, S.S., Bero, L.A. & Redberg, R.F. 2009, "Strength of study evidence examined by the FDA in premarket approval of cardiovascular devices", *JAMA,* vol. 302, pp. 2679-2685.

Diaz-Rodriguez, A., Esponda-Prado, J. & Ize-Lamache, L. 2004, "Placement of nasoenteral feeding tubes under electrocardiographic guidance in critically ill patients", *Cirugia y Cirujanos,* vol. 72, no. 2, pp. 85-88.

Dobkin, E.D., Valcour, A., McCloskey, C.R., Allen, L., Kamble, J.C., Gleason, E., Orlando III, R., Berger, R. & Yeston, N.S. 1990, "Does pH paper accurately reflect gastric pH?", *Critical Care Medicine,* vol. 18, no. 9, pp. 985-988.

Dodrill, P., Donovan, T., Cleghorn, G., McMahon, S. & Davies, P. 2008, "Attainment of early feeding milestones in preterm neonates", *Journal of Perinatology,* vol. 28, no. 8, pp. 549-555.

Dornan, T. 2006, *Core Clinical Skills for OSCEs in Medicine,* 2nd edn, Churchill Livingstone, Edinburgh.

Druin, A. 2002, "The role of children in the design of new technology", *Behaviour & Information Technology,* vol. 21, no. 1, pp. 1-25.

D'Souza, ,C.R., Kilam, S.A., D'Souza, U., Janzen, E.P. & Sipos, R.A. 1994, "Pulmonary complications of feeding tubes: a new technique of insertion and monitoring malposition", *Canadian Journal Of Surgery.Journal Canadien De Chirurgie,* vol. 37, no. 5, pp. 404-408.

Dyer, C. 2003, "Junior doctor is cleared of manslaughter after feeding tube error", *BMJ: British Medical Journal,* vol. 326, no. 7386, pp. 414.

Dymond, E., Long, A., McCarthy, A. & Drake, M.J. 2012, "Developing a new treatment device: how to get an idea to the marketplace", *Neurourology and urodynamics,* vol. 31, no. 4, pp. 429-436.

Ehrenberg, W. 1958, *Electric conduction in semiconductors and metals,* Clarendon Press, Oxford.

Eisenberg, P., Spies, M. & Metheny, N.A. 1987, "Characteristics of patients who remove their nasal feeding tube", *Clinical Nurse Specialist,* vol. 1, no. 3, pp. 94-98.

Ellett, M.L.C., Cohen, M.D., Croffie, J., Lane, K.A., Austin, J.K. & Perkins, S.M. 2014, "Comparing bedside methods of determining placement of gastric tubes in children", *Journal for Specialists in Pediatric Nursing,* vol. 19, no. 1, pp. 68-79.

Ellett, M.L.C., Cohen, M.D., Perkins, S.M., Croffie, J., Lane, K.A. & Austin, J.K. 2012, "Comparing methods of determining insertion length for placing gastric tubes in children 1 month to 17 years of age", *Journal for Specialists in Pediatric Nursing,* vol. 17, no. 1, pp. 19-32.

Ellett, M.L.C., Cohen, M.D., Perkins, S.M., Smith, C.E., Lane, K.A. & Austin, J.K. 2011, "Predicting the insertion length for gastric tube placement in neonates", *Journal of Obstetric, Gynecologic, & Neonatal Nursing,* vol. 40, no. 4, pp. 412-421.

Ellett, M.L. & Beckstrand, J. 2001, "Predicting the distance for nasojejunal tube insertion in children", *Journal of The Society of Pediatric Nurses: JSPN,* vol. 6, no. 3, pp. 123-132.

Ellett, M.L. 1996, *Examination of Gavage tube placement*, Indiana University School of Nursing.

Ellett, M.L., Maahs, J. & Forsee, S. 1998, "Prevalence of feeding tube placement errors and associated risk factors in children", *MCN American Journal of Maternal Child Nursing,* vol. 23, no. 5, pp. 234-239.

Ellett, M.L.C., Beckstrand, J., Flueckiger, J., Perkins, S.M. & Johnson, C.S. 2005a, "Predicting the Insertion Distance for Placing Gastric Tubes", *Clinical Nursing Research,* vol. 14, no. 1, pp. 11-27.

Ellett, M.L.C., Croffie, J.M.B., Cohen, M.D. & Perkins, S.M. 2005b, "Gastric tube placement in young children", *Clinical Nursing Research,* vol. 14, no. 3, pp. 238-252.

Ellett, M.L.C., Woodruff, K.A. & Stewart, D.L. 2007, "The use of carbon dioxide monitoring to determine orogastric tube placement in premature infants: a pilot study", *Gastroenterology Nursing,* vol. 30, no. 6, pp. 414-417.

Ellett, M. 2004, "What is known about methods of correctly placing gastric tubes in adults and children", *Gastroenterology Nursing,* vol. 27, no. 6, pp. 253-261.

Ellett, M. & Beckstrand, J. 1999, "Examination of gavage tube placement in children", *Journal of the Society of Pediatric Nurses,* vol. 4, no. 2, pp. 51-60.

Elpern, E.H., Killeen, K., Talla, E., Perez, G. & Gurka, D. 2007, "Capnometry and air insufflation for assessing initial placement of gastric tubes", *American Journal Of Critical Care,* vol. 16, no. 6, pp. 544-549.

Erdman, A.G., Keefe, D.F. & Schiestl, R. 2013, "Grand challenge: applying regulatory science and big data to improve medical device innovation", *IEEE transactions on bio-medical engineering,* vol. 60, no. 3, pp. 700-706.

European Commission Scientific Committee on Consumer Safety 2010, *Opinion on Vitamin K1 (Phytonadione)* [Homepage of European Union], [Online]. Available: http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_014.pdf [2014, 18 July].

European Medical Technology Industry (Eucomed) 2012a, *Contributing to a Healthy and Sustainable Europe. Medtech Report 2010-2011* [Homepage of Eucomed], [Online]. Available: http://www.eucomed.com/uploads/Modules/Publications/20120222_eucomed_20102011_medtech_report.pdf [2014, 20 June].

European Medical Technology Industry (Eucomed) 2012b, May 2012-last update, *Eucomed Statement on Unsafe and Ineffective Devices Approved in the EU that were not approved in the US, US Food and Drug Administration (FDA)* [Homepage of Eucomed], [Online]. Available: http://www.eucomed.be/uploads/Modules/Publications/2012-eucomed-statement-on-fda-report.pdf. [2014, 31 March].

Farrington, M., Lang, S., Cullen, L. & Stewart, S. 2009, "Nasogastric Tube Placement Verification in Pediatric and Neonatal Patients", *Pediatric Nursing,* vol. 35, no. 1, pp. 17-24.

Fernandez, R.S., Chau, J.P., Thompson, D.R., Griffiths, R. & Lo, H. 2010, "Accuracy of biochemical markers for predicting nasogastric tube placement in adults—A systematic review of diagnostic studies", *International Journal of Nursing Studies,* vol. 47, no. 8, pp. 1037-1046.

Ferreras, J., Junquera, L.M. & Garcia-Consuegra, L. 2000, "Intracranial placement of a nasogastric tube after severe craniofacial trauma", *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology & Endodontology,* vol. 90, no. 5, pp. 564-566.

Fisher, A.C. 1996, *Electrode Dynamics (Oxford Chemistry Primers),* 1st edn, Oxford University Press, Oxford.

Freeman, D., Saxton, V. & Holberton, J. 2012, "A weight-based formula for the estimation of gastric tube insertion length in newborns", *Advances in Neonatal Care,* vol. 12, no. 3, pp. 179-182.

Freer, Y. & Lyon, A. 2005, "Nasogastric tube aspirate pH values associated with typical enteral feeding patterns in infants admitted to an NICU", *Journal of Neonatal Nursing,* vol. 11, no. 3, pp. 106-109.

Freij, R.M. & Mullett, S.T. 1997, "Inadvertent intracranial insertion of a nasogastric tube in a non-trauma patient", *Journal of Accident & Emergency Medicine,* vol. 14, no. 1, pp. 45-47.

Fremstad, J.D. & Martin, S.H. 1978, "Lethal complication from insertion of nasogastric tube after severe basilar skull fracture", *Journal of Trauma-Injury, Infection, and Critical Care,* vol. 18, no. 12, pp. 820-822.

Friedrich, W. 1988, *Vitamins,* 1st edn, Walter de Gruyter, New York.

Fuchs, J., Schummer, C., Giesser, J., Bayer, O. & Schummer, W. 2007, "Detection of tracheal malpositioning of nasogastric tubes using endotracheal cuff pressure measurement", *Acta Anaesthesiologica Scandinavica,* vol. 51, no. 9, pp. 1245-1249.

Fulbrook, P., Bongers, A. & Albarran, J.W. 2007, *A European survey of enteral nutrition practices and procedures in adult intensive care units*, Wiley-Blackwell.

Gabriel, S.A. & Ackermann, R.J. 2004, "Placement of nasoenteral feeding tubes using external magnetic guidance", *JPEN.Journal of Parenteral and Enteral Nutrition,* vol. 28, no. 2, pp. 119-122.

Gateshead Health NHS Foundation Trust 2012, *, Enteral Feeding Policy* [Homepage of Gateshead Health], [Online]. Available: http://www.gegateshead.nhs.uk/sites/default/files/users/user1/RM62%20Enteral%20Feeding%20Policy.pdf [2014, 14 July].

Gelatin Manufacturers Institute of America 2012, *Gelatin Handbook,* GMIA.

Genu, P.R., de Oliveira, D.M., Vasconcellos, R.J., Nogueira, R.V.B. & Vasconcellos, B.C.E. 2004, "Inadvertent Intracranial Placement of a Noasogastric Tube in a Patient with Severe Craniofacial Trauma: A Case Report", *Journal of Oral and Maxillofacial Surgery,* vol. 62, no. 11, pp. 1435-1438.

Gharpure, V., Meert, K.L., Sarnaik, A.P. & Metheny, N.A. 2000, "Indicators of postpyloric feeding tube placement in children", *Critical Care Medicine,* vol. 28, no. 8, pp. 2962-2966.

Gilbertson, H.R., Rogers, E.J. & Ukoumunne, O.C. 2011, "Determination of a Practical pH Cutoff Level for Reliable Confirmation of Nasogastric Tube Placement", *JPEN Journal of Parenteral & Enteral Nutrition,* vol. 35, no. 4, pp. 540-544.

Glasser, S.A., Garfinkle, W. & Scanlon, M. 1990, "Intracranial complication during insertion of a nasogastric tube", *AJNR.American journal of neuroradiology,* vol. 11, no. 6, pp. 1170.

Gold rate 24 2014, *Price of Gold and Silver*. Available: http://www.goldrate24.com/gold-prices/europe/united_kingdom/. [2014, 02/18].

Gough, D. & Thomas, J. 2012, "Commonality and Diversity in Reviews" in *An Introduction to Systematic Reviews*, eds. D. Gough, S. Oliver & J. Thomas, Sage Publications Ltd, London.

Gray, R., Tynan, C., Reed, L., Hasse, J., Kramlich, M., Roberts, S., Suneson, J., Thompson, J. & Neylon, J. 2007, "Bedside electromagnetic-guided feeding tube placement: an improvement over traditional placement technique?", *Nutrition in Clinical Practice,* vol. 22, no. 4, pp. 436-444.

Great Ormond Street Hospital for Children 2014, *, Naos-gastric and oro-gastric tube management. Clinical Guideline* [Homepage of GOSH], [Online]. Available: http://www.gosh.nhs.uk/health-professionals/clinical-guidelines/nasogastric-and-orogastric-tube-management/ [2014, 18 August].

Green, M.L., Walsh, B.K., Wolf, G.K. & Arnold, J.H. 2011, "Electrocardiographic guidance for the placement of gastric feeding tubes: a pediatric case series", *Respiratory Care,* vol. 56, no. 4, pp. 467-471.

Gregory, B. 2005, "Hunger striking prisoners: the doctors' dilemma", *BMJ,* vol. 331, no. 7521, pp. 913.

Griffin, O. 2011, "Nutrition, Fluid Balance and Blood Transfusion" in *The Royal Marsden Hospital Manual of Clinical Nursing Procedures*, eds. L. Dougherty & S. Lister, 8th edn, Wiley Blackwell, Chichester.

Grocott, P., Blackwell, R., Weir, H. & Pillay, E. 2013, "Living in dressings and bandages: findings from workshops with people with Epidermolysis bullosa", *International Wound Journal,* vol. 10, no. 3, pp. 274-284.

Haga, Y., Yamanouchi, T., Matsukura, S., Nagamatsu, Y., Yoshidomi, K., Fukano, K., Kawano, M., Abematsu, Y., Matoba, K., Koga, T. & Tonai, T. 2008, "Advice for prevention of inadvertent respiratory placement of nasogastric feeding tube", *International Journal of Risk & Safety in Medicine,* vol. 20, no. 4, pp. 241-247.

Halloran, O., Grecu, B. & Sinha, A. 2011, "Methods and complications of nasoenteral intubation", *JPEN.Journal of Parenteral and Enteral Nutrition,* vol. 35, no. 1, pp. 61-66.

Hanley, B., Bradburn, J., Barnes, M., Evans, C., Goodare, H., Kelson, M., Kent, A., Oliver, S., Thomas, S. & Wallcroft, J. 2004, *Involving the public in NHS, public health, and social care research: Briefing notes for researchers (second edition)*, INVOLVE.

Hanna, G., Phillips, L., Priest, O. & Ni, M. 2010, *Improving the safety of nasogastric feeding tube insertion. Developing guidelines for the safe verification of feeding tube position - a decision analysis approach. A report for the NHS Patient Safety Research Portfolio* [Homepage of NHS], [Online]. Available: http://www.birmingham.ac.uk/Documents/college-mds/haps/projects/cfhep/psrp/finalreports/PS048ImprovingthesafetyofnasogastricfeedingtubeinsertionREVISEDHannaetal.pdf [2014, 15 May].

Harkness, L. 2002, "The history of enteral nutrition therapy: from raw eggs and nasal tubes to purified amino acids and early postoperative jejunal delivery", *Journal of the American Dietetic Association,* vol. 102, no. 3, pp. 399-404.

Hart, D., Hillier, M. & Wall, B. 2009, "National reference doses for common radiographic, fluoroscopic and dental X-ray examinations in the UK", *The British Journal of Radiology,* [Online], vol. 82, no. 973. Available from: http://www.birpublications.org/doi/full/10.1259/bjr/12568539. [16 August 2014].

Hart, J.P. 1990, *Electroanalysis of Biologically Important Compounds,* 1st edn, Ellis Horwood, New York.

Hearnshaw, S.A. & Thompson, N.P. 2007, "Use of parenteral nutrition in hospitals in the North of England", *Journal of Human Nutrition & Dietetics,* vol. 20, no. 1, pp. 14-26.

Heidegger, C.P., Dawson, P. & Pichard, C. 2008, "Enteral versus parenteral nutrition for the critically ill patient: a combined effort should be preferred", *Current Opinion in Critical Care,* vol. 14, pp. 408-414.

Heneghan, C. 2012, "The saga of Poly Implant Prosthese breast implants", *BMJ-British Medical Journal,* vol. 344, no. 7839, pp. 10.

Heneghan, C., Thompson, M., Billingsley, M. & Cohen, D. 2011, "Medical-device recalls in the UK and the device-regulation process: retrospective review of safety notices and alerts", *BMJ Open,* vol. 1, no. 1, pp. e000155-e000155.

Henshall, C., Mardhani-Bayne, L., Frønsdal, K.,B. & Klemp, M. 2011, "Interactions between health technology assessment, coverage, and regulatory processes: emerging issues, goals, and opportunities", *International Journal of Technology Assessment in Health Care,* vol. 27, no. 3, pp. 253-260.

Hernandez-Socorro, C.R., Marin, J., Ruiz-Santana, S., Santana, L. & Manzano, J.L. 1996, "Bedside sonographic-guided versus blind nasoenteric feeding tube placement in critically ill patients", *Critical Care Medicine,* vol. 24, no. 10, pp. 1690-1694.

Heyland, D.K., Drover, J.W., Dhaliwal, R. & Greenwood, J. 2002, "Optimizing the benefits and minimizing the risks of enteral nutrition in the critically ill: role of small bowel feeding", *JPEN.Journal of Parenteral and Enteral Nutrition,* vol. 26, no. 6 Suppl, pp. S51-5; discussion S56-7.

Heymsfield, S.B., Bethel, R.A., Ansley, J.D., Nixon, D.W. & Rudman, D. 1979, "Enteral hyperalimentation: an alternative to central venous hyperalimentation", *Annals of Internal Medicine,* vol. 90, no. 1, pp. 63-71.

Hill, S.S., Shaw, B.R. & Wu, A.H.B. 2003, "Plasticizers, antioxidants and other contaminants found in air delivered by PVC tubing used in respiratory therapy", *Biomedical Chromatography,* vol. 17, pp. 250-262.

HM Government 2005, *Mental Capacity Act, chapter 9* [Homepage of HMSO], [Online]. Available: http://www.legislation.gov.uk/ukpga/2005/9/pdfs/ukpga_20050009_en.pdf [2014, 13 July].

HM Government 2004, *Children Act, Chapter 31* [Homepage of HMSO], [Online]. Available: http://www.legislation.gov.uk/ukpga/2004/31/pdfs/ukpga_20040031_en.pdf [2014, 21 September].

Hodgson, N. 2014, "Medical firm Westco placed into administration", *Liverpool Echo,* 9 April

Hogg, C. 2006, "Patient and public involvement: what next for the NHS?" *Health Expectations,* vol. 10, no. 2, pp. 129-138.

Holden, C.E., MacDonald, A., Ward, M., Ford, K., Patchell, C., Handy, D., Chell, M., Brown, G.B. & Booth, I.W. 1997, "Psychological preparation for nasogastric feeding in children", *British Journal of Nursing,* vol. 6, no. 7, pp. 376-385.

Holland, A., Smith, F. & Penny, K. 2013, *Carbon dioxide detection for testing nasogastric tube placement in adults (protocol)*, John Wiley & Sons Ltd, The Cochrane Collaboration.

Howe, A., Delaney, S., Romero, J., Tinsley, A. & Vicary, P. 2010, "Public involvement in health research: a case study of one NHS project over 5 years", *Primary Health Care Research & Development,* vol. 11, no. 1, pp. 17-28.

Howe, R., Forbes, D. & Baker, C. 2010, "Providing optimum nutrition and hydration" in *Developing Practical Skills for Nursing Children and Young People*, eds. E.A. Glasper, M. Aylott & C. Battrick, Hodder Arnold Ltd, London.

Howes, D.W., Shelley, E.S. & Pickett, W. 2005, "Calorimetric carbon dioxide detector to determine accidental tracheal feeding tube placement", *Canadian Journal of Anesthesia,* vol. 52, no. 4, pp. 428-432.

Huffman, S., Jarczyk, k.S., O'Brien, E., Pieper, P. & Bayne, A. 2004, "Methods to confirm feeding tube placement; application of research in practice", *Pediatric nursing,* vol. 30, no. 1, pp. 10-13.

Hulstaert, F., Neyt, M., Vinck, I., Stordeur, S., Huic, M., Sauerland, S., Kuijpers, M.R., Abrishami, P., Vondeling, H., Flamion, B., Garattini, S., Pavlovic, M. & van Brabandt, H. 2012, "Pre-market clinical evaluations of innovative high-risk medical devices in Europe", *International Journal of Technology Assessment in Health Care,* vol. 28, no. 3, pp. 278-284.

Hung, M., Hsieh, P., Lee, S. & Chan, K. 2007, "Another source of airway-leakage: inadvertent endobronchial misplacement of nasogastric tube in a patient intubated with double-lumen endotracheal tube under anesthesia", *Acta Anaesthesiologica Taiwanica: Official Journal Of The Taiwan Society Of Anesthesiologists,* vol. 45, no. 4, pp. 241-244.

Hussain, A. 2006, "Should simple and common procedures be taken lightly?: nasobronchial feeding: a case report", *Internet Journal of Emergency & Intensive Care Medicine,* vol. 9, no. 1, pp. 6p.

Ibanez, J., Penafiel, A., Marse, P., Jorda, R., Raurich, J.M. & Mata, F. 2000, "Incidence of gastroesophageal reflux and aspiration in mechanically ventilated patients using small-bore nasogastric tubes", *JPEN.Journal of Parenteral and Enteral Nutrition,* vol. 24, no. 2, pp. 103-106.

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use 1996, *ICH Harmonised Tripartite Guideline for Good Clinical Practice E6(R1)*, Step 4 edn, accessed 10 Feb2014, http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf.

Invest in Cheshire 2012, *£25m Fund for Biomedical makes investments worth £100,000* [Homepage of Invest in CheshireCheshire], [Online]. Available: http://www.investincheshire.com/ellesmereport/info-centre/news/2012/1/24/25m-fund-for-biomedical-makes-investments-worth-100-000-a354 [2014, 11 July].

INVOLVE 2014, *What is public involvement in research?* [Homepage of National Institute for Health Research], [Online]. Available: http://www.invo.org.uk/find-out-more/what-is-public-involvement-in-research-2/ [2014, 13 August].

INVOLVE 2013a, *Values, principles and standards for public involvement in research* [Homepage of National Institute for Health Research], [Online]. Available: http://www.invo.org.uk/wp-content/uploads/2013/12/INVOLVE-Principles-and-standards-for-public-involvement-1-November-2013.pdf [2014, 13 August].

INVOLVE 2013b, *Welcome to INVOLVE - National advisory group that supports greater public involvement in NHS, public health and social care research.*

[Homepage of INVOLVE], [Online]. Available: http://www.invo.org.uk/ [2013, 09/24].

INVOLVE and The National Research Ethics Service 2009, January 2009-last update, *Patient and public involvement in research and research ethics committee Review: Joint Statement* [Homepage of NIHR], [Online]. Available: http://www.hra.nhs.uk/EasySiteWeb/GatewayLink.aspx?alId=287555 [2013, 09/24].

Ionescu, R.E., Cosnier , S. & Marks, R.S. 2006, "Protease Amperometric Sensor", *Annals of Chemistry,* vol. 78, pp. 6327-6331.

Irving, S., Y., Lyman, B., Northington, L., Bartlett, J., A. & Kemper, C. 2014, "Nasogastric Tube Placement and Verification in Children: Review cf the Current Literature", *Critical Care Nurse,* vol. 34, no. 3, pp. 67-78.

Iserson, K.V. 1987, "J.-F.-B. Charriere: the man behind the “French” gauge", *The Journal of Emergency Medicine,* vol. 5, no. 6, pp. 545-548.

Jackson, R.H., Payne, D.K. & Bacon, B.R. 1990, "Esophageal perforation due to nasogastric intubation", *American Journal of Gastroenterology,* vol. 85, no. 4, pp. 439-442.

Jaffe, M.B. 2008, "Infrared measurement of carbon dioxide in the human breath: "breathe-through" devices from Tyndall to the present day", *Anesthesia and Analgesia,* vol. 107, no. 3, pp. 890-904.

James, R. 1978, "An unusual complication of passing a narrow bore nasogastric tube", *Anaesthesia,* vol. 33, no. 8, pp. 716-718.

Jenke, D. 2006, "Extractable substances from plastic materials used in solution contact applications:an updated review", *PDA Journal of Pharmaceutic Scientific Technology,* vol. 60, pp. 191-207.

Jiang, X., Li, N. & Li, J. 2003, "Intestinal permeability in patients after surgical trauma and effect of enteral nutrition versus parenteral nutrition", *World Journal of Gastroenterology,* vol. 9, no. 8, pp. 1878-1880.

Jolley, J., Elliott, B. & Williams, R. 2005, "Commentary on Nyqvist KH , Sorell A & Ewald U (2005) Litmus tests for verification of feeding tube locations in infants: evaluation of their clinical use", *Journal of Clinical Nursing,* vol. 14, no. 8, pp. 1029-1030.

Kaffarnik, M.F., Lock, J.F., Wassilew, G. & Neuhaus, P. 2013, "The use of bedside electromagnetically guided nasointestinal tube for jejunal feeding of critical ill surgical patients", *Technology & Health Care,* vol. 21, no. 1, pp. 1-8.

Kalfarentzos, F., Kehagias, J., Mead, N., Kokkinis, K. & Gogos, C. 1997, "Enteral nutrition is superior to parenteral nutrition in severe acute pancreatitis: results of a randomized prospective trial", *British Journal of Surgery,* vol. 84, no. 12, pp. 1665-1669.

Kaufman, J.P., Hughes, W.B. & Kerstein, M.D. 2001, "Pneumothorax after Nasoenteral Feeding Tube Placement", *American Surgeon,* vol. 67, no. 8, pp. 772.

Kazi, N. & Mobarhan, S. 1996, "Enteral feeding associated gastroesophageal reflux and aspiration pneumonia: A review", *Nutrition Reviews,* vol. 54, no. 10, pp. 324-328.

Kenny, D.J. & Goodman, P. 2010, "Care of the patient with enteral tube feeding: an evidence-based practice protocol", *Nursing Research,* vol. 59, no. 1 Suppl, pp. S22-31.

Khilnani, P. 2007, "Errors in placement of enteral tubes in critically ill children: are we foolproof yet?", *Pediatric Critical Care Medicine,* vol. 8, no. 2, pp. 193-194.

Kindopp, A.S., Drover, J.W. & Heyland, D.K. 2001, "Capnography confirms correct feeding tube placement in intensive care unit patients", *Canadian Journal Of Anaesthesia = Journal Canadien D'anesthésie,* vol. 48, no. 7, pp. 705-710.

Kirk, S. 2007, "Methodological and ethical issues in conducting qualitative research with children and young people: A literature review", *International Journal of Nursing Studies,* vol. 44, no. 7, pp. 1250-1260.

Klasner, A.E., Luke, D.A. & Scalzo, A.J. 2002, "Pediatric orogastric and nasogastric tubes: a new formula evaluated", *Annals of Emergency Medicine,* vol. 39, no. 3, pp. 268-272.

Kreitner, M. 2010, "Think liquid silicone rubber for medical device molding ", *Medical Design,* [Online], . Available from: http://medicaldesign.com/materials/think-liquid-silicone-rubber-medical-device-molding. [02/18/2014].

Krucoff, M.W., Brindis, R.G., Hodgson, P.K., Mack, M.J. & Holmes,David R.,,Jr 2012, "Medical device innovation: prospective solutions for an ecosystem in crisis. Adding a professional society perspective", *JACC.Cardiovascular Interventions,* vol. 5, no. 7, pp. 790-796.

Lamont, T., Beaumont, C., Fayaz, A., Healey, F., Huehns, T., Law, R., Lecko, C., Panesar, S., Surkitt-Parr, M., Stroud, M. & Warner, B. 2011, "Checking placement of nasogastric feeding tubes in adults (interpretation of x ray images): summery of a safety report from the National Patient Safety Agency", *British Medical Journal,* vol. 10, no. 6, pp. 342.

Lang, A., R., Martin, J., L., Sharples, S., Crowe, J., A. & Murphy, E. 2014, "Not a minor problem: involving adolescents in medical device design research", *Theoretical Issues in Ergonomics Science,* vol. 15, no. 2, pp. 181-192.

Levin, A.L. 1921, "A New Gastroduodenal Catheter", *JAMA,* vol. 76, pp. 1007.

Li, P.K., Spittler, C., Taylor, C.W. & et al., 1997, "In vitro effects of simulated gastric juice on swallowed metal objects: implications for practical management", *Gastrointestinal Endoscopy,* vol. 46, no. 2, pp. 152-155.

Li, H. & Yue, L.Q. 2008, "Statistical and regulatory issues in nonrandomized medical device clinical studies", *Journal of Biopharmaceutical Statistics,* vol. 18, no. 1, pp. 20-30.

Lo, J.O., Wu, V., Reh, D., Nadig, S. & Wax, M.K. 2008, "Diagnosis and management of a misplaced nasogastric tube into the pulmonary pleura", *Archives of Otolaryngology–Head & Neck Surgery,* vol. 134, no. 5, pp. 547-550.

Lucas, A., Bloom, S.R. & Aynsley-Green, A. 1983, "Metabolic and endocrine consequences of depriving preterm infants of enteral nutrition", *Acta Paediatrica,* vol. 72, no. 2, pp. 245-249.

Macklin, D. 1999, "What's physics got to do with it? A review of the physical principles of fluid administration", *Journal of Vascular Access Devices,* vol. 4, no. 2, pp. 7-11.

Maggard, M.A., Shugarman, L.R., Suttorp, M., Maglione, M., Sugaerman, H.J., Livingston, E.H., Nguyen, N.T., Li, Z., Mojica, W.A., Hilton, L., Rhodes, S., Morton, S.C. & Shekelle, P.G. 2005, "Meta-Analysis: Surgical Treatment of Obesity. Clinical Guidelines", *Annals of Internal Medicine,* [Online], vol. 142, no. 7. Available from: Downloaded From: http://annals.org/. [02/10/2014].

Maggio, L., Costa, S., Zecca, C. & Giordano, L. 2012, "Methods of enteral feeding in preterm infants", *Early Human Development,* vol. 88, pp. S31-S33.

Magnusson, P.R., Mathing, J. & Kristensson, P. 2003, "Managing User Involvement in Service Innovation: Experiments with Innovating End Users", *Journal of Service Research,* vol. 6, no. 2, pp. 111-124.

Maisel, W.H. 2004, "Medicine and public issues. Medical device regulation: an introduction for the practicing physician", *Annals of Internal Medicine,* vol. 140, no. 4, pp. 296-302.

Mankoff, S.P., Brander, C., Ferrone, S. & Marincola, F.M. 2004, "Lost in Translation: Obstacles to Translational Medicine", *Journal of Translational Medicine,* vol. 2, no. 1, pp. 14.

Marik, P.E. 2001, "Aspiration pneumonitis and aspiration pneumonia", *New England Journal of Medicine,* vol. 344, no. 9, pp. 665-671.

Marik, P.E. & Zaloga, G.P. 2004, "Meta-analysis of parenteral nutrition versus enteral nutrition in patients with acute pancreatitis", *BMJ (Clinical research ed.),* vol. 328, no. 7453, pp. 1407.

Marincola, F.M. 2003, "Translational medicine: a two-way road", *Journal of Translational Medicine,* [Online], vol. 1, no. 1, pp. 1. Available from: http://www.biomedcentral.com/content/pdf/1479-5876-1-1.pdf. [16 August 2014].

Martin, J.L., Clark, D.J., Morgan, S.P., Crowe, J.A. & Murphy, E. 2012, "A user-centred approach to requirements elicitation in medical device development: A case study from industry perspective", *Applied Ergonomics,* vol. 43, no. 2, pp. 184-190.

Martin, J.L. & Barnett, J. 2012, "Integrating the results of user research into medical device development:insights from a case study", *BMC Medical Informatics and Decision Making,* vol. 12, pp. 74-84.

Maruyama, K., Shiojima, T. & Koizumi, T. 2003, "Sonographic detection of a malpositioned feeding tube causing esophageal perforation in a neonate", *Journal of Clinical Ultrasound,* vol. 31, no. 2, pp. 108-110.

May, S. 2007, "Testing nasogastric tube positioning in the critically ill: exploring the evidence", *British Journal of Nursing (BJN),* vol. 16, no. 7, pp. 414-418.

McClave, S.A., Martindale, R.G., Vanek, V.W., McCarthy, M., Roberts, P., Taylor, B., Ochoa, J.B., Napolitano, L., Cresci, G., A.S.P.E.N. Board of Directors, American College of Critical Care Medicine & Society of Critical Care Medicine 2009, "Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.)", *JPEN.Journal of Parenteral and Enteral Nutrition,* vol. 33, no. 3, pp. 277-316.

McGuire, W. & McEwan, P. 2007, "Transpyloric versus gastric tube feeding for preterm infants", *Cochrane Database Syst Rev,* vol. 3.

Medipex Innovation Healthcare Hub 2013, *, 2013 Innovation Award - Medical Devices and Diagnostics* [Homepage of Medipex], [Online]. Available: http://www.medipex.co.uk/events/nhs-innovation-awards-2013/2013-innovation-award-medical-devices-and-diagnostics/ [2014, 10 July].

Medlin, S. 2012, "Recent developments in enteral feeding for adults: an update", *British Journal of Nursing,* vol. 21, no. 18, pp. 1061-1067.

Meert, K.L., Daphtary, K.M. & Metheny, N.A. 2004, "Gastric vs small-bowel feeding in critically ill children receiving mechanical ventilation: a randomized controlled trial", *Chest,* vol. 126, no. 3, pp. 872-878.

Melki, I., Matar, N., Maalouf, S. & Rassi, S. 2010, "Knotting of nasogastric tube around a nasotracheal tube: an unusual cause of hypercapnia in a 3-month-old infant", *American Journal of Critical Care,* vol. 19, no. 2, pp. 197-198.

Metheny, N., McSweeney, M., Wehrle, M.A. & Wiersema, L. 1990, "Effectiveness of the auscultatory method in predicting feeding tube location", *Nursing research,* vol. 39, no. 5, pp. 262-267.

Metheny, N., Reed, L., Berglund, B. & Wehrle, M.A. 1994, "Visual characteristics of aspirates from feeding tubes as a method for predicting tube location", *Nursing Research,* vol. 43, no. 5, pp. 282-287.

Metheny, N., Reed, L., Wiersema, L., McSweeney, M., Wehrle, M.A. & Clark, J. 1993, "Effectiveness of pH measurements in predicting feeding tube placement: an update", *Nursing Research,* vol. 42, no. 6, pp. 324-331.

Metheny, N., Williams, P., Wiersema, L., Wehrle, M.A., Eisenberg, P. & McSweeney, M. 1989, "Effectiveness of pH measurements in predicting feeding tube placement", *Nursing Research,* vol. 38, no. 5, pp. 280-285.

Metheny, N.A. 2002, "Inadvertant intracranial nasogastric tube placement", *American Journal of Nursing,* vol. 102, no. 1, pp. 25-27.

Metheny, N.A., Eikov, R., Rountree, V. & Lengettie, E. 1999, "Clinical Research: Indicators of Feeding-Tube Placement in Neonates", *Nutrition in Clinical Practice,* vol. 14, no. 6, pp. 307-314.

Metheny, N.A., Smith, L. & Stewart, B.J. 2000, "Development of a reliable and valid bedside test for bilirubin and its utility for improving prediction of feeding tube location", *Nursing Research,* vol. 49, no. 2, pp. 302-309.

Metheny, N.A. & Meert, K.L. 2014a, "Effectiveness of an Electromagnetic Feeding Tube Placement Device in Detecting Inadvertent Respiratory Placement", *American Journal of Critical Care,* vol. 23, no. 3, pp. 240-248.

Metheny, N.A. & Meert, K.L. 2014b, "A Review of Published Case Reports of Inadvertent Pulmonary Placement of Nasogastric Tubes in Children", *Journal of Pediatric Nursing,* vol. 29, no. 1, pp. e7-e12.

Metheny, N.A., Schnelker, R., McGinnis, J., Zimmerman, G., Duke, C., Merritt, B., Banotai, M. & Oliver, D.A. 2005, "Indicators of tubesite during feedings", *Journal of Neuroscience Nursing,* vol. 37, no. 6, pp. 320-325.

Metheny, N.A. & Stewart, B.J. 2002, "Testing feeding tube placement during continuous tube feedings", *Applied Nursing Research,* vol. 15, no. 4, pp. 254-258.

Metheny, N.A., Stewart, B.J., Smith, L., Yan, H., Diebold, M. & Clouse, R.E. 1999, "pH and concentration of bilirubin in feeding tube aspirates as predictors of tube placement", *Nursing Research,* vol. 48, no. 4, pp. 189-197.

Metheny, N., Meert, K.L. & Clouse, R.E. 2007, "Complications related to feeding tube placement", *Current Opinion in Gastroenterology,* vol. 23, no. 2, pp. 178-182.

Metheny, N., Reed, L., Worseck, M. & Clark, J. 1993, "How to Aspirate Fluid from Small-Bone Feeding Tubes", *AJN The American Journal of Nursing,* vol. 93, no. 5, pp. 86-88.

Metheny, N., Wehrle, M.A., Wiersema, L. & Clark, J. 1998, "Testing feeding tube placement: Auscultation vs. pH method", *AJN The American Journal of Nursing,* vol. 98, no. 5, pp. 37-42.

Metheny, N.A., Aud, M.A. & Ignatavicius, D.D. 1998, "Detection of improperly positioned feeding tubes", *Journal Of Healthcare Risk Management,* vol. 18, no. 3, pp. 37-48.

Metheny, N.A., Spies, M.A. & Eisenberg, P. 1988, "Measures to test placement of nasoenteral feeding tubes", *Western Journal of Nursing Research,* vol. 10, no. 4, pp. 367-383.

Metheny, N.A. & Titler, M.G. 2001, "Assessing placement of feeding tubes", *The American Journal of Nursing,* vol. 101, no. 5, pp. 36-45.

Metheny, N.A. 2002, "Risk Factors for Aspiration", *Journal of Parenteral and Enteral Nutrition,* vol. 26, no. 6, pp. S26-S31.

Metheny, N., Dettenmeier, P., Hampton, K., Wiersema, L. & Williams, P. 1990a, "Detection of inadvertent respiratory placement of small-bore feeding tubes: a report of 10 cases", *Heart & Lung: The Journal Of Critical Care,* vol. 19, no. 6, pp. 631-638.

Metheny, N., McSweeney, M., Wehrle, M.A. & Wiersema, L. 1990b, "Effectiveness of the auscultatory method in predicting feeding tube location", *Nursing Research,* vol. 39, no. 5, pp. 262-267.

Metheny, N.A. 2006a, "Preventing respiratory complications of tube feedings: evidence-based practice", *American Journal of Critical Care,* vol. 15, no. 3, pp. 252-252.

Metheny, N.A. 2006b, "Preventing respiratory complications of tube feedings: evidence-based practice", *American Journal of Critical Care,* vol. 15, no. 4, pp. 360-369.

Metheny, N.A., Clouse, R.E., Chang, Y.H., Stewart, B.J., Oliver, D.A. & Kollef, M.H. 2006, "Tracheobronchial aspiration of gastric contents in critically ill tube-fed patients: frequency, outcomes, and risk factors", *Critical Care Medicine,* vol. 34, no. 4, pp. 1007-1015.

Metheny, N.A., Clouse, R.E., Clark, J.M., Reed, L., Wehrle, M.A. & Wiersema, L. 1994, "Techniques & procedures. pH testing of feeding-tube aspirates to determine placement", *Nutrition in Clinical Practice,* vol. 9, no. 5, pp. 185-190.

Metheny, N.A., Dahms, T.E., Stewart, B.J., Stone, K.S., Frank, P.A. & Clouse, R.E. 2005, "Verification of inefficacy of the glucose method in detecting aspiration associated with tube feedings", *MEDSURG Nursing,* vol. 14, no. 2, pp. 112.

Metheny, N.A. & Frantz, R.A. 2013, "Head-of-bed elevation in critically ill patients: a review", *Critical Care Nurse,* vol. 33, no. 3, pp. 53-66; quiz 67.

Metheny, N.A., Stewart, B.J. & McClave, S.A. 2011, "Relationship between feeding tube site and respiratory outcomes", *JPEN.Journal of Parenteral and Enteral Nutrition,* vol. 35, no. 3, pp. 346-355.

Metheny, N.A., Stewart, B.J., Smith, L., Yan, H., Diebold, M. & Clouse, R.E. 1997, "pH and concentrations of pepsin and trypsin in feeding tube aspirates as predictors of tube placement", *JPEN.Journal of parenteral and enteral nutrition,* vol. 21, no. 5, pp. 279-285.

Metheny, N.A. & Meert, K.L. 2004, "Monitoring feeding tube placement", *Nutrition In Clinical Practice,* vol. 19, no. 5, pp. 487-495.

Metheny, N., A. 2011, "Tube-feeding practices", *AACN Bold Voices,* vol. 3, no. 3, pp. 33-33.

Meyer, P., Henry, M., Maury, E., Baudel, J., Guidet, B. & Offenstadt, G. 2009, "Colorimetric capnography to ensure correct nasogastric tube position", *Journal of Critical Care,* vol. 24, no. 2, pp. 231-235.

Meyer, R., Harrison, S., Cooper, M. & Habibi, P. 2007, "Successful blind placement of nasojejunal tubes in paediatric intensive care: impact of training and audit", *Journal of Advanced Nursing,* vol. 60, no. 4, pp. 402-408.

MHRA November 2013, *Guidance on legislation: Clinical investigations of medical devices – guidance for manufacturers* [Homepage of Medicines and Healthcare products Regulatory Agency], [Online]. Available:

http://www.mhra.gov.uk/home/groups/es-era/documents/publication/con007504.pdf [2014, 14 August].

MHRA 2013, 08.16.13-last update, *Medical Devices Classification* [Homepage of MHRA], [Online]. Available: http://www.mhra.gov.uk/Howweregulate/Devices/Classification/index.htm [2014, 31 March].

MHRA 2012, *Medicines and Medical Devices Regulation: What you need to know* [Homepage of The Medicines and Healthcare Products Regulatory Agency], [Online]. Available: http://www.mhra.gov.uk/home/groups/comms-ic/documents/websiteresources/con2031677.pdf [2014, 31 March].

Money, A.G., Barnett, J., Kuljis, J., Craven, M.P., Martin, J.L. & Young, T. 2011, "The role of the user within medical device design and development process: medical device manufacturers' perspectives", *Medical Informatics and Decision Making,* vol. 11, no. 15, pp. 1-8.

Moore, F.A., Feliciano, D.V., Andrassy, R.J., McArdle, A.H., Booth, F.V., Morgenstein-Wagner, T.B., Kellum, J.M., Welling, R.E. & Moore, E.E. 1992, "Early enteral feeding, compared with parenteral, reduces postoperative septic complications: the results of a meta-analysis", *Annals of Surgery,* vol. 216, no. 2, pp. 172-183.

Mulholland, J.H., Tui, C., Wright, A.M. & Vinci, V.J. 1943, "Nitrogen Metabolism, Caloric Intake and Weight Loss in Postoperative Convalescence : a Study of Eight Patients Undergoing Partial Gastrectomy for Duodenal Ulcers", *Annals of Surgery,* vol. 117, no. 4, pp. 512-534.

Munera-Seeley, V., Ochoa, J.B., Brown, N., Bayless, A., Correia, M.I., Bryk, J. & Zenati, M. 2008, "Use of a colorimetric carbon dioxide sensor for nasoenteric feeding tube placement in critical care patients compared with clinical methods and radiography", *Nutrition In Clinical Practice,* vol. 23, no. 3, pp. 318-321.

National Institute for Health and Care Excellence (NICE) 2013, , *Health Technologies Adoption Programme* [Homepage of NICE], [Online]. Available: http://www.nice.org.uk/usingguidance/healthtechnologiesadoptionprogramme/HealthTechnologiesAdoptionProgramme.jsp [2014, 03/04].

National Institute for Health and Clinical Excellence (NICE) 2006, , *Nutrition support for adults- oral nutrition support, enteral tube feeding and parenteral nutrition. Clinical guideline G32* [Homepage of NICE], [Online]. Available: http://guidance.nice.org.uk/CG32 [2014, 16 August].

National Institute for Health Research 2013, , *PPI - Information for researchers: Supporting the delivery of people focussed research* [Homepage of NIHR CCN CC], [Online]. Available: http://www.crncc.nihr.ac.uk/about_us/ccrn/cdtv/PPI/PPI_Researchers [2013, 09/25].

National Institute for Health Research 2011, *A pocket guide to Good Clinical Practice, including the Declaration of Helsinki,* Version 2.1 edn, NIHR Clinical Research Network, Leeds.

National Institute for Health Research (NIHR) 2014, *Biomedical Research Centres* [Homepage of NIHR], [Online]. Available:

http://www.nihr.ac.uk/infrastructure/Pages/infrastructure_biomedical_research_centres.aspx [2014, 30 June].

National Institutes of Health (NIH) 2013, *NIH Organisation* [Homepage of NIH], [Online]. Available: http://www.nih.gov/about/organization.htm [2014, 15 August].

National Patient Safety Agency 2012, *Harm from flushing of nasogastric tubes before confirmation of placement* [Homepage of NPSA], [Online]. Available: http://www.nrls.npsa.nhs.uk/alerts/?entryid45=133441 [2014, 11 July].

National Patient Safety Agency 2011a, *Reducing the harm caused by misplaced nasogastric tubes in adults, children and infants (Patient Safety Alert)* [Homepage of NPSA], [Online]. Available: http://www.nrls.npsa.nhs.uk/resources/?entryid45=129640&p=2 [2014, 9 July].

National Patient Safety Agency 2011b, *Reducing the harm caused by misplaced nasogastric feeding tubes in adults, children and infants Patient Safety Alert NPSA/2011/PSA002: Supporting Information* [Homepage of NPSA], [Online]. Available: http://www.nrls.npsa.nhs.uk/EasySiteWeb/getresource.axd?AssetID=129697& [2014, 13 June].

National Patient Safety Agency 2007, , *Patient Safety Alert 19: Promoting safer measurement and administration of liquid medicines via oral and other enteral routes* [Homepage of NPSA], [Online]. Available: http://www.nrls.npsa.nhs.uk/resources/type/alerts/?entryid45=59808&q=0%c2%ac2007%c2%ac [2014, 9 July].

National Patient Safety Agency 2005a, *Patient Safety Alert 05: Reducing harm caused by the misplacement of nasogastric feeding tubes* [Homepage of NPSA], [Online]. Available: http://www.nrls.npsa.nhs.uk/resources/?entryid45=59794%20 [2014, 9 July].

National Patient Safety Agency 2005b, *Reducing the harm caused by misplaced naso and orogastric feeding tubes in babies under the care of neonatal units* [Homepage of NPSA], [Online]. Available: http://www.nrls.npsa.nhs.uk/resources/?entryid45=59798&q=0%25c2%25acnasogastric%25c2%25ac_ [2014, 9 July].

National Patient Safety Agency 2005, *How to confirm the correct position of naso and orogastric feeding tubes in babies under the care of neonatal units. Reducing the harm caused by misplaced gastric feeding tubes in babies under the care of neonatal units -interim advice for healthcare staff.*, 1st edn, NHS, United Kingdom.

National Patient Safety Agency & National Reporting and Learning Service 2010, *Never Events Annual Report* [Homepage of NPSA], [Online]. Available: http://www.nrls.npsa.nhs.uk/resources/collections/never-events/ [2014, 16 August].

Neiderman, M., Farley, A., Richardson, J. & Lask, B. 2001, "Nasogastric feeding in children and adolescents with eating disorders: toward good practice", *International Journal of Eating Disorders,* vol. 29, no. 4, pp. 441-448.

Neumann, D.A. & DeLegge, M.H. 2002, "Gastric versus small-bowel tube feeding in the intensive care unit: A prospective comparison of efficacy*", *Critical Care Medicine,* vol. 30, no. 7, pp. 1436-1438.

Neumann, M.J., Meyer, C.T., Dutton, J.L. & Smith, R. 1995, "Hold that X-ray: aspitrate pH and auscultation prove enteral tube placement", *Journal of Clinical Gastroenterology,* vol. 20, no. 4, pp. 293-295.

NHS England Patient Safety Domain Team 2013, *, The Never Events List 2013/14 Update* [Homepage of NHS England], [Online]. Available: http://www.england.nhs.uk/wp-content/uploads/2013/12/nev-ev-list-1314-clar.pdf [2014, 9 July].

Norman, D.A. 2002, *The Design of Everyday Things,* 2nd edn, Basic Books, New York.

Nyqvist, K.H., Sorrell, A. & Ewald, U. 2005, "Litmus tests for verification of feeding tube location in infants: evaluation of their clinical use", *Journal of Clinical Nursing,* vol. 14, no. 3, pp. 486-495.

O'Flaherty, D. & Adams, A.P. 1990, "The end-tidal carbon dioxide detector: Assessment of a new method to distinguish oesophageal from tracheal intubation", *Anaesthesia,* vol. 45, no. 8, pp. 653-655.

Pain, H., Jackson, S., McLellan, D.L. & Gore, S. 1999, "User evaluation of handling equipment for moving dependent people in bed", *Technology & Disability,* vol. 11, no. 1, pp. 13-19.

Paine, J.R. 1934, "The history of the invention and development of the stomach and duodenal tubes", *Annals of Internal Medicine,* vol. 8, no. 6, pp. 752-763.

Parmar, A., Macleod, I., McDonald, S. & Tierney, P. 2011, "Safe and adequate placement of nasogastric tubes in the presence of a cuffed tracheostomy tube", *Annals of the Royal College of Surgeons of England,* vol. 93, no. 6, pp. 94E-95E.

Parviainen, I., Vaisänen, O., Ruokonen, E. & Takala, J. 1996, "Effect of nasogastric suction and ranitidine on the calculated gastric intramucosal pH", *Intensive care medicine,* vol. 22, no. 4, pp. 319-323.

Paterson, C. 2004, "'Take small steps to go a long way'consumer involvement in research into complementary and alternative therapies", *Complementary Therapies in Nursing and Midwifery,* vol. 10, no. 3, pp. 150-161.

Payne-James, J., Grimble, G. & Silk, D. 2001, "Enteral Nutrition: tubes and techniques of delivery" in *Artificial Nutrition Support in Clinical Practice*, eds. J. Payne-James, G. Grimble & D. Silk, Greenwich Medical Media, London.

Pennine Healthcare 2014, *, Graduated Infant Feeding Tubes*. Available: http://www.penninehealthcare.co.uk/medical-devices/gastroenterology/infant-feeding-tubes/graduated-infant-feeding-tubes/ [2014, 02/18].

Penrod, J., Morse, J.M. & Wilson, S. 1999, "Comforting strategies used during nasogastric tube insertion", *Journal of Clinical Nursing,* vol. 8, no. 1, pp. 31-38.

Pepe, M.S. 2003, *The statistical evaluation of medical tests for classification and prediction,* Oxford University Press., Oxford.

Perel, P., Roberts, I., Sena, E., Wheble, P., Briscoe, C., Sandercock, P., Macleod, M., Mignini, L.E., Jayaram, P. & Khan, K.S. 2006, "Comparison of treatment effects

between animal experiments and clinical trials: systematic review", *BMJ: British Medical Journal,* [Online], vol. 334, no. 197. Available from: http://www.bmj.com/highwire/filestream/338291/field_highwire_article_pdf/0/197. [12 Feb 2013].

Peter, C.S., Wiechers, C., Bohnhorst, B., Silny, J. & Poets, C.F. 2002, "Influence of nasogastric tubes on gastroesophageal reflux in preterm infants: a multiple intraluminal impedance study", *The Journal of Pediatrics,* vol. 141, no. 2, pp. 277-279.

Peter, S. & Gill, F. 2009, "Development of a clinical practice guideline for testing nasogastric tube placement", *Journal for Specialists in Pediatric Nursing,* vol. 14, no. 1, pp. 3-11.

Phillips, N.M. 2006, "Nasogastric Tubes: An Historical Context", *MEDSURG Nursing,* vol. 15, no. 2, pp. 84-88.

PiiAF Study Group 2014, *Public Involvement Impact Assessment Framework (PiiAF)* [Homepage of Medical Research Council Methodology Research Programme], [Online]. Available: http://piiaf.org.uk/ [2014, 28 August].

Pinchuk, L. 1994, "A review of the biostability and carcinogenicity of polyrethanes in medicine and the new generation of biostable polyurethanes", *Journal of Biomaterials Science Polymer Edition,* vol. 6, pp. 225-267.

PINNT Patients on Intravenous & Nasogastric Nutrition Therapy 2014, *A Support Group for People Receiving Artificial Nutrition*. Available: http://pinnt.com/ [2014, 23 Oct].

Pobiel, R.S., Bisset, G.S., 3 & Pobiel, M.S. 1994, "Nasojejunal feeding tube placement in children: four-year cumulative experience", *Radiology,* vol. 190, no. 1, pp. 127-129.

Polit, D.F. & Beck, C.T. 2010, *Essentials of nursing research: appraising evidence for nursing practice,* 7th edn, Wolters Kluwer Health/Lippincott Williams & Wilkins, Philadelphia, Pa. ; London.

Premji, S.S. 2005, "Enteral Feeding for High-risk Neonates: A digest for nurses into putative risk and benefits to ensure safe and comfortable care", *Journal of Perinatal and Neonatal Nursing,* vol. 19, no. 1, pp. 59-71.

Quandt, D., Schraner, T., Ulrich Bucher, H. & Arlettaz Mieth, R. 2009, "Malposition of feeding tubes in neonates: is it an issue?",*Journal of pediatric gastroenterology and nutrition,* vol. 48, no. 5, pp. 608-611.

Randall, H.T. 1984, "The History of enteral nutrition" in *Enteral and Parenteral Nutrition* , eds. J.L. Rombeau & M.D. Caldwell, WB Saunders, pp. 1–10, Philadelphia, Pa.

Rao, M.M., Kallam, R., Arsalanizadeh, R., Gatt, M. & MacFie, J. 2009, "Placing of feeding tubes by the bedside using an electromagnetic sensing device", *British Journal of Intensive Care,* vol. Summer, pp. 13-17.

Rassias, A.J., Ball, P.A. & Corwin, H.L. 1998, "A prospective study of tracheopulmonary complications associated with the placement of narrow-bore enteral feeding tubes", *Critical Care,* vol. 2, no. 1, pp. 25-29.

Rawlings, J.O., Pantula, S.G. & Dickey, D.A. 1998, *Applied Regression Analysis: A Research Tool,* 2nd edn, Springer-Verlag, New York, U.S.A.

Renfrew, M., Woolridge, M.W. & McGill, H.R. 2000, *Enabling women to breastfeed: a review of practices which promote or inhibit breastfeeding-with evidence-based guidance for practice,* Stationery Office London.

Rise, M.B., Solbjør, M., Lara, M.C., Westerlund, H., Grimstad, H. & Steinsbekk, A. 2013, "Same description, different values. How service users and providers define patient and public involvement in health care", *Health Expectations,* vol. 16, no. 3, pp. 266-276.

Roberts, S., Echeverria, P. & Gabriel, S.A. 2007, "Devices and techniques for bedside enteral feeding tube placement", *Nutrition in Clinical Practice,* vol. 22, no. 4, pp. 412-420.

Roberts, S.F., Fischhoff, M.A., Sakowski, S.A. & Feldman, E.L. 2012, "Perspective: Transforming science into medicine: how clinician-scientists can build bridges across research's "valley of death"", *Academic Medicine : Journal of the Association of American Medical Colleges,* vol. 87, no. 3, pp. 266-270.

Robinson, K.L. & Lawrence, N.S. 2006, "Redox-Sensitive Copolymer: A single component pH Sensor", *Analytical Chemistry,* vol. 78, no. 7, pp. 2450-2455.

Roka, Y.B., Shrestha, M., Puri, P.R. & Aryal, S. 2010, "Fatal inadvertent intracranial insertion of a nasogastric tube", *Neurology India,* vol. 58, no. 5, pp. 802-804.

Ross, S., Weijer, C., Gafni, A., Ducey, A., Thompson, C. & Lafreniere, R. 2010, "Ethics, economics and the regulation and adoption of new medical devices: case studies in pelvic floor surgery", *BMC Medical Ethics,* vol. 11, pp. 14-14.

Roubenoff, R. & Ravich, W.J. 1989, "Pneumothorax due to nasogastric feeding tubes. Report of four cases, review of the literature, and recommendations for prevention", *Archives of Internal Medicine,* vol. 149, no. 1, pp. 184-188.

Royal College of Physicians and British Society of Gastroenterology 2010, *Oral feeding difficulties and dilemmas. A guide to practical care, particularly towards the end of life.*, RCP, London.

Rubenstein, L.S. & Annas, G.J. 2009, "Medical ethics at Guantanamo Bay detention centre and in the US military: a time for reform", *The Lancet,* vol. 374, no. 9686, pp. 353-355.

Saisch, S.G. 1994, "An introduction to capnography", *Biofeedback and self-regulation,* vol. 19, no. 2, pp. 115-134.

Sakuma, I. 2013, "Education and training in regulatory science for medical device development", *Conference Proceedings: ...Annual International Conference Of The IEEE Engineering In Medicine And Biology Society.IEEE Engineering In Medicine And Biology Society.Conference,* vol. 2013, pp. 3155-3158.

Sattar, S.P., Ahmed, M.S., Madison, J., Olsen, D.R., Bhatia, S.C., Ellahi, S., Majeed, F., Ramaswamy, S., Petty, F. & Wilson, D.R. 2004, "Patient and Physician Attitudes to Using Medications with
Religiously Forbidden Ingredients", *The Annals of Pharmacotherapy,* vol. 38:, pp. 1830-1835.

Sayers, G.M. & Gabe, S.M. 2007, "Restraint in order to feed: justifying a lawful policy for the UK", *European Journal of Health Law,* vol. 14, no. 1, pp. 3-20.

Scott, D.H. 1930, *Modern Professional Nursing,* (vol 3) edn, Caxton, London.

Sekino, M., Yoshitomi, O., Nakamura, T., Makita, T. & Sumikawa, K. 2012, "A new technique for post-pyloric feeding tube placement by palpation in lean critically ill patients", *Anaesthesia & Intensive Care,* vol. 40, no. 1, pp. 154-158.

Senova Systems 2014, *Phit Platform* [Homepage of Senova Systems, Sunnyvale, California], [Online]. Available: http://senovasystems.com/ [2014, 16 July].

Shah, S.G.S. 2007, "Benefits of and barriers to involving users in medical device technology development and evaluation", *Journal of Technology Assessment in Health Care,* vol. 23, no. 1, pp. 131-137.

Shah, S.G.S., Farrow, A. & Robinson, I. 2009, "The representation of healthcare end users' perspectives by surrogates in healthcare decisions: a literature review", *Scandinavian Journal of Caring Sciences,* vol. 23, pp. 809-819.

Shah, S.G.S. & Robinson, I. 2008, "Medical device technologies: who is the user?", *International Journal of Healthcare Technology Management,* vol. 9, pp. 181-197.

Shah, S.G.S. & Robinson, I. 2006, "User Involvement in Healthcare Technology Development and Assessment: structured literature review", *International Journal of Health Care Quality Assurance,* vol. 19, no. 6, pp. 500-515.

Shah, S.G.S. 2011, "A Framework for Users' Involvement in Medical Device Technology Development and Evaluation", *EMDT: European Medical Device Technology,* vol. 2, no. 1, pp. 26-29.

Sharples, S., Martin, J., Lang, A., Craven, M., O'Neill, S. & Barnett, J. 2012, "Medical device design in context: A model of user-device interaction and consequences", *Displays,* vol. 33, no. 3, pp. 221-232.

Shebl, N.A., Franklin, B.D. & Barber, N. 2009, "Is failure mode and effect analysis reliable?", *Journal of Patient Safety,* vol. 5, no. 2, pp. 86-94.

Shenton, C. 2011, 11.14.11-last update*, Meeting Regulatory Requirements: The Design History File* [Homepage of Med-tech Innovation], [Online]. Available: http://www.med-techinnovation.com/Articles/articles/article/34. [2014, 03.31].

Shiao, S.P.K. & Difiore, T.E. 1996, "A Survey of Gastric Tube Practices in Level Hand Level III Nurseries", *Issues in Comprehensive Pediatric Nursing,* vol. 19, no. 3, pp. 209-220.

Shippee, N.D., Domecq Garces, J.P., Prutsky Lopez, G.J., Wang, Z., Elraiyah, T.A., Nabhan, M., Brito, J.P., Boehmer, K., Hasan, R., Firwana, B., Erwin, P.J., Montori,

V.M. & Murad, M.H. 2013, "Patient and service user engagement in research: a systematic review and synthesized framework", *Health Expectations,* , pp. n/a-n/a.

Simmonds, N.J. 2010, "Ethical issues in nutrition support: a view from the coalface", *Frontline Gastroenterology,* vol. 1, no. 1, pp. 7-12.

Sirringhaus, H., Sele, C.W., von Werne, T. & Ramsdale, C. 2006, "Manufacturing of Organic Transistor Circuits by Solution-based Printing" in ***Organic Electronics: Materials, Manufacturing, and Applications*** , ed. H. Klauk, Wiley VCH, Weinheim.

Smith, E., Ross, F., Donovan, S., Manthorpe, J., Brearley, S., Sitzia, J. & Beresford, P. 2008, "Service User Involvement in nursing, midwifery and health visiting research: a review of evidence and practice", *International Journal of Nursing Studies,* vol. 45, no. 2, pp. 298-315.

Smith, F., Holland, A., Penny, K., Elen, M. & McGirr, D. 2014, *Carbon dioxide detection for diagnosis of inadvertent respiratory tract placement of enterogastric tubes in children (protocol)*, John Wiley &Sons Ltd, The Cochrane Collaboration.

Smith, R. 1984, "The state of the prisons. Deaths in prison", *British Medical Journal (Clinical Research ed.),* vol. 288, no. 6412, pp. 208-212.

Sorokin, R. & Gottlieb, J.E. 2006, "Enhancing patient safety during feeding-tube insertion: a review of more than 2,000 insertions", *JPEN Journal of Parenteral & Enteral Nutrition,* vol. 30, no. 5, pp. 440-445.

Sparks, D.A., Chase, D.M., Coughlin, L.M. & Perry, E. 2011, "Pulmonary complications of 9931 narrow-bore nasoenteric tubes during blind placement: a critical review", *JPEN.Journal of parenteral and enteral nutrition,* vol. 35, no. 5, pp. 625-629.

Srinivasa, V. & Kodali, B. 2007, "Caution When Using Colorimetry to Confirm Endotracheal Intubation", *Anaesthesia and Analgesia,* vol. 104, no. 3, pp. 738-738.

Sriram, K., Jayanthi, V., Lakshmi, R.G. & George, V.S. 1997, "Prophylactic locking of enteral feeding tubes with pancreatic enzymes", *JPEN.Journal of parenteral and enteral nutrition,* vol. 21, no. 6, pp. 353-356.

Stack, R.S. & Harrington, R.A. 2011, "Biomedical innovation: a risky business at risk", *Science Translational Medicine,* vol. 3, no. 96, pp. 96cm23-96cm23.

Stepter, C.R. 2012, "Maintaining Placement of Temporary Enteral Feeding Tubes in Adults: A Critical Appraisal of the Evidence", *MEDSURG Nursing,* vol. 21, no. 2, pp. 61-102.

Stock, A., Gilbertson, H. & Babl, F.E. 2008, "Confirming nasogastric tube position in the emergency department: pH testing is reliable", *Pediatric Emergency Care,* vol. 24, no. 12, pp. 805-809.

Streeton, R., Cooke, M. & Campbell, J. 2004, "Researching the researchers: using a snowballing technique", *Nurse Researcher,* vol. 12, no. 1, pp. 35-46.

Sussman, S., Valente, T.W., Rohrbach, L.A., Skara, S. & Pentz, M.A. 2006, "Translation in the health professions: converting science into action", *Evaluation & the health professions,* vol. 29, no. 1, pp. 7-32.

Tamhne, S., Tuthill, D. & Evans, A. 2006, "Should ultrasound be routinely used to confirm correct positioning of nasogastric tubes in neonates?", *Archives of Disease in Childhood.Fetal and Neonatal edition,* vol. 91, no. 5, pp. F388.

Taylor, A.M., Cloherty, M., Alexander, J., Holloway, I., Galvin, K. & Inch, S. 2009, "Parental distress around supplementing breastfed babies using nasogastric tubes on the post-natal ward: a theme from an ethnographic study", *Maternal & Child Nutrition,* vol. 5, no. 2, pp. 117-124.

Taylor, S.J. & Clemente, R. 2005, "Confirmation of nasogastric tube position by pH testing", *Journal of Human Nutrition & Dietetics,* vol. 18, no. 5, pp. 371-375.

Taylor, S., Allan, K., McWilliam, H., Manara, A., Brown, J., Toher, D. & Rayner, W. 2014, "Confirming nasogastric tube position with electromagnetic tracking versus pH or X-ray and tube radio-opacity", *British Journal of Nursing,* vol. 23, no. 7, pp. 352-358.

Tedeschi, L., Atimer, L. & Warner, B. 2005, "Improving the accuracy of indwelling gastric feeding tube placement in the neonatal population", *Neonatal Intensive Care: The Journal of Perinatology-Neonatology, Supplement,* vol. 18, no. 4, pp. 6-8.

Telford, R., Beverley, C.A., Cooper, C.L. & Boote, J.D. 2002, "Consumer involvement in health research: fact or fiction?", *British Journal of Clinical Governance,* vol. 7, no. 2, pp. 92-103.

The Council of the European Communities 1993, *COUNCIL DIRECTIVE 93/42/EEC of 14 June 1993 concerning medical devices* [Homepage of CEC], [Online]. Available: http://ec.europa.eu/health/medical-devices/documents/index_en.htm [2014, 21 March].

The European Commision 1993, *COUNCIL DIRECTIVE 93/42/EEC of 14 June 1993 concerning medical devices* [Homepage of EU], [Online]. Available: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1993L0042:20071011:EN:PDF [2014, 9 October].

The Institution of Engineering and Technology July 2013, *, Colour Vision Defects - a factfile from the IET*. Available: http://www.theiet.org/factfiles/health/colourdefects-page.cfm [2014, 20 June].

The Royal College of Anaesthetists 2014, *Confirming Endotracheal Tube Placement* [Homepage of RCOA], [Online]. Available: http://www.rcoa.ac.uk/e-la [2014, 11 July].

Theodore, A.C., Frank, J.A., Ende, J., Snider, G.L. & Beer, D.J. 1984, "Errant Placement of Nasoenteric Tubes", *Chest,* vol. 86, no. 6, pp. 931-933.

Tho, P.C., Mordiffi, S., Ang, E. & Chen, H. 2011, "Implementation of the evidence review on best practice for confirming the correct placement of nasogastric tube in

patients in an acute care hospital", *International Journal of Evidence-Based Healthcare (Wiley-Blackwell),* vol. 9, no. 1, pp. 51-60.

Thomas, B.W. & Falcone, R.E. 1998, "Confirmation of Nasogastric Tube Placement by Calorimetric Indicator Detection of Carbon Dioxide: A Preliminary Report", *Journal of American College of Nutrition,* vol. 17, no. 2, pp. 195-197.

Thompson, J., Barber, R., Ward, P.R., Boote, J.D., Cooper, C.L., Armitage, C.J. & Jones, G. 2009, "Health researchers' attitudes towards public involvement in health research", *Health Expectations,* vol. 12, no. 2, pp. 209-220.

TibTech Innovations 2012, *Properties table of Stainless steel, Metals and other Conductive Materials* [Homepage of TibTech Innovations], [Online]. Available: http://www.tibtech.com/conductivity.php [2012, 27/01].

Tinkler, J. 2009, "Regional Differences in Medical Device Development", *Clinical Trials Online,* vol. February 3.

Torres, A., Serra-Bailles, J., Ros, E. & et al. 1992, "Pulmonary aspiration of gastric contents in patients receiving mechanical ventilation: the effect of body position. ", *Annals of Internal Medicine,* vol. 116, pp. 540-543.

Torrington, K. & Bowman, M. 1981, "Fatal hydrothorax and empyema complicating a malpositioned nasogastric tube.", *CHEST Journal,* vol. 79, no. 2, pp. 240-242.

Trochim, W.M.K. & Donnelly, J.P. 2007, *The Research Methods Knowledge Base,* 3rd edn, Thomson/Atomic Dog, Mason, Ohio.

Turgay, A.S. & Khorshid, L. 2010, "Effectiveness of the auscultatory and pH methods in predicting feeding tube placement", *Journal of Clinical Nursing,* vol. 19, pp. 1553-1559.

Vahid, B. 2007, "Inadvertent placement of a feeding tube in brainstem and spinal cord", *Internal Medicine Journal,* vol. 37, no. 8, pp. 577-578.

Valdes, S. & McGuire, P. 2004, "Contract research organizations (CROs) may be the next trend in clinical trials liability", *The Journal of Biolaw & Business,* vol. 7, no. 3, pp. 11-15.

Valentine, R.J. & Turner, W.W. 1985, "Pleural Complications of Nasoenteric Feeding Tubes", *Journal of Parenteral and Enteral Nutrition,* vol. 9, no. 5, pp. 605-607.

Verma, R. & Nelson, R. 2007, "Prophylactic nasogastric decompression after abdominal surgery", *Cochrane Database Syst Rev,* vol. 3.

Viall, C.D. 1996, "Location, location, location", *Nursing,* vol. 26, no. 9, pp. 43-45.

von Hippel, E. 1986, "Lead Users: a source of novel product concepts", *Management Science,* vol. 32, pp. 791-805.

Wadhawan, J., Greenman, J., ElHabbal, M., Shields, L., Imrie, C. & Elliott, B. 2007, *Catheter with a sensing region for redox reactions CA 2654338 A1*, PCT/GB2007/050326, United Kingdom.

Wain, A.J., Wadhawan, J.D. & Compton, R.G. 2003, "Electrochemical studies of vitamin K1 microdroplets: electrocatalytic hydrogen evolution,", *ChemPhysChem,* vol. 4, no. 3, pp. 974-982.

Ward, P.R., Thompson, J., Barber, R., Armitage, C.J., Boote, J.D., Cooper, C.L. & Jones, G.L. 2010, "Critical perspectives on 'consumer involvement'in health research Epistemological dissonance and the know-do gap", *Journal of Sociology,* vol. 46, no. 1, pp. 63-82.

Ward, M.M., McEwen, A.M., Robbins, P.M. & Bennett, M.J. 2009, "A simple aspiration test to determine the accuracy of oesophageal placement of fine-bore feeding tubes", *Intensive Care Medicine,* vol. 35, no. 4, pp. 722-724.

Watson, J. & McGuire, W. 2013a, *Nasal versus oral route for placing feeding tubes in preterm or low birth weight infants*, Cochrane Collaboration, John Wiley and Sons Ltd.

Watson, J. & McGuire, W. 2013b, *Transpyloric versus gastric tube feeding for preterm infants*, Cochrane Collaboration, John Wiley and Sons Ltd.

Webb, G., Gupta, P., Fitchett, J., Simmons, J. & De Silva, A. 2012, "Efficacy of nasal bridles in avoiding percutaneous endoscopic gastrostomy placement", *Frontline Gastroenterology,* vol. 3, no. 2, pp. 109-111.

Weightman, A.P.H., Preston, N., Holt, R., Allsop, M., Levesley, M. & Bhakta, B. 2010, "Engaging Children in Healthcare Technology Design: Developing Rehabilitation Technology for Children with Cerebral Palsy", *Journal of Engineering Design,* vol. 21, no. 5, pp. 579-600.

Weilby, T.T., Adamson, M., Clinkscales, N., Curran, J. & Bramson, R. 1987, "Gavage Tube Insertion in the Premature Infant", *MCN The American Journal of Maternal/Child Nursing,* vol. 12, no. 1, pp. 24-27.

Westhus, N. 2004, "Methods to test feeding tube placement in children", *MCN American Journal of Maternal Child Nursing,* vol. 29, no. 5, pp. 282-287.

White, H., Sosnowski, K., Tran, K., Reeves, A. & Jones, M. 2009, "A randomised controlled comparison of early post-pyloric versus early gastric feeding to meet nutritional targets in ventilated intensive care patients", *Critical Care,* vol. 13, no. 6, pp. R187.

Wightamn, R.M. & Wipf, D.O. 1989, "Voltammetry at ultramicroelectrodes," in *Electroanalytical Chemistry: A Series of Advances*, ed. A.J. Bard, volume 15 edn, Marcel Dekker, New York, pp. 267-354.

Wilkes-Holmes, C. 2006, "Safe placement of nasogastric tubes in children", *Paediatric Nursing,* vol. 18, no. 9, pp. 14-17.

Williams, T.A. & Leslie, G.D. 2004, "A review of the nursing care of enteral feeding tubes in critically ill adults: part I", *Intensive and Critical Care Nursing,* vol. 20, no. 6, pp. 330-343.

Windle, E.M., Beddow, D., Hall, E., Wright, J. & Sundar, N. 2010, "Implementation of an electromagnetic imaging system to facilitate nasogastric and post-pyloric

feeding tube placement in patients with and without critical illness", *Journal of Human Nutrition & Dietetics,* vol. 23, no. 1, pp. 61-68.

Windle, M. 2010, "Electromagnetic sensing devices as a cost-effective and safer option for bedside placement of postpyloric feeding tubes", *Journal of Burn Care & Research,* vol. 31, no. 3, pp. 505-505.

Wittgrove, A.C. & Clark, G.W. 2000, "Laparoscopic Gastric Bypass, Roux en-Y –500 Patients: Technique and Results, with 3-60 month follow-up ", *Obesity Surgery,* vol. 10, pp. 233-239.

Woods, N. 2013, 04.11.13-last update*, Forget US Sales Tax: new EU rules won't just hurt, they'll kill* [Homepage of Med latest], [Online]. Available: http://www.medlatest.com/2013/09/30/forget-sales-tax-new-eu-rules-wont-just-hurt-theyll-kill/ [2014, 03.31].

World Health Organisation 2004, *Copper in Drinking-water: Background document for development of WHO Guidelines for Drinking-water Quality*, World Health Organization 2004, Geneva.

World Health Organisation Food and Agricultural Organisation of the United Nations 2002, *Human Vitamin and Mineral Requirements*, FAO/WHO, Rome.

World Intellectual Property Organisation (WIPO) 2014, *PCT- The International Patent System* [Homepage of WIPO], [Online]. Available: http://www.wipo.int/pct/en/faqs/faqs.html [2014, 21 August].

World Medical Association 2014, *, WMA Declaration of Tokyo - Guidelines for Physicians Concerning Torture and other Cruel, Inhuman or Degrading Treatment or Punishment in Relation to Detention and Imprisonment* [Homepage of World Medical Association], [Online]. Available: http://www.wma.net/en/30publications/10policies/c18/ [2014, 9 July].

Wu, N.Y., Zang, Y.B., Gao, W. & Xu, M.T. 2013, "Zero Current Potentiometry for Measuring the Interface Potential at the Electrode/Solution Interface. Theoretical and Experimental Study", *Electroanalysis,* vol. 25, no. 9, pp. 2175-2180.

Wu, P.Y., Kang, T.J., Hui, C.K., Hung, M.H., Sun, W.Z. & Chan, W.H. 2006, "Fatal massive haemorrhage caused by nasogastric tube misplacemment in a patient with mediastinitis", *Journal of Formosan Medical Association,* vol. 105, no. 1, pp. 80-85.

Wynne, D., Borg, H., Geddes, N. & Fredericks, B. 2003, "Nasogastric tube misplacement into Eustachian tube", *International Journal of Pediatric Otorhinolaryngology,* vol. 67, no. 2, pp. 185-187.

Yardley, I.E. & Donaldson, L.J. 2010, "Patient safety matters: reducing the risks of nasogastric tubes", *Clinical medicine (London, England),* vol. 10, no. 3, pp. 228-230.

Yong, S., Ma, J., Chen, F., Chung, M. & Yang, K.D. 2014, "Nasogastric Tube Placement and Esophageal Perforation in Extremely Low Birth Weight Infants", *Pediatrics & Neonatology,* [Online], . Available from: http://www.pediatr-neonatol.com/article/S1875-9572(13)00231-3/fulltext. [16 Aug 2014].

Young, A. & Leedham, L. 2011, "Nasobridles as a retaining device to provide nutrition support", *Gut,* vol. 60, no. Suppl 1, pp. A52-A52.

Zuckerman, D.M., Brown, P. & Nissen, S.E. 2011, "Medical device recalls and the FDA approval process", *Archives of Internal Medicine,* vol. 171, no. 11, pp. 1006-1011.

Appendices

Appendix 1: Interim Report for National Institute of Health Research

Appendix 2: Decision tree for nasogastric tube placement-checks in adults

Appendix 3: American Association of Critical Care Nurses Practice Guidelines

Appendix 4: Toxicology Report for Vitamin K_1

Appendix 5: LINGT iteration 1 Ethical approval letter

Please see CD inserted at the end of the thesis for appendices 1-5

Appendix 6: Work Instructions for preparation of electrodes

DOCUMENT AUTHOR: Dr M Schoenleber

DOCUMENT APPROVAL

Approval: **Date**: 10 June 2014

MONIKA SCHOENLEBER
Controlling Manager

Approval: **Date**: 10 June 2014

BARBARA ELLIOTT
Project Leader

DISTRIBUTION LIST

Recipients:
Project Leader
Controlling Manager
Nominated Deputy Controlling Manager
Chief Electrochemist
Project Surgeon
Internal Auditor
Project Administrator

REVISION HISTORY			
Revision Level	**Reason For Change**	**Revision Initiated By**	**Issue Date**
V01	**Update**	**MS**	**19/02/2014**
V02	**Update**	**BE**	**26/022014**
V03	**Update**	**MS**	**15/05/2014**
V03	**Revision**	**MS**	**28/05/2014**

1 PURPOSE

1.1 This Work Instruction **WI 05** – Coating Preparation Of Location Indicating Naso-Gastric Tubes LINGT) For Placement Sensing Applications describes the methodology used by appropriate members of the UOHLINGT Project Team for preparing the electrode surfaces of said nasogastric tubes (NGT) for development and prototyping activities within the UOHLINGT Project.

2 SCOPE

2.1 This Work Instruction **WI 05** – Coating Preparation Of Location Indicating Naso-Gastric Tubes (LINGT) For Placement Sensing Applications describes a method which is applicable to NGT electrode surfaces such as stainless steel wire.

3. SUMMARY OF METHOD

3.1 The intraluminal conducting wires have been exposed at the distal tip of the tube by cutting away (skiving) a 6 mm length of the outer surface of the tube. This exposed surface of the conducting wires are utilised as working electrode and reference electrode

3.2 The preparation for these wires to function as electrodes is using a multi-step process, starting with dipping the tip of the NGT into aqueous ethanol, which is followed by mechanical polishing the exposed wires with a soft paper cloth to obtain a clean electrode surface free of residual impurities.

3.3 Wire (a) functioning as the working electrode, is coated with Vitamin K_1, and wire (b) functioning as the reference electrode is coated with silver/silver-chloride (Ag/AgCl) ink.

3.4 The NGT comprising both coatings are exposed to elevated temperatures to be fully cured.

3.5 Fully prepared and cured NGT are stored in the refrigerator at $+4^0$C prior use.

4 SAMPLE HANDLING

4.1 Both coating procedures are conducted at room temperature.

4.2 No specific precautions for NGT are required, however, material safety data sheets (MSDS) and/or technical data sheets (TDS) of reagents (See **Section 7**) should be obtained and read.

4.3 Sample handling is subject to risk assessment according to **SOP 05** - Risk Management Procedure (Process And Products).

5 CORRECTIVE AND PREVENTIVE ACTIONS

5.1 Any sample constituent which covers the electrode surfaces except for Vitamin K_1 and Ag/AgCl ink can cause a sluggish electrochemical response. The electrodes must be kept clean.

5.2 Problems associated with sluggish current responses (See **Section 10**, below) may be traced to the electrode surface containing a covering of some sort. This can be resolved by rinsing the electrode tip in demineralised water or, if more vigorous cleaning is required, dipping the electrode into acidic solution (e.g. 0.1 molar hydrochloric acid) prior to rinsing with demineralised water.

5.3 Problems associated with low current responses (See **Section 10**, below) may be traced to either the electrode surface being damaged or due to delaminating of either Vitamin K_1 or Ag/AgCl ink coating. In such a case, the NGT has to be discarded.

5.4 This methodology is carried out according to appropriate principles of **Good Laboratory Practice** as defined in a variety of applicable documents including those listed in **Sections 12.4** and **12.5**.

6 APPARATUS

6.1 Deerac Fluidics Equator (TM) Low Volume Pipetting System – referred to as micro-spotter.

6.2 Naso-Gastric tubes (NGT) containing conductive wires.

6.3 Small brush

6.4 All suppliers of apparatus are subject to **SOP 08** – Supplier Evaluation Procedure and its provisions.

7 REAGENTS

7.1 Demineralised water

7.2 Ethanol, absolute.

7.3 Aqueous ethanol, 70%

7.4 10 mM Vitamin K_1 dissolved in absolute ethanol

7.5 Silver/Silver-Chloride (Ag/AgCl) ink (used as supplied)

7.6 All suppliers of reagents are subject to **SOP 08** – Supplier Evaluation Procedure and its provisions.

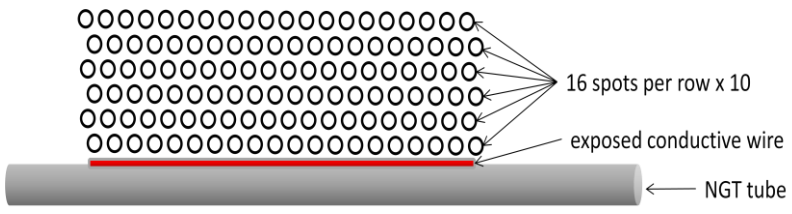
8 ANALYTICAL METHOD

8.1 The electrode surface of both wires are cleaned by dipping the tip of the NGT into aqueous ethanol, 70%, then the exposed wires are mechanically polished with a soft paper cloth.

8.2 The electrode tip is mounted on a micro-spotter into a designated tube holder/jig with the wire functioning as the working electrode facing upwards (See Figure 1 (a)). The sample container of the micro-spotter is filled with 10 mM Vitamin K_1 dissolved in absolute ethanol and replenished throughout the spotting procedure.

8.3 The spotting procedure for wire (a) functioning as the working electrode is as follows:

a) Micro-spotter is set for a volume of 300 nl per spot.
b) Spot sequence: 16 spots per row (6 mm wire length).
c) 6 x 10 rows in an off-set spotting sequence varying XY axis settings (see Figure 2 a and b) to achieve full coverage of the external wire.
d) Total amount equal 288 µl on 6 mm wire length.



(a)

(b)

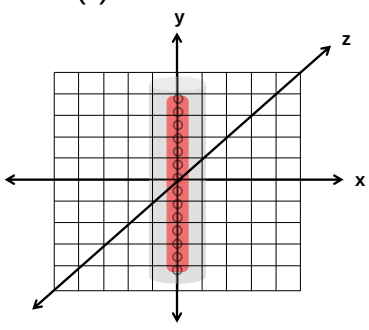


Figure 2. (a) Illustration of Off-set spotting sequence for micro-spotting NGT and

(b) horizontal view of NGT with variant of XYZ axis settings

8.4 Wire (b) functioning as the reference electrode is coated with Ag/AgCl ink using a small brush with which a sufficient amount of ink is carefully applied to cover the exposed wire (a), slightly overlapping onto the tubing.

8.5 The fully coated NGT is placed into an oven set at +72ºC ±2 for 15 minutes and then stored in refrigerator at +4ºC prior use.

9 VERIFICATION

9.1 A voltmeter is used to check for conductivity across the whole length of each wire before and after the coating procedure.

QUALITY ASSURANCE

10.1 Both electrode surfaces are examined for full coverage of the coating using a microscope.

11 RECORDS

11.1 Records of each instance of conditioning of working electrodes shall be made and kept in accordance with **SOP 03** – Quality Records Procedure.

12 REFERENCES

12.1 **SOP 03** – Quality Records Procedure
12.2 **SOP 05** - Risk Management Procedure (Process And Products)
12.3 **SOP 08** – Supplier Evaluation Procedure
12.4 Good Laboratory Practice (GLP) Quality practices for regulated non-clinical research and development 2009 2nd Ed. TDR WHO.
12.5 Guideline On Bioanalytical Method Validation, European Medicines Agency, 21 July 2011.

Appendix 7: LINGT iteration 2 ethical approval letter

Please see CD inserted at the end of the thesis for appendix 7

Appendix 8: Protocol for study on resected stomach tissue

Ex-vivo testing of a location-indicating nasogastric tube

Protocol

Summary

The objective of this feasibility study is to establish that, when the tip of a modified nasogastric tube is placed inside a recently resected stomach, the reaction between the tip of the tube and the stomach lining can be detected and measured by a monitor attached to the other end of the tube and outside the stomach.

Whole or partial stomachs removed from 20 adult patients undergoing upper gastro-intestinal surgery will be accessed in theatre immediately after removal. Patients requiring surgery at Castle Hill Hospital for removal of whole or part of their stomach for the management of obesity will be identified by the consultant surgeon for inclusion in the study. The principal investigator will be informed of the date and time of the surgery but will be given no patient details except age within 5 year band and reason for surgery. All data collected will be completely anonymous.

The chief investigator will conduct a 10 minute assessment of up to 3 modified nasogastric tubes in the theatre immediately after the gastric specimen is available. On completion of the assessments the gastric specimen will be disposed of in the normal way. The researcher will ensure that these assessments are all carried out quickly and efficiently. No patient tissue or fluid will be removed from the operating environment. Only the patient's age and reason for surgery will be recorded. This design has been chosen rather than animal testing as there is no detrimental effect to the removed stomach and the results will be more applicable to further studies on human stomachs. Laboratory tests on aspirated gastric fluid have already been successfully conducted.

Patient consent will be sought by the principal investigator even though their surgery and treatment will not be affected in any way by participation in the study. They will not receive any intervention for purposes of research and no personal information will be collected from or about them. No additional tissue will be removed or stored for the research study.

Procedure

- Medical secretary informs principal investigator of patients listed for bariatric surgery in the following month and their date of surgery
- Principal investigator explains study to the patient and gives information sheet
- Principal investigator obtains informed consent from the patient
- Principal investigator attends theatre on the day of surgery and dresses in appropriate surgical scrubs and enters theatre sluice
- Surgeon informs principal investigator that stomach tissue has been removed and places in a suitable container
- Principal investigator takes the container to theatre sluice room

- Principal investigator places a tube in contact with the stomach lining and attaches to current reader. No pressure will be applied to the tissue, the tube simply being placed upon the mucosal surface.
- Electric current is continuously monitored for 10 – 30 minutes and noted manually on chart every 30 seconds. This is repeated with a second tube if considered possible.
- Tubes are removed and disposed of in clinical waste
- Stomach is placed in container for disposal or transport and formalin added in accordance with normal procedure for surgical specimens
- Specimen is removed to laboratory for investigation as required by patient's condition and requested by surgeon or disposed of in the normal way

Appendix 9: Patient Information Sheet – resected stomach tissue

Patient Information Sheet

A study to test a new tube on surgically removed stomachs

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve for you. The principal investigator, Mrs Barbara Elliott, will go through this information sheet with you and answer any questions you have. This will take approximately 15 minutes.

The information sheet will be left with you, please talk to others about the research if you wish and show them the information sheet.

Part 1 Tells you the purpose of the research and what will happen if you take part

Part 2 Gives you more detailed information about the conduct of the study

Mrs Elliott will return, probably the following day, to answer any questions you may have and explain anything that is unclear.

Part 1

- The purpose of the study is to test a new type of feeding tube.
- You have been asked to take part because you are having surgery to remove part of your stomach. We would like to test our tube on a small piece of this after the surgeon has removed it.
- It is entirely up to you whether you would like to participate in the study. We will explain the study to you and go through this information sheet. If you then agree to take part we will ask you to sign a consent form. You may change your mind and withdraw your consent at any time without giving a reason. The standard of your care will not be affected.
- If you agree to take part in the study your operation will not be affected. When the surgeon has taken out the part of your stomach that needs to be removed it will be put into a container and taken into a side room attached to the operating theatre. Our researcher will then assess up to 3 of the new tubes in the specimen before it is removed from the theatre. This will take approximately 10 minutes.
- The researcher will take readings from a monitor attached to the tubes. These will be written on a sheet of paper with your research number and your age range. No other personal information will be recorded.
- The researcher is not part of the team performing your operation so your surgery will continue in the normal way. Your operation, care and recovery will not be affected and you will not be expected to do anything further for the study. Please be assured that the amount of stomach the surgeon removes will not be affected by our study.
- There will be no damage to the tissue and it will be treated in the usual way following the 10 minute assessment.
- The study will not benefit you but we hope that in the future the new tubes we are developing will help patients who require tubes inserted into their stomach.

- Any complaint about the way you have been dealt with during the study will be addressed. Please see information given at the end of the form for contact details.
- We will follow ethical and legal practice and all information will be handled in confidence. The details are included in part 2.

If the information in Part 1 interests you and you are considering taking part in the study please read the additional information in Part 2 before making any decision.

Part 2

- If, before you go for your operation, you change your mind about taking part in the study you can let the doctor or nurses caring for you know. They will inform the research team. Your surgery and care will not be affected and you do not have to give a reason.
- All information which is collected during the study will be kept strictly confidential and any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised. At the end of the research period all data will be destroyed.
- Your General Practitioner will be informed of your participation in the research although your surgery, care and follow up treatment will not be affected by your participation. A brief summary of the research will be given to your GP.
- No additional tissue will be removed and no tissue will be retained for the purposes of this research study.
- The results of the study will be used in the development of the next version of the tube and will be published in the report for the National Health Service and in a paper for a scientific journal. You will not be identified in any way in these publications.
- The research is funded by the NHS and managed by the University of Hull. Your doctor is not being paid for including you in the study.
- All research in the NHS is looked at by independent group of people called a Research Ethics Committee to protect your interests. This study has been reviewed and given a favourable opinion by Leeds (West) Research Ethics Committee
- If you have any concerns about any aspect of this study please contact the research team who will do their best to answer your questions. Barbara Elliott, the principal investigator, can be contacted on 01482 464518 or email b.e.elliott@hull.ac.uk.
- If you remain unhappy about the study and wish to complain formally please contact the Patient Advice and Liaison Service (PALS) on 01482 623065 or the Complaints Department, 4th Floor, Alderson House, Hull Royal Infirmary, Anlaby Road, Hull HU3 2JZ, tel 01482 605284.
- Further information about the management of research in the NHS can be found in the Research Governance Framework for Health and Social Care available from Mrs Elliott or on the NHS website.

Thank you for taking the time to read this information sheet

Appendix 10: Case Report Form

Appendix 11: GP letter

Appendix 12: NHS Research Ethics approval letter

Please see CD inserted at the end of the thesis for appendices 10-12

Appendix 13: Patient information sheet – gastric fluid or sputum

A study to test a new tube on samples of gastric fluid or sputum

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve for you.

The principal investigator, Mrs Barbara Elliott, will go through this information sheet with you and answer any questions you have. This will take approximately 15 minutes.

The information sheet will be left with you, please talk to others about the research if you wish and show them the information sheet. Mrs Elliott will return, probably the following day, to answer any questions you may have and explain anything that is unclear.

What is the purpose of the study?
The purpose of the study is to test a new type of feeding tube on samples of human fluid. The new tube is an "intelligent" tube that is designed to distinguish between stomach and lung lining. The study is being conducted as part of a PHD research study.

Why have I been asked to take part?
You have been asked to take part because your current treatment involves either removal of fluid from your stomach via a tube or your lungs by coughing. This fluid is normally collected in a pot and then disposed of. We would like to test our tube on this fluid before it is thrown away.

Do I have to take part?
It is entirely up to you whether you would like to participate in the study. We will explain the study to you and go through this information sheet. If you then agree to take part we will ask you to sign a consent form. You may change your mind and withdraw your consent at any time without giving a reason. The standard of your care will not be affected.

What will happen to me if I agree to take part?
If you agree to take part in the study your care and treatment will not be affected in any way. Fluid will be removed from your stomach or lungs and collected as required by your medical condition and directed by your doctor. No additional fluid will be removed for the purposes of this research study. Fluid will be stored in a pot on the ward and then taken to our laboratory. It will be identified only by a research number and stored for up to a month in the laboratory.
In the laboratory our feeding tube will be placed in the fluid and we will take readings from a monitor attached to the tube. These numbers will either be written on a sheet of paper with your research number or stored electronically. No other personal information will be recorded.
Your fluid will not be used for any other research and will be disposed of safely after 1 month.

What are the possible disadvantages and risks of taking part?
The researcher is not part of the team delivering your hospital treatment so your care will continue in the normal way. Your treatment, care and recovery will not be affected and you will not be expected to do anything further for the study.

What are the possible benefits of taking part?
The study will not benefit you but we hope that in the future the new tubes we are developing will help patients who require tubes inserted into their stomach.

What if there is a problem?
Any complaint about the way you have been dealt with during the study will be addressed. If you have any concerns about any aspect of this study please contact the research team who will do their best to answer your questions. Contact details are given at the bottom of this page. If you remain unhappy about the study and wish to complain formally please contact the Patient Advice and Liaison Service (PALS) on 01482 623065 or the Complaints Department, 4th Floor, Alderson House, Hull Royal Infirmary, Anlaby Road, Hull HU3 2JZ, tel 01482 605284

Will my taking part in the study be kept confidential?
We will follow ethical and legal practice and all information will be handled in confidence. Only your name and signature will appear on the consent form.
Your General Practitioner will be informed of your participation in the research although your treatment, care and follow up will not be affected by your participation. A brief summary of the research will be given to your GP.

What if I change my mind about taking part in the study?
If you change your mind about taking part in the study you can let the doctor or nurses caring for you know. They will inform the research team. Your treatment and care will not be affected and you do not have to give a reason.

What will happen to the results of the research study?
The results of the study will be used in the development of the next version of the tube and will be published in the report for the National Institute for Health Research and in papers for scientific journals. You will not be identified in any way in these publications. If you wish to receive a copy of the study results please contact Barbara Elliott (details below).

Who is organising and funding the research?
The research is funded by the NHS and managed by the University of Hull. These institutions provide insurance for the research study. Your doctor is not being paid for including you in the study.

Who has reviewed this study?
All research in the NHS is looked at by independent group of people called a Research Ethics Committee to protect your interests. This study has been reviewed and given a favourable opinion by South Central Berkshire –B Research Ethics Committee

Further information about the study can be obtained from:
Barbara Elliott, the principal investigator, can be contacted on 01482 464518 or email b.e.elliott@hull.ac.uk.

Further information about the management of research in the NHS can be found in the Research Governance Framework for Health and Social Care available from Mrs Elliott or on the NHS website.

Appendix 14: Medical device classification

Appendix 15: Quality Policy and Objectives

Appendix 16: List of Standard Operating Procedures (SOP's)

Appendix 17: List of Operating Procedure Forms (OPF's)

Appendix 18: Questions for Risk Assessment

Appendix 19: Failure Mode Effect Analysis (FMEA)

Appendix 20: GANT Chart

Please see CD inserted at the end of the thesis for appendices 14 - 20

Appendix 21: User Involvement Strategy

Location Indicating Nasogastric Tube (LINGT) Project
User Carer Involvement Strategy

Background

This project was initiated in response to patient and carer need identified in conversations with parents being taught to administer nasogastric feeds to their sick children. Current placement detection methods cause parents great anxiety, particularly when unsupervised at home. Studies confirm that caring for a child with a nasogastric tube at home frightens parents.

Subsequent discussions with adult and children's nurses confirmed that current methods of verifying correct placement remain problematic for patients, nurses and carers. A reliable bedside method for determining tube placement is essential for patient safety. Consultations with nurses, patients and parents support the view that there is an important unmet clinical need for a quick, conclusive method, which does not require fluid aspiration.

Patient and carer (professional and family) feedback before NIHR funding was awarded, confirmed the need for the project and informed the proposal for the funding. It is essential that continuing user carer involvement should be a part of the development process.

Principles

Conversations with patients, carers and professionals initiated this project. There is an ongoing commitment to ensure that the views of users and carers, be they professionals or members of the public, will be sought and included by the team. Within the remit of the project, Patient and Public Involvement will focus on engaging those who have experience of using nasogastric tubes or caring for someone with a nasogastric tube, in effect users and carers.

A range of ways of engaging users and carers will be offered, including facilitating group meetings. Care will be taken to ensure that information and views gained through user and carer involvement will be collated and fed into the project. We will ensure that users and carers are aware of this through an ongoing dialogue with individuals and groups.

The aim is that users' and carers' views will be integral to the development of the Location Indicating Nasogastric Tube.

Strategy

The purpose of this strategy is to outline a framework for ongoing and developing user carer involvement in the LINGT project.

Whilst the project is time limited, with a short time scale, the aim is to link into existing good practice and develop mechanisms to ensure opportunities for meaningful engagement are developed and challenges overcome.

Resources

Human Resources

Members of the team chiefly involved in user / carer involvement are the:

- Principal Investigator: Barbara Elliott

Barbara Elliott has contacted the Local Involvement Network, and Patient and Public Involvement (PPI) Leads of relevant NIHR Research Networks and discussed plans for PPI with personnel at INVOLVE. She has attended a NIHR Research Design Service for Yorkshire and Humber workshop at York University on PPI in Research Design (October 2009). She has contacted the Faculty Lead for User Carer Involvement and a number of NHS and Charity personnel regarding recruiting users and carers.

- Post Doctoral Research Associate: Monika Schoenleber

As research scientist, Monika Schoenleber is able to update users and carers on the progress of the project (within the bounds of confidentiality).

- Project Administrator: Margaret Crawley

Margaret Crawley has previous experience of working in PPI, having worked with the Hull & East Riding Multidisciplinary Audit Advisory Group, accessing and utilising training in user led audit and qualitative research methods. PPI experience was also gained working as a Community Health Development Worker for Yorkshire Wolds and Coast Primary Care Trust and as Patient and Public Involvement Officer for Langbaurgh Primary Care Trust.

Financial Resources

Financial resources are available to reimburse expenses, for example, travel, carer and childcare payments. Resources can also be used to ensure a comfortable environment for meetings, for example, room booking and refreshments. Resources are available for producing information and feedback in formats required by those involved with the project.

Information Resources

The project team has access to information resources through the University of Hull library and IT and the potential to develop links with local user carer networks.

Timescales

The LINGT project is a three year project, ending 1 July 2014. This will inevitably have implications for user carer involvement. Care will continue to be taken to ensure that users and carers contributing to the project are aware of the limited timeframe of the project and of the potential timescale before commercial production becomes a reality.

The limitations on time present specific challenges in building and maintaining a network of users and carers, but by ensuring a flexible approach in how and when we engage with users and carers and a commitment to ensure information flows into the project and back to users and carers, user carer involvement can remain an essential part of the project.

Confidentiality
Confidentiality was addressed with regard to patent issues (part of the development of a medical device), by asking users and carers to sign a confidentiality agreement. In terms of data protection, users and carers have signed a project data protection form giving the team permission to hold their contact details. These forms and user carer feedback are kept in a locked filing cabinet in a locked office and can only be accessed by members of the project team.

Copies of the forms are included at the end of this strategy.

Methods of Involvement
Members of the project team working in user carer involvement are committed to ensuring flexibility in the ways we involve people in tune with the preferences of the people we involve.
To date we have had:

- Meetings with parents in the university setting
- Meetings with professionals (nurses) in the university
- Individual meetings with professionals and with carers
- Telephone conversations with carers
- Email contact with carers

We ensure that people we contact are aware that the team can be contacted through:

- telephone
- email
- meetings in a variety of venues

and that views and feedback can be offered at any time outside of meetings.

For users and carers who might prefer to offer their views in writing, consideration has been given to the production of a questionnaire, based on the discussions during meetings. Participant payments and expenses are available (see above) and consideration is given to the accessibility of meeting venues. Enlisting the help of users and carers remains an ongoing process, in effect a ‘snowballing’ process. No limit has been set as to the number of people who can be involved. Numbers of people involved in the user carer network is currently (November 2012) twelve, six health professional members and six members of the public.

Levels of Involvement
The project's short timescale means that user carer involvement will also be short term, although there may be the possibility of users and carers linking into other user carer involvement opportunities within the Faculty.

Information collection
Involvement to date has been a process of information collection with regard to the lived experience of users and carers using nasogastric tubes from the perspectives of lay members and professionals. Notes are taken at meetings and after telephone conversations, and these are sent to the users and carers involved to ensure that they are a true record.

Information will be collated and will feed into:

- risk assessment
- monitor and tube design
- the design of research participant information.

Communication

Users and carers have been invited to contact the Project Lead at any time and have been given her contact details, which include, email, telephone (with answerphone), and university address.

Consideration has also been given as to how users and carers can be updated with regard to the project outside of meetings. A Project Bulletin in the form of a short newsletter will be produced quarterly and in addition to project updates, the Bulletin is an opportunity to encourage further input.

Information should be accessible to all. We will endeavour to ensure that information from the project will be as jargon free as possible, easy to understand and in formats required by those involved or who would like to be involved.

Monitoring and Evaluation

Ongoing monitoring takes the form of an ongoing dialogue with users and carers in terms of satisfaction with meeting places, communication and update. It is intended that the project newsletter will become one way to facilitate this.
Formal monitoring of user carer input will be done through regular update of a user carer activity table, which will be reviewed at the fortnightly project team meetings.

Evaluation will take the form of a review of the process and outcomes through meetings and questionnaires towards the end of the project.

University of Hull Location Indicating Nasogastric Tube (LINGT) Project

Thank you for agreeing to join the User-Carer Advisory Group for the LINGT Project. Your participation is much appreciated.

The project is based in the Faculty of Health and Social Care, University of Hull, Cottingham Road, Hull HU6 7RX. It is a three year project which started in July 2011 and will be completed in July 2014.

We hope to be able to meet with you from time to time, to update you on progress and seek your advice based on your own experiences. In order to do this we need your permission to keep your contact details on our files and if you have an email address, we would like to add that to our email contact list for the project.

Your details will remain confidential and will not be passed on to anyone outside the LINGT team, without your permission.

You can contact the LINGT team on the above address, telephone 01482 463351 or email b.e.elliott@hull.ac.uk) at any time for further information or if you would like to remove your contact details from our files.
Thank you again for your help.

Barbara Elliott
(Project leader)

If you agree to your details being held by the LINGT project team, please complete and sign the following:

First Name: Surname:

Address:

Telephone Number: Email:

Preferred means of contact

I agree to my contact details being held by the project team until the project is completed or until I wish to withdraw from the User-Carer Advisory Group.

Signed: Date:

CONFIDENTIALITY UNDERTAKING

This Deed is made the 2012

We, the undersigned, understand that as a result of our attendance at a meeting of the Naso-gastric tube user group (the Meeting) at the University of Hull (the University) we may have access to information of a confidential nature belonging to the University (Information).

Information means any and all information of a technical, confidential, business or proprietary nature howsoever disclosed during or as a result of the Meeting.

Each person attending the Meeting undertakes as follows:

1. to maintain as confidential all Information which may be revealed or disclosed during or as a result of the Meeting;

2. not to access, use or copy any Information for any purpose unless given specific written authorisation to do so by the University;

3. not to reveal, disclose or publish the Information to any other person or party without prior written consent from the University;

4. this undertaking does not apply to Information which:

    i. is in the public domain at the time of disclosure or which later enters the public domain other than by breach of this undertaking;

    ii. is lawfully known to the receiving party at the time of disclosure or release;

    iii. is revealed by a third party who has the right to do so without duty of confidentiality;

    iv. is required to be disclosed by law, court or similar regulatory authority.

These obligations will continue in force for a period of 6 years.

NAME (PRINT) SIGNATURE

Appendix 22: Information sheet for User Advisory Group

Appendix 23: Project Bulletin Information and Invitation Edition

Appendix 24: Bulletin 3

Appendix 25: User Network Activity Table

Appendix 26: User Requirement Specification

Appendix 27: Design LINGT iteration 3

Please see CD inserted at the end of the thesis for appendices 22-27

NHS
National Institute for Health Research

Invention for Innovation (i4i)
Stream 2 Interim Report Form

For office use only

IMPORTANT
Note the maximum field sizes shown include both printing and non-printing characters, such as spaces and carriage returns.

Reference Number: II-AR-1109-11057

Date submitted: 5 February 2014

1. Project Details

Project Title:	Location-Indicating Naso-Gastric Tube (NGT)		
Contracting Organisation:	University of Hull		
Project Duration: (months)	36.0 plus 12 month extension		
Start Date:	02/07/11	Agreed Extension: (months)	12 months
End Date:	01/07/14	Revised End Date:	01/07/15

2. Grant Holder's Details

Title:	Mrs
Surname:	Elliott
Forename	Barbara
Department:	Faculty of Health and Social Care
Role in project:	Principle Investigator
Institution:	University of Hull
Street	Cottingham Road
Town/City:	Hull
County:	East Yorkshire
Post Code:	HU6 7RX
Telephone:	01482 464518

3. Research Performance

Please provide a list of the milestones which should have been achieved during this period, indicating the proposed completion date and the actual completion date. Please indicate if work on a particular milestone is ongoing.

List of the specific milestones for the relevant period **(Maximum 500 characters)**	Proposed date of completion	Actual date of completion
UoHLINGT v5 tube and monitor completed. Design Freeze and manufacturer of nasogasric tubes identified and appointed	October 2013	**Tube:** Proposals received and visits to 3 potential manufacturers made in October/November 2013. Final selection and contract with INTERVENE Ltd drawn up **January 2014. Monitor:** Contract with Image to Implant signed July 2013. Prototype monitor design agreed **23 January 2014.**
Additional in-vitro clinical evaluation of iteration 4 tubes	October 2013.	Results of tests on 3 samples of sputum and 7 samples of gastric fluid discussed at QRM **16 October 2013**. Agreed further samples required and additional hospital site to be used. REC and R&D approval sought for minor amendment and granted Dec 2013. Further in vitro studies conducted **January & February 2014**

4. Milestones for the Next Period

List of planned milestones for the next period, including any proposed revisions as result of research results from the project to date or variations to the contract.

Milestone **(Maximum 500 characters)**	Description **(Maximum 2,000 characters)**
Pre-production product for pilot trials and commercial evaluation completed	Variation to contract form moved this milestone to June 2014. Contract is being prepared with INTERVENE Ltd who estimate 7.5 months to develop and manufacture tubes. This means product should be available mid September 2014.
MHRA notice of no objection received	Variation to contract form suggested that this milestone would be achieved by August 2014. As sixty days notice must be given to Secretary of State before clinical trials begin this may not be achieved until November 2014. However application will be made sooner if possible.

5. Exploitation and Dissemination of Results

This section should inform about any project activities pertinent to exploitation and dissemination of results such as:

- patentable results, including a list of patents applied for;
- publications and conference presentations resulting from the project;
- contacts with potential users and indication of customers requirements;
- demonstrations given;
- practical applications and industrial fallout's of project results;
- technical and economic potential for exploitation;
- other aspects concerning dissemination of results.

Activity **(Maximum 200 characters)**	Description **(Maximum 500 characters)**
Stand at Hull and East Yorkshire Hospitals Trust Innovation Day "Creative Futures – Transforming our Hospitals".	Project Leader, Barbara Elliott and post doctoral research associate Monika Schoenleber supported the Trust's Research and Development Department by having a poster and stand at the Innovation Day. They discussed the project with staff and visitors and gave out the "Information and Invitation edition of the project newsletter. The day was an opportunity to showcase how services are being transformed for the better to staff, patients and visitors.
Universal Biotech Innovation Awards Finalists - presentation to judging panel in Paris 12 September 2013, Winner announced at Innovation Days 7-9 October 2013	The University of Hull Location Indicating Nasogastric Tube (UoHLINGT) project was selected as one of five finalists (from over 200 applications) for this European award. Rob Singh and Barbara Elliott presented the project before a panel of judges in September 2013. RS attended the Innovation Days in Paris in October 2013 and repeated the presentation to an audience of delegates from Biotech Industries. The project was not selected as the ultimate winner but being a finalist resulted in excellent publicity and contacts.
Medipex NHS Innovation Awards – finalists in the "Medical Devices and Diagnostics" Category.	Barbara Elliott and Monika Schoenleber attended the Medipex NHS Innovation Awards and Showcase dinner on 10 October 2013. The project did not win their category but contact with potential manufacturers was made.
Patent	Patent prosecution is progressing smoothly in the key territories of USA and Europe where we are awaiting further comments from the Examiners. Patent to be granted in Europe expected soon: claims with a good scope of protection appear to be allowable based on the Examiners' comments and should proceed to grant. Examination is ongoing in USA: an expert declaration has been prepare that refutes the Examiners' combination of prior art. Comments from the Canadian Patent Examiner have been received – these largely echo the comments form the US and European Examiners and a response is being prepared. Patent granted in Australia.
User Advisory Group meetings	Meetings with professional users were held in November 2013 to discuss information leaflets and instructions for use. Meetings with individual lay users were held in November and December due to their inability to attend group meetings. Non Disclosure

	Agreements have been signed by members of the User Advisory Group in order to protect the invention.
Production and circulation of newsletter to members of User/Carer group and team members	A draft of the third newsletter is in preparation for circulation Spring 2014. An “Introduction and Invitation” newsletter has been circulated to facilitate ongoing recruitment to the User Group.
Publicity in Hull Daily Mail, Yorkshire Post and local radio	Press release was agreed by NIHR communications team via Katalin Torok on 30 September 2013 and sent to the media on 2 October 2013 resulting in articles in local press and an interview with Barbara Elliott on Radio Humberside.

6. Summary of Progress to Date

A summary of work to date, describing objectives, actual work performed, achievements to date and expected end results and intentions for their uses. Please give details about any changes to the original protocol and objectives, explaining why amendments have been made. Please inform us of any changes in the staff named as joint applicants on the original proposal, or any change in address of the administering centre. Comments on your experience with patient and public involvement are also requested. **(Maximum 10,000 characters)**

Project Management

The core team remains unchanged from the original application. Fortnightly team meetings continue and minutes are posted on the University of Hull electronic shared drive accessible only by team members. Dr Schoenleber (PDRA) provides regular reports which are also available on the shared drive. Quarterly Review meetings were held on 16 October 2013 and 29 January 2014.

Chemistry Experiments and prototype development

Prototype nasogastric tubes (NGT), manufactured by Arrotek Medical Ltd, were prepared using an established protocol, referred to as work instruction WI05 – Coating Preparation of Location Indicating Naso-Gastric Tubes (LINGT) for placement sensing applications. The 2 exposed electrodes on the NGT were prepared as follows: one was micro-spotted with vitamin K_1 to form the working electrode and the other was coated with Ag/AgCl ink to form the reference electrode. The finished NGT are referred to as 'fully prepared tubes'.

To comply with ISO13485, enquiries for a supplier of medical grade Ag/AgCl was undertaken. Creative Materials appeared to be the best choice. Medical grade ink 117-23 was ordered and applied.

Stability test of sterilised NGT

Fully prepared NGT were sterilised using ethylene oxide and gamma irradiation sterilisation methods by a company P3 Medical Ltd. The stability of medical grade Ag/AgCl ink coating (reference electrode) and Vitamin K_1 coating (working electrode) were assessed by comparing the results with previously assessed non-sterilised NGT in phosphate buffer at same pH ranges. The experiment was run in triplicate.

It was found that the current responses showed relatively stable readings for each individual NGT at each individual pH when compared with those for non-sterilised fully prepared NGT. With the commercial reference electrode, the current responses were relatively higher compared to those using Ag/AgCl ink; this was most noticeable at lower pHs. Overall, fully prepared NGT showed relatively similar trends regarding current response/stability after sterilisation with ethylene oxide and gamma irradiation.

Toxicity Test

Richard Reece-Jones (Reece-Jones Consulting Ltd) has been engaged as external consultant for assessing the toxicity of Vitamin K_1 and medical grade Ag/AgCl. For Vitamin K_1, a literature search was suggested for verifying non-toxicity and this was conducted by Richard Reece-Jones. For Ag/AgCl ink, the amount of ink applied onto each NGT was estimated by weighing studies of the tubes before and after Ag/AgCl ink application. With that estimate, the theoretical amount of free silver ions was calculated and evaluated regarding toxicity. Richard Reece-Jones has prepared a toxicity report for each compound which has been circulated to the project team and a meeting is to be held in February 2014 to discuss any further evidence required.

Outer gel coating of NGT

Following discussions with Richard Reece-Jones (Toxicologist) and the project team, the outer gel/hydrogel coating for fully prepared NGT was investigated regarding the type of gel, if any, to be used. Initial studies reported earlier have used both gelatine and vege- gel.

The proposed requirements for outer coating for NGT were discussed with the project team and Professor Vesselin Paunov at University of Hull. The following table summarises the requirements and outcomes of the discussion.

Proposed requirements:	Outcome from discussions:
• Non-animal derived material • Easily obtainable • Non-toxic and biocompatible • High purity for medical application • Synthesis at room temperature • Non-complex handling properties	There is a large range of materials available which would be of sufficient purity/medical grade. Overall, these requirements are not perceived as a problem.
• Permeable to gastric juice	Gels/Hydrogels can be made permeable to gastric juice. However, to get an electrochemical response time at a short period of time would be a challenge
• Chemically stable in acidic conditions	Compromises have to be made, which could be achieved to an acceptable level.
• Mechanical integrity sufficient to be passed in and out of stomach	The mechanical properties of gels/hydrogels are in general not considered to be good. However, there are options to improve these properties to a certain level.
• Adherence to polyurethane tubes	This was considered as the biggest problem as gels/hydrogels tend not to adhere well to polyurethane. However, the surface of polyurethane could be modified to achieve adherence – there is a large amount of literature available (for example polyacrylate could be used).

Overall, the biggest problems are the response time of the electrode and the adherence of the outer coating to the underlying material (tube). As an alternative, a porous sponge, a foam or a mesh as outer coating could be used instead. These could be wrapped around the electrode tip using some 'machined' process. However, it was agreed that this might result in more and/or other problems and discussions with manufacturers of NGT agreed that this was not a viable option due to risk of dislodgement in the gastrointestinal or respiratory tract. Hence it was decided not to use any outer coating for the initial tube.

Quality Management System (QMS)

An audit schedule (OPF23) was established and the first internal audit took place on the 16th August 2013. Dr. Robert Singh is the assigned auditor and Dr. Monika Schoenleber and/or Barbara Elliott the auditee. Subsequent internal audits followed as scheduled. These are undertaken to be compliant with ISO 13485. The Design History File has been assembled and the Design Master Record is to be established over the next month (February 2014). Accreditation of the system to ISO 13485 is planned for April 2014.

Clinical Evaluation Studies

The electrochemical response of fully prepared NGT was assessed in 7 fresh samples of gastric juice and 3 samples of sputum; all samples were of human origin. Ten NGT were fully prepared in an identical manner and assessed in the samples above, one tube for each sample.

The sample fluid was used as received for the first measurement and then the pH of each sample was altered with 0.1M HCl or antacid (milk of magnesia) to obtain pH values of about 1, 4 and 7. The experiment was conducted in bio-hood (HEPA filter) at 37^0C, the pH was measured using a pH indicator stick.

It was established that:

- discrete differences in current readings (amperometry) of sputum samples could be observed at pH0 in comparison to pH 4 and 6
- current readings (amperometry) of sputum samples obtained at pH 4 and 6 did not show significant differences in relation to each other
- most current readings (amperomety) of gastric juice samples showed no differences at pH 4 in relation to pH 6
- current readings taken from gastric juice samples (pH 0.5 to 2) showed differences in current readings compared to pH 3/4, however not to those obtained at pH 6
- the transition occurs at pH of ~2.2, which is a limitation to this technique for the NGT

It is essential that the system can distinguish between pH values in the stomach (less than or equal to pH 5.5) and pH values in the respiratory tract, oesophagus or duodenum. The critical route forward is to increase the transition range. To accomplish that, a tenfold increase in Vitamin K1 (10mM instead of 1mM) concentration was agreed to increase the current output. Surplus human gastric juice samples (from frozen) were assessed for electrochemical response with fully prepared NGT, microspotted with 10mM K_1/EtOH instead of 1mM.

By doing this, the amperometric evaluation with the gastric juice samples of pH as received showed some unexpected results. The average current of NGT of fresh gastric juice (readings taken from sample pH as received) of 1mM K1 coated NGT showed the lowest reading at pH2 (NGT06) and higher readings with not much current variation at pH 3-4. The 10mM Vit K1 coated NGT however showed the lowest reading at pH4 and the highest reading at pH2 – in a near reversed behaviour.

Amperometric studies with pH varied gastric juice samples showed that all fresh gastric juice samples with 1mM K1 exhibited no district current readings with increasing pH. However, two out of four NGT with 10mM K1 showed distinct (and desirable) readings according to varied pH.

Overall, these experiments suggest that the NGT are in full working order; there is a strong possibility that the sample liquid is causing some unexplained electrochemical behaviour due to patient condition or treatment. Therefore more samples of gastric juice are required to evaluate and understand the system better. These are being sent from Scarborough General Hospital over the next month.

Patient and Public Involvement

A meeting was held with professional users of nasogastric tubes on 7 November 2013 and 2 new members, a nutrition specialist nurse and ICU research nurse, joined the group. A useful discussion took place regarding the design of the nasogastric tube and current methods of teaching professional and lay users about how to verify correct placement. Meetings were also held with current lay users and a new member, a young adult who had received nasogastric feeds for 2 weeks, was interviewed in Otober. Useful comments were received regarding the design of the indicator box and nasogastric tube as well as the risk management strategy and both lay and professional users are keen to be involved in writing the Instructions for Use and information leefletets for clinical trials.

The third edition to the project Bulletin is being produced and will be circulated to all members of the User Carer Network as a means of informing them of the progress of the project. The “Introduction and Invitation” edition has been circulated widely resulting in the 3 new members. Members of the Trans Humber Research Panel have been in contact with the Project Leader to offer their support in the project if needed.

The User Carer Strategy has been evaluated and user carer involvement is discussed at every project meeting and a record maintained. Improvements in methods of communication and involvement are

continually discussed and members of the network will be invited to feedback their experiences and evaluation at the end of the project.

Commercial

The revised milestone for this period was the selection of a manufacturer for and agreed design of iteration 5 of the nasogastric tube and indicator box. A manufacturer for the Indicator Box had been selected in May 2013 and contracts signed however the project team encountered serious problems identifying an appropriate manufacturer for the nasogastric tube resulting in the request for a no cost extension in August 2013.

Nasogastric Tube

At the last report 4 manufacturers were preparing proposals but only one was received by September 2013 from Arrotek Medical Ltd. Other companies demonstrated interest but did not follow up with costed proposals as requested in spite of follow up emails and phone calls.

Therefore Professor David Young conducted an extensive review of current manufacturers of nasogastric tubes who supply tubes to the National Health Service in the UK. This review was circulated to the team at the end of September 2013. The report updated and built on the original market survey conducted by Cion in 2007. Following discussions with Professor Young it was agreed that he would approach three of the top 5 suppliers of nasogastric tubes to the NHS namely GBUK Enteral, Intervene Ltd and Medicina Ltd.

Initial telephone introductions were made by Professor Young followed up by visits to each of the three companies by Dr Robert Singh and Barbara Elliott in October and November 2013. A revised "User Requirement Specification" document was shared with the companies and detailed discussions took place. Return visits were made to Intervene Ltd and Enteral UK Ltd.

All 3 companies were invited to submit proposals for the manufacture of the prototype tubes for the clinical trials and these were to be considered alongside that received from Arrotek Medical Ltd who designed iteration 3 and 4 of the UoHLINGT. After careful consideration it was agreed by the whole project team that the proposal from Intervene Ltd was the preferred option and a contract was prepared in January 2014. To be agreed and signed February 2014.

The Managing Director, Technical Director and Project Manager from Intervene Ltd attended the project Quarterly Review Meeting on 29 January 2014 and plans for the development of iteration 5 of the tube finalised.

Indicator Box

Director, Eric Abel and Alan Hood from "Image to Implant" visited the University of Hull on 23 January 2014 to present their work on the indicator box. They presented 4 prototype Indicator boxes for the team to review and gave a detailed presentation of their work to develop an appropriate device which would meet the required electrical and safety standards. These included:

- an enclosure specified to IP54 (ingress protection) with a battery compartment for two AA batteries (Boxes 1,2 and 3) or two AAA batteries (Box 4)
- a push button switch to turn on the box
- an NGT Indicator, which flashes red when the Box is turned on and until a threshold voltage is reached, when it indicates a continuous green, reverting back to flashing red if the threshold is no longer reached. The threshold voltage used was for demonstration purposes only. Its actual value will be specified by UoH for the Final Prototype.
- a Low Battery Indicator, smaller than the NGT Indicator, which turns on (red) when the battery voltage reduces below a predetermined level. There is a line drawing on the Indicator Box of a battery, located beside the Low Battery Indicator so that it is clear that this indicator refers to the battery status. This drawing would be screen or pad printed on the Indicator Box in a final version.

The NGT Indicator has a Fresnel lens and was clearly visible even at oblique viewing angles. Each of the four boxes had a different type of Low Battery Indicator. The functions of each Indicator Box

demonstrated are controlled by a microcontroller running a computer program. This approach allows modifications to the operation of the Indicator Box, for example the flashing speed of the NGT Indicator and the time it should take for this indicator to change from flashing red to green and vice versa based on the sensor readings. I2I explained that microprocessors and microcontrollers were commonly used in modern medical devices. There would, however, be a need for compliance with IEC 62304 covering software for medical devices.

I2I proposed that a datalogger should be included in the Indicator Box for clinical trial purposes only, so that the sensor signal could be recorded during testing and analysed by the UoH team. This would require a USB connection on the Indicator Box, so that data stored within the Indicator Box could be downloaded to a PC. The presence of a USB connector could compromise the IP54 specification during clinical trials, but I2I will provide a means of covering the connector to prevent exposure of any of the connectors.

The team agreed upon the preferred ergonomic design and further work will continue to refine this prototype and the required microcontroller and associated electronics.

Finance Update

Detailed expenditure reports are sent to the PI each month from the central University Finance Department and the PI prepares summary documents for discussion with the whole team at the Quarterly Review Meetings.

The Research Expenditure Report for December 2013 indicates that £291,645 has been spent in the first 2.5 years of the project with a Budget Remaining of £375,897. A no cost extension has been agreed and revised payment schedule will recommence in July 2014. Financial resources are committed to funding the manufacture of the prototype tubes, the Indicator Box and purchase of a spotter machine, as well as regulatory approvals and clinical trials. It is not envisaged that there will be an under spend by the completion of the project.

7. Presentations and Publications

Please list here any forthcoming presentations and publications which have resulted from the work. This should include journal articles, conference proceedings and all publications in the lay and scientific press. **Please note that you are contractually obliged to provide 28 days notification prior to any publication.**

Author(s) **Max 100 Characters**	Title **Max 150 Characters**	Reference **Max 100 Characters**
Barbara Elliott, Monika Schoenleber, Jay Wadhawan, John MacFie, Robert Singh, John Greenman	"University Invention to Improve Patient Safety"	Hull Daily Mail, Wednesday 9 October 2013, pp 22
Barbara Elliott, Monika Schoenleber, Jay Wadhawan, John MacFie, Robert Singh, John Greenman	"Innovation aims to cut death toll from feeding tube errors"	Yorkshire Post, Thursday 3 October 2013, pp7

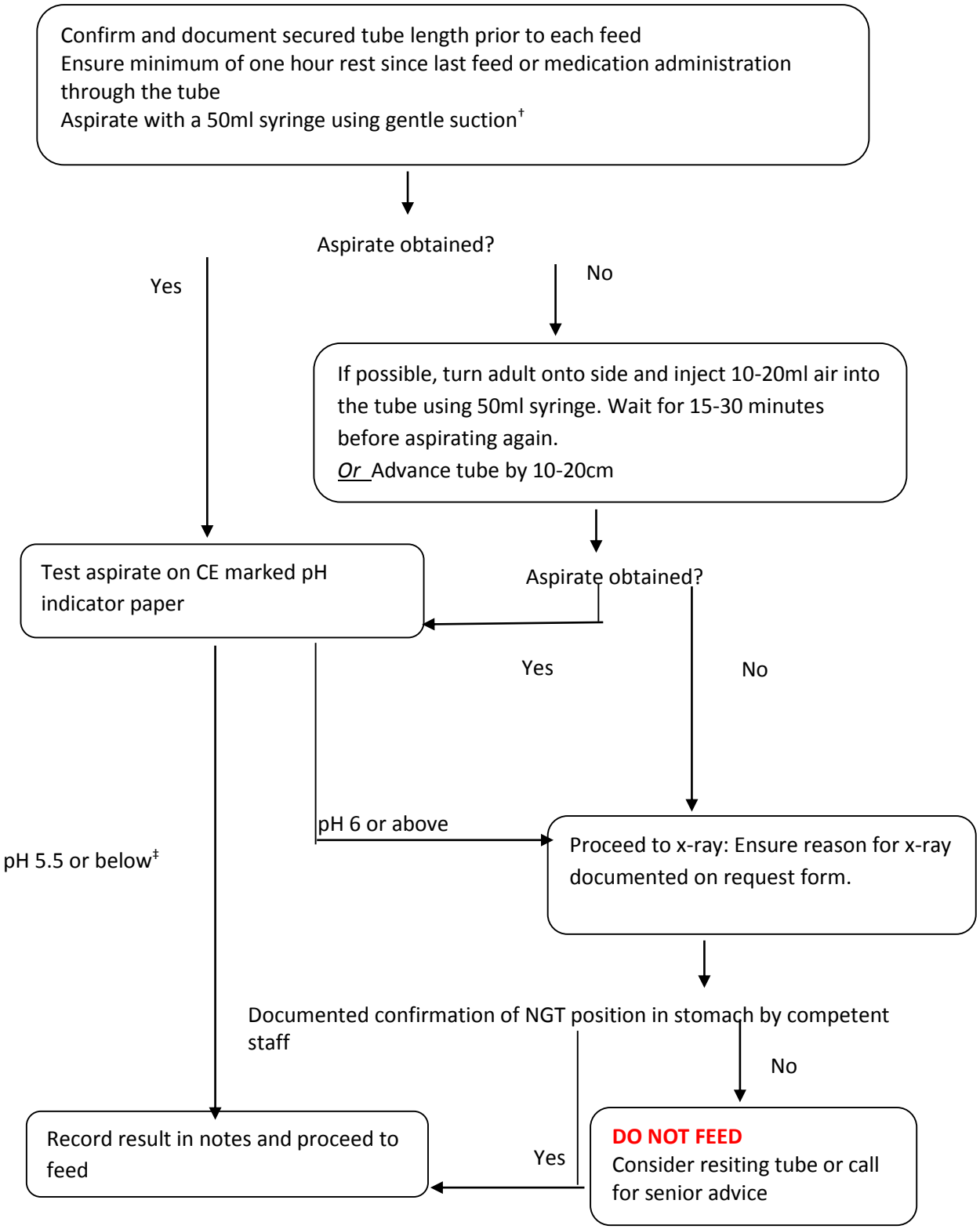
8. Matters Requiring the Attention of the CCF

Please outline any areas that require the attention of, or action from, the Central Commissioning Facility. Please identify any problems with the project which may impact on the delivery of the project within the pre-determined timescales. **(Maximum 1,500 characters)**

The Variation to contract issued on 1 August 2013 has granted a 12 month extension to allow for the delays encountered when trying to identify an appropriate manufacturer for the nasogastric tubes. Whilst a manufacturer has now been identified and contracts are being drawn up the 7.5 months required to develop and manufacture the prototypes will cause a slight further delay to the revised time plan. However the project team will make every effort to complete the project on or before July 2015.

The results from experiments in gastric fluid and sputum have not been as clear and repeatable as those conducted earlier in buffer solutions and food samples. Further experiments are therefore planned for late January and early February 2014 in order to maximise the signal from the system. However it is envisaged that these can be completed in the timescale available whilst finalising contracts with the manufacturer.

Appendix 2: Decision tree for nasogastric tube placement-checks in adults



† Patients who are at high risk of aspiration should proceed directly to x-ray, without prior pH testing. This group includes intubated patients and patients with tracheostomies in place.

‡ A pH of below 5.5 is reliable confirmation that the tube is not in the lung, however it does not confirm gastric placement as between 4-5.5 there is a small chance the tube may sit in the oesophagus where it carries a higher risk of aspiration. If this is a concern, the patient should proceed to x-ray in order to confirm tube position.

Appendix 3: American Association of Critical Care Nurses Practice Guidelines

AACN PracticeAlert™

Verification of Feeding Tube Placement

Expected Practice:

☑ Use a variety of bedside methods to predict tube location ***during*** the insertion procedure:

- Observe for signs of respiratory distress.
- Use capnography if available.
- Measure pH of aspirate from tube if pH-strips are available.
- Observe visual characteristics of aspirate from the tube.
- Recognize that auscultatory (air bolus) and water bubbling methods are unreliable. [Level B]

☑ Obtain radiographic confirmation of correct placement of any blindly inserted tube prior to its initial use for feedings or medication administration.

- The radiograph should visualize the entire course of the feeding tube in the gastrointestinal tract and should be read by a radiologist to avoid errors in interpretation. Mark and document the tube's exit site from the nose or mouth immediately after radiographic confirmation of correct tube placement. [Level A]

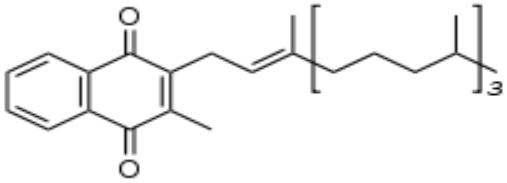
☑ Check tube location at 4-hour intervals after feedings are started:

- Observe for a change in length of the external portion of the feeding tube (as determined by movement of the marked portion of the tube).
- Review routine chest and abdominal x-ray reports to look for notations about tube location.
- Observe changes in volume of aspirate from feeding tube.
- If pH strips are available, measure pH of feeding tube aspirates if feedings are interrupted for more than a few hours.
- Observe the appearance of feeding tube aspirates if feedings are interrupted for more than a few hours.
- Obtain an x-ray to confirm tube position if there is doubt about the tube's location. [Level B]

Appendix 4: Toxicology Report for Vitamin K_1

Introduction:

Vitamin K_1 is a fat soluble vitamin also known as phylloquinone. It naturally occurs in green plants where it has an intrinsic role in photosynthesis.



In mammals this essential vitamin targets gamma gutamyl carboxylase and is involved as a co-factor in the post-ribosome stages of the clotting cascade (Choonara et al, 1985, Stenflo et al, 1977). Within the proposed naso-gastric device the vitamin K_1 is incorporated for its electro-chemical properties rather than its pharmacology and is adhered to the tubing to sit in the gastric lumen. Whilst systemic exposure will be low the vitamin may exert a local effect on the surrounding mucosal wall and any safety issues may relate to its underlying pharmacology rather than its intrinsic electrochemistry.

Pharmacology:

Medicinal Overview:

Pharmacologically vitamin K_1 (vit K_1) is a co-factor in the post-ribosomal synthesis of a series of clotting factors including II, VII, IX and X (Stenflo et al, 1977). Within the clotting cascades the vitamin dependent step is the production of the precursors to these factors involving the conversion of glutamyl residues to γ –carboxyglutamyl residues. It is during this carboxylation that vit K_1 is converted to the biologically inactive metabolite K_1 2,3-epoxide. Subsequently this epoxide is reduced back to active vit K_1 in the vitamin K_1-expoxide cycle (Bell, 1978).

Vitamin K deficiency produces unexpected bleeding and in the new born the syndrome of Early Vitamin K Deficiency Bleeding (VKDB) is well documented and is treated prophylactically by vit K_1 supplementation. The American Academy of Paediatrics Committee on Fetus and Newborn (2003) recommended prophylactic vit K_1 for late onset deficiency bleeding.

Pharmacodynamics:

Vitamin K_1 has a reported terminal half-life of 1-2 hours after intravenous injection in the rabbit (Wilson and Park, 1983). Work performed on volunteer patients undergoing warfarin

treatment have shown that the kinetics of vit K_1 are variable (Table 1), making estimates of accidental small concentration exposure difficult to assess.

Thijsesen (1993) showed that this variability was probably due to differences in the rate of epoxide metabolism in the liver, demonstrating in volunteer patients up to 5 fold differences in the activity of Vitamin K_1 epoxide reductase enzyme systems.

Table 1 Pharmacokinetic parameters for vit K_1 and epoxide metabolite (Choonara et al, 1985)

Vitamin K_1			Vitamin K_1 2,3 epoxide
Patient No	Elimination Half Life (h)	AUC ($\mu g\ ml^{-1}\ h$)	AUC ($\mu g\ ml^{-1}\ h$)
1	1.23	1.74	2.48
2	2.69	2.43	18.86
3	0.93	5.23	10.33
4	1.37	5.05	6.44
5	2.78	4.68	10.66
6	1.12	1.88	10.68
7	1.58	2.62	7.41
8	1.62	2.54	2.88
9	1.78	2.57	10.60
10	2.58	2.28	3.86
11	1.19	2.60	9.28
Mean	1.72	3.06	8.50
s.d	0.67	1.28	4.69

Orally presented vit K_1 is bacterially converted in the large intestine to vit K_2, with the bacteria producing several K_2 forms notably the MK 7 to MK11 menaquinones. However these forms, whilst needed for bacterial anaerobic respiration, have been shown to be non-toxic.

Toxicology Data:

Due to the nature of the proposed medical device where vit K_1 is a bound component of a naso-gastric tube, only local and oral toxicity need to be considered. Therefore, the concern around excessive bleeding after intravenous or intramuscular injections of vit K_1 formulations as highlighted by EU Scientific Committee for Consumer Safety (SCCS) are not appropriate in this review. This concern around excessive bleeding is highlighted in SCCS monograph 1313/10.

Dermal application of vit K_1 for cosmetic use was in some marketed products at levels of up to 8%. However, its use in cosmetics was banned by the Scientific Committee on Consumer Products of the European Commission (SCCP) due to hypersensitivity reactions (Wong and Freeman, 2010). This hypersensitivity was noted both clinically at concentrations up to 1% when administered intramuscularly and in test protocols including the Local Lymph Node Assay (SCCS 1313/10). The levels administered in these preparations are excessive in relation to the "worst case" exposure expected with the proposed device. Therefore, this dermal application issue is not of concern within this review

Similarly, the adverse effects such as hyperbilirubineamia, transient flushing, hypotension and temporary resistance to prothrombin-depressing anti-coagulants, have only been observed after systemic administration of relatively high clinical systemic doses (SCCS/1313/10) and are consequently of no concern here.

The European Food Safety Authority (EFSA) gives the oral LD_{50} dose (dose that kills 50%) as > 12g/kg and >4g/kg for the mouse and rat, respectively. This lack of lethality is supported by the manufacturer`s materials data sheet (MSDS) (Sigma-Aldrich 2011). Regarding general toxicity assessments data indicate single and repeat oral exposure toxicity is low, not mutagenic and without teratogenic or embryonic effects, but it should be noted that the data base was considered inadequate to confirm general safety. However, the EFSA have stated that due to the lack of evidence of side effects, vitamin K_1 is considered safe as a food supplement. (SCCS/1313/10).

Risk assessment and Safety Calculations:

In order to assess any risk from the bound vit K_1 both locally and systemically, a "worst case" paradigm is considered below where all the vit K_1 associated with the device becomes available to the body. The calculation is as follows:

Amount of K_1 incorporated on wire = 288 µL on 6 mm length of wire. (University of Hull SOP W105 p4)

Vit K_1 concentration used for wire coating = 10mM – taken from (University of Hull SOP W105 p3)

Molecular Weight vit K_1 450.7 (Sigma-Aldrich 2011)

1M vit K_1 = 450.7 g in 1000 mL

= 0.4507 g/mL

Therefore a 10 mM solution is:

0.4507 g/mL / 100 = $4.507\ 10^{-3}$ g/mL or $4.507\ 10^{-6}$ g/µL

Therefore total mass of vit K_1 available in 288 µL = $4.507\ 10^{-6}$ g/µL x 288 µL = $1298\ 10^{-6}$ g

Mass of human subject = 70 kg

"Worst case" exposure value = $1298\ 10^{-6}$ g / 70 kg = $18.54\ 10^{-6}$g/kg

Oral rat LD 50 = 33 487 mg/kg =33.5 g/kg (Sigma- Aldrich 2011) giving a margin of safety of 180 690 fold.

Therefore the amount of vit K_1 to be used in the proposed devise and its associated margin of safety is far too low to be considered as either a local or systemic clinical risk.

Conclusion

The safety data base for vitamin K_1 may be considered as insufficient in some regards and there are concerns regarding its use cosmetically. However, in the proposed device the degree of exposure both locally and systemically is minimal. Together with the very low concentrations available in the "worst case" scenario indicates that under the intended method of use, the incorporated vitamin K_1 is of no safety concern.

Richard Reece-Jones MIBiol, FSB, CBiol, ERT Date:

Principal Consultant

Reece-Jones Consulting Ltd.

References

Choonara IA, Scowt AK, Haynes BP, Cholerton S, Breckenridge AM and Park BK (1985), Vitamin K_1 metabolism in relation to pharmacodynamic response in anticoagulated patients. Br.J.clin.Pharmac., 20, 643-648

Bell RG (1978), Metabolism of vitamin K and prothrombin synthesis: anticoagulants and the vitamin K-epoxide cycle. Fed. Proc., 37, 2599-2604
Stenflo J and Suttie JW (1977), Vitamin K-dependent formation of γ-carboxyglutamic acid. Ann.Rev.Biochem., 46, 154-172
Thijssen HH and Drittij-Reijnders MJ (1993), Vitamin K metabolism and vitamin K_1 status in human liver samples: a search for inter-individual differences in warfarin sensitivity. Br J Haematol., 84(4), 681-5
Wilson AC, Park BK (1983), Quantitative analysis of pharmacological levels of Vitamin K and vitamin K_1 2,3-epoxide in rabbit plasma by high performance liquid chromatography. J.Chromatogr., 277, 292-299
Wong DA and Freeman S (1999), Cutaneous allergic reaction to intramuscular Vitamin K_1. Australasian J of Derm., 40, 147-152.
American Academy of Paediatrics Committee on Foetus and Newborn (2003), Controversies Concerning Vitamin K and the Newborn, Paediatrics, 112 (1), 191-193
EFSA (2003), Scientific Committee on Food, Opinion on the Tolerable Upper Intake Level on Vitamin K. doc. n° SCF/CS/NUT/UPPLEV/32 Final. 4 April 2003.
EU Scientific Committee for Consumer Safety (2010), monograph 1313/10
Sigma-Aldrich, Safety Data Sheet (MSDS) Vitamin K_1, Rev 4.1, 2011.
University of Hull SOP W105

Appendix 5: LINGT iteration 1 Ethical approval letter

Research Ethics Committee Office
Second Floor
Humber Mental Health Teaching NHS Trust HQ
Willerby Hill Business Park
Willerby
HU10 6ED

Tel: 01482 389246
Fax: 01482 303908
Email: louise.hunn@humber.nhs.uk

06 June 2008

Dr John Greenman
Division of Cancer
Postgraduate Medical Institute
Medical Research Laboratory
University of Hull
Cottingham Road
Hull
HU6 7RX

Dear Dr Greenman,

RE: The HUNG (Hull University Naso Gastric) tube: a proposal for preliminary pre-clinical appraisal

Thank you for your letter dated 15th May 2008 in which you seek the advice of the chairman regarding the above study.

It is noted that you wish to test the newly developed feeding tubes on freshly resected gastric specimens taken from patients undergoing surgery for malignancy.

The testing will be carried out in theatre immediately after the gastric specimen is available and before it is forwarded onto pathology. You have clarified that the assessments will be carried out in such a way that there will be no detrimental effect on subsequent histological analysis.

I can confirm that the Chair of the committee acting under delegated authority has reviewed the information you provided and is happy that the assessments give rise to no ethical issues; however he wishes to point out that at the point where “live testing” becomes necessary the committee would wish to see an application for formal ethical review.

Yours Sincerely

Mrs Louise Hunn
LREC Co-ordinator

NHS

National Research Ethics Service

Leeds (West) Research Ethics Committee
First Floor
Millside
Mill Pond Lane
Leeds
LS6 4RA

Telephone: 0113 3050122
Facsimile:

23 February 2011

Mrs Barbara Elliott
Senior Lecturer
University of Hull
Room 127 Dearne Building
Faculty of Health and Social Care
University of Hull
HU6 7RX

Dear Mrs Elliott

Study Title:	**A feasibility study to test a manufactured prototype of a location indicating naso-gastric tube in freshly resected human stomachs**
REC reference number:	**10/H1307/136**
Protocol number:	**N/A**

Thank you for your letter of 16 February 2011, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. I will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at non-NHS sites.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where the only involvement of the NHS organisation is as a Participant Identification Centre (PIC), management permission for research is not required but the R&D office should be notified of the study and agree to the organisation's involvement. Guidance on procedures for PICs is available in IRAS. Further advice should be sought from the R&D office where necessary.

Sponsors are not required to notify the Committee of approvals from host organisations.

Notice of no objection must be obtained from the Medicines and Healthcare products Regulatory Agency (MHRA).

The sponsor is asked to provide the Committee with a copy of the notice from the MHRA, either confirming no objection or giving grounds for objection, as soon as this is available.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Protocol	1	19 November 2010
GP/Consultant Information Sheets	1	20 January 2011
REC application		24 November 2010
Investigator CV		24 November 2010
Participant Consent Form	1	20 January 2011
CV for Prof Greenman		
Letter from Dr Musa		15 November 2010
Participant Information Sheet	1	20 January 2011
Email from funder		15 November 2010
Email from MHRA		22 November 2010
Response to Request for Further Information		27 January 2011
Response to Request for Further Information		16 February 2011

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research

Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

10/H1307/136	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

Dr Rhona Bratt
Chair

Email: Elaine.hazell@leedsth.nhs.uk

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Mr James Illingworth*

Study Code: 13/SC/0314	Patient Resaerch no:				Subject initials:			

CASE REPORT FORM

Laboratory testing of manufactured prototypes of a location indicating nasogastric tube(LINGT) in gastric fluid and pulmonarysecretions removed from patients as part of their normal treatment

LINGT Gastric Fluid/Sputum Stomach Study

Study reference number **02**

CLINICAL TRIAL SITE/UNIT: **Castle Hill Hospital**

PRINCIPAL INVESTIGATOR: **Barbara Elliott**

Subject Initials: | | | |

Subject Research Number: | | | |

I am confident that the information supplied in this case record form is complete and accurate data. I confirm that the study was conducted in accordance with the protocol and any protocol amendments and that written informed consent was obtained prior to the study.

Investigator's Signature: .....

Date of signature: | | | | | | | | | |

D d m m m y y y y

Study Code: 10/H1307/1136	Research participant no:		Subject initials:	

Inclusion Criteria

		Yes	No*
1	Is the subject aged between 18 and 90 years?		
2	Has s the subject got a nasogastric tube in situ on free drainage?		
3	Has the subject willingly given written informed consent?		

*If any inclusion criteria are ticked no then the patient is not eligible for the study.

Exclusion Criteria

		Yes*	No
1	Is the patient under 18 years of age?		
2	Is the patient's nasogastric tube being used for feeding?		

* If any exclusion criteria are ticked yes then the patient is not eligible for the study.

Study Code: 10/H1307/1136	Research participant no:		Subject initials:	

VISIT 1 (Screening and Information Giving)

Date: _

INFORMED CONSENT

Please note: written informed consent must be given before any study specific procedures take place

Has the subject freely given written informed consent? Yes ☐ No ☐

PRESCRIBED MEDICATION

Please indicate whether the patient is taking Protein Pump Inhibitors (PPI)

*Yes ☐ No ☐

*If Yes please state name and dose of drug

.....

End of Visit Checklist: to be completed by Investigator

		Yes	No
1	Does the subject satisfy the inclusion and exclusion criteria to date?	☐	☐
2	Is the subject willing for GP to be contacted?	☐	☐
3	Is the subject willing to proceed?	☐	☐

Investigator

	Yes	No
Is the subject to continue?	☐	☐

Signature: ..... Date: ☐☐☐☐☐☐☐☐

d d m m m y y y y

Name of Researcher .....

Study Code: 10/H1307/1136	Research participant no:				Subject initials:			

Name and address of GP .....

.....

.....

.....

.....

Research Records Please tick and date when completed					
Consent Form					GP letter
Date obtained	File	Patient Notes	Patient		

Date 2012

Dr

Faculty of Health and Social Care
University of Hull
Hull
HU6 7RX

01482 464518

Dear Doctor

Re: Your patient date of birth

The above patient has agreed to take part in a research study to test a new nasogastric tube. The research project is funded by National Institute of Health Research and has been given approval by Leeds (West) Research Ethics Committee. The REC reference number for the project is 10/H1307/136.

The patient is having surgery which may remove part of their stomach and our researcher will test the new nasogastric tube in theatre on part of the freshly resected stomach tissue immediately after removal. This will take approximately 10 minutes after which the tissue will be treated in the normal way. The patient's surgery will continue uninterrupted and their care and treatment will not be affected in anyway by the research. In particular the patient has been reassured that the amount of stomach tissue removed will not be affected by the research and no tissue samples will be retained for research purposes.

If you have any questions about the research please contact the principal investigator, Barbara Elliott, on 01482 886174 or b.e.elliott@hull.ac.uk or Professor John Greenman J.Greenman@hull.ac.uk

Yours sincerely

Barbara Elliott MSc, BNurs, RGN, RSCN
Senior Lecturer

NRES Committee South Central - Berkshire B
Bristol REC Centre
Whitefriars
Level 3, Block B
Lewins Mead
Bristol
BS1 2NT

Telephone: 0117 342 1391

28 May 2013

Mrs Barbara Elliott
Senior Lecturer
University of Hull
Faculty of Health and Social Care
University of Hull
Cottingham Road
HU6 7RX

Dear Mrs Elliott,

Study title:	**Laboratory testing of manufactured prototypes of a location-indicating nasogastric tube in gastric fluid and pulmonary secretions removed from patients as part of their normal treatment.**
REC reference:	**13/SC/0314**
Protocol number:	**N/A**
IRAS project ID:	**105704**

The Proportionate Review Sub-committee of the NRES Committee South Central - Berkshire B reviewed the above application on 26 May 2013 in correspondence.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the Co-ordinator Miss Kelly Pullin, nrescommittee.southcentral-berkshireb@nhs.net.

Ethical opinion

There were no ethical issues.

On behalf of the Committee, the sub-committee gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations.

- The Committee did not feel that it is necessary to split the PIS into Part One and Part Two as they do not feel it is appropriate for a study of this nature. Please amend the PIS accordingly.

- Please change the word sluice to ward on page one of the PIS.

- Please remove the reference to ensuring anonymity in regards to samples and data on page two of the PIS as it is already mentioned on page one.

- Please remove the bullet points from the PIS instead please list information under appropriate headings. For example - What is the purpose of the study? Do I have to take part? What are the benefits to taking part?
  NRES guidance on information sheets and consent forms is available at http://www.nres.nhs.uk/applications/guidance/consent-guidance-and-forms/?1311929_entryid62=67013

- Please amend the PIS to state that this study is being completed as part of a PhD research study.

- Please amend the PIS to state that the new tube is an "intelligent" tube that is designed to distinguish between stomach and lung lining.

- Please amend the PIS to advise how participants could request to receive a copy of the study results.

- Please specify the insurance arrangements for the study in the PIS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which can be made available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

Approved documents

The documents reviewed and approved were:

Document	*Version*	*Date*
Covering Letter		21 May 2013
GP/Consultant Information Sheets	A version 1	17 May 2013
GP/Consultant Information Sheets	B version 1	17 May 2013
Investigator CV	BE	17 May 2013
Investigator CV	JG	17 May 2013
Participant Consent Form: A study to test a new tube on gastric fluid or sputum	1	17 May 2013
Participant Information Sheet: A study to test a new tube on gastric fluid or sputum	1	17 May 2013
Protocol	1	17 May 2013
REC application		21 May 2013
Referees or other scientific critique report	Reviewer Ref - 1	
Referees or other scientific critique report	Reviewer Ref - 2	

Membership of the Proportionate Review Sub-Committee

The members of the Sub-Committee who took part in the review are listed on the attached sheet.

There were no declarations of interest.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

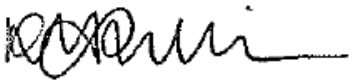
You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.
information is available at National Research Ethics Service website > After Review

13/SC/0314	**Please quote this number on all correspondence**

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

With the Committee's best wishes for the success of this project.

Yours sincerely



pp.

Dr John B Sheridan
Chair

Email:	nrescommittee.southcentral-berkshireb@nhs.net
Enclosures:	*List of names and professions of members who took part in the review* *"After ethical review – guidance for researchers"*
Copy to:	*Mr James Illingworth, National Institute for Health Research, Invention for Innovation (i4i) programme*

NRES Committee South Central - Berkshire B

Attendance at PRS Sub-Committee of the REC meeting on 26 May 2013

Committee Members:

Name	*Profession*	*Present*	*Notes*
Mr Michael Arnott	Consultant Research Services	Yes	
Dr John B Sheridan	Consultant Toxicologist and Chemist	Yes	
Miss Louise Anne Stainer	Biomedical Scientist	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Miss Kelly Pullin	Assistant Committee Coordinator

Appendix 14: Medical device classification

ASSESSMENT AGAINST MDD 93/42/EEC ANNEX I

No.	Essential Requirements	Applicable Yes/No	Standards/Requirements/Guidelines Applied i.e. How Is Requirement Met?	Evidence/ Reference to Documentation
1	**General Requirements**			
1.	The device must be designed and manufactured in such a way that, when used under the conditions and for the purposes intended, it will not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety. This shall include: · reducing, as far as possible, the risk of use error due to the ergonomic features of the device and the environment in which the device is intended to be used (design for patient safety), and · consideration of the technical knowledge, experience, education and training and where applicable the medical and physical conditions of intended users (design for lay, professional, disabled or other users.	Yes	Device is subject of a vigorous risk management process and a clinical investigation to establish its performance and identify risks. Instructions for use contain warnings to ensure risks are reduced	Risk Management File, Clinical Investigation Plan, Instructions For Use
2.	The solutions adopted by the manufacturer for the design and construction of the devices must conform to safety principles, taking account of the generally acknowledged state of the art.	Yes	As above, and the results of the assessment against requirements of harmonised standards	Risk Management File

	In selecting the most appropriate solutions, the manufacturer must apply the following principles in the following order: · eliminate or reduce risks as far as possible (inherently safe design and construction), · where appropriate take adequate protection measures including alarms if necessary, in relation to risks that cannot be eliminated, · inform users of the residual risks due to any shortcomings of the protection measures adopted.	Yes Yes Yes	Risks have been managed by considering clinical as well as other risks risk assessment has been carried out and documented risk assessment has been carried out and documented	Risk management documents and mitigation measures. Risk management documents and mitigation measures Instructions For Use
3.	The devices must achieve the performances intended by the manufacturer and be designed, manufactured and packaged in such a way that they are suitable for one or more of the functions referred to in Article 1 (2) (a), as specified by the manufacturer.	Yes	The device and its function have been subject of a comprehensive risk assessment from the clinical as well as technical perspectives, and adequate mitigation measures have been devised and described	Clinical investigation plan
4.	The characteristics and performances referred to in sections 1, 2 and 3 must not be adversely affected to such a degree that the clinical condition and safety of the patients and, where applicable, of other persons are compromised during the lifetime of the device as indicated by the manufacturer, when the device is subjected to the stresses which can occur during normal conditions of use.	Yes	The device and its function have been subject of a comprehensive risk assessment from the clinical as well as technical perspectives, and adequate mitigation measures have been devised and described	Risk Management File and Instructions For use
5.	The devices must be designed, manufactured and packed in such a way that their characteristics and performances during their intended use will not be adversely affected during transport and storage taking account of the instructions and information provided by the manufacturer.	Yes	The device is subjected to pre-use checks to verify that it is functioning correctly. Safety tests are carried out during placement and prior to use.	Instructions For Use
6.	Any undesirable side effects must constitute an acceptable risk when weighed against the performances intended.	Yes	preliminary risk analysis has been undertaken and no unacceptable risks have been identified. The risk analysis will continually be updated during the clinical investigation as new data is gathered	Risk Management File and Clinical Investigation Plan

6a.	Demonstration of conformity with the essential requirements must include a clinical evaluation in accordance with Annex X.	Yes	clinical investigation is undertaken in accordance with section 2 of Annex X.	MHRA submission documents to be supplied on completion of scheduled clinical investigation
II	**Requirements Regarding Design And Construction**			
7	**Chemical, Physical And Biological Properties**			
7.1	The devices must be designed and manufactured in such a way as to guarantee the characteristics and performances referred to in Section 1 on the "General requirements". Particular attention must be paid to:	Yes	The device components in combination are/will be the subject of clinical investigation and a protocol is established for the user to verify correct functioning of the device before each use.	Risk Management File + Clinical Investigation Plan + Instructions For Use
	the choice of materials used, particularly as regards toxicity and, where appropriate flammability,	Yes	individual components have been/will be tested to ensure compliance with toxicity and other requirements	Investigation Plan includes testing provisions.
			The environment in which the device is intended to be used is hospital wards, home care and possibly care homes	comparison of the hospital ward and the domestic environment to support the decision to deploy a single device design in both.
	the compatibility between the materials used and biological tissues, cells and body fluids, taking account of the intended purpose of the device.	Yes	Only the tube and its tip coating come into contact with the body. The tube is made from medical grade material. The tip coating is Vitamin K1 (phylloquinone) which is a food substance (Scientific Opinion on the substantiation of health claims related to vitamin K EFSA Journal 2009; 7, 9,1228) for which no dietary or pharmaceutical claims are made.	market history and validated and verified sourcing of Vitamin K1 produced to prevailing quality standards.
	where appropriate, the results of biophysical or modelling research whose validity has been demonstrated beforehand.	Yes	Subject of comprehensive risk assessment and in vitro, ex vivo and clinical trials.	Investigation Plan + Trials reports

7.2	The devices must be designed, manufactured and packed in such a way as to minimise the risk posed by contaminants and residues to the persons involved in the transport, storage and use of the devices and to the patients, taking account of the intended purpose of the product. Particular attention must be paid to the tissues exposed and the duration and frequency of the exposure.	Yes	The device is a 'single patient' device used once for up to 30 days and design, particularly materials selection, sterilisation and packaging are specifically and carefully directed to this intent. There is a specific protocol for use of the product. The portion of the product in contact with tissues (gastric mucosa, oesophageal mucosa and nasal mucosa) comprises medical grade plastic (polyurethane) tubing and Vitamin K1 (phylloquinone), a foodstuff and silver silver chloride. Toxicology reports available for these substances.	Risk Management File + Instructions For Use. Exclusion criteria in the Clinical Investigation Plan and the Instructions For use.
7.3	The devices must be designed and manufactured in such a way that they can be used safely with the materials, substances and gases with which they enter into contact during their normal use or during routine procedures; if the devices are intended to administer medicinal products they must be designed and manufactured in such a way as to be compatible with the medicinal products concerned according to the provisions and restrictions governing those products and that their performance is maintained in accordance with the intended use.	Yes	The portion of the product in contact with tissues (gastric mucosa, oesophageal mucosa and nasal mucosa) comprises medical grade plastic (polyurethane) tubing and Vitamin K1 (phylloquinone), a foodstuff and silver silver chloride. Toxicology reports available for these substances. The device is not intended to administer medicinal products	Investigation Plan and the Instructions For use. Device description
7.4	Where a device incorporates, as an integral part, a substance which, if used separately, may be considered to be a medicinal product as defined in Article 1 of Directive 2001/83/EC and which is liable to act upon the body with action ancillary to that of the device, the safety, quality and usefulness of the substance must be verified, taking account of the intended purpose of the device, by analogy with the methods specified in Annex 1 to Directive 2001/83/EC.	It is acknowledged that this provision may apply because of the use vitamin k1	The device incorporates Vitamin K1 (phylloquinone) at its tip which, when the tube is correctly placed, lies within the stomach. Vitamin K1 is a foodstuff, not a medicinal product.	Risk Management File + Instructions For Use.

	For the substances referred to in the first paragraph, the notified body shall, having verified the usefulness of the substance as part of the medical device and taking account of the intended purpose of the device, seek a scientific opinion from one of the competent authorities designated by the Member States or the European Medicines Agency (EMEA) acting particularly through its committee in accordance with Regulation (EC) No 726/2004 on the quality and safety of the substance including the clinical benefit/risk profile of the incorporation of the substance into the device. When issuing its opinion, the competent authority of the EMEA shall take into account the manufacturing process and the data related to the usefulness of incorporation of the substance into the device as determined by the notified body.		CONSIDER VIT K1	Risk Management File + Instructions For Use.
	Where a device incorporates, as an integral part, a human blood derivative, the notified body shall, having verified the usefulness of the substance as part of the medical device and taking into account the intended purpose of the device, seek a scientific opinion from the EMEA, acting particularly through its committee, on the quality and safety of the substance including the clinical benefit/ risk profile of the incorporation of the human blood derivative into the device. When issuing its opinion, the EMEA shall take into account the manufacturing process and the data related to the usefulness of incorporation of the substance into the device as determined by the notified body.	No	the device does not incorporate a human blood derivative	Device description
	Where changes are made to an ancillary substance incorporated in a device, in particular related to its manufacturing process, the notified body shall be informed of the changes and shall consult the relevant medicines competent authority (i.e. the one involved in the initial consultation), in order to confirm the quality and safety of the ancillary substance are maintained. The competent authority shall take into account the data related to the usefulness of incorporation of the substance into the device as determined by the notified body, in order to ensure that the changes have no	No	No changes to the ancillary substance, Vitamin K1, are made	Device description

	negative impact on the established benefit/risk profile of the addition of the substance in the medical device. When the relevant medicines competent authority (i.e. the one involved in the initial consultation) has obtained information on the ancillary substance, which could have an impact on the established benefit/risk profile of the addition of the substance in the medical device, it shall provide the notified body with advice, whether this information has an impact on the established benefit/risk profile of the addition of the substance in the medical device or not. The notified body shall take the updated scientific opinion into account in reconsidering its assessment of the conformity assessment procedure.	Yes	The MHRA will advise/rule on this	Device description – Vitamin K1 is well known
7.5	The devices must be designed and manufactured in such a way as to reduce to a minimum the risks posed by substances leaking from the device. Special attention shall be given to substances which are carcinogenic, mutagenic or toxic to reproduction, in accordance with Annex I to Council Directive 67/548/EEC of 27 June 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances. If parts of a device (or a device itself) intended to administer and/or remove medicines, body liquids or other substances to or from the body, or devices intended for transport and storage of such body fluids or substances, contain phthalates which are classified as carcinogenic, mutagenic or toxic to reproduction, of category 1 or 2, in accordance with Annex I to Directive 67/548/EEC, these devices must be labelled on the device itself and/or on the packaging for each unit or, where appropriate, on the sales packaging as a device containing phthalates. If the intended use of such devices includes treatment of children or treatment of pregnant or nursing women, the manufacturer must provide a specific justification for the use of these substances with regard to compliance with the essential requirements, in particular of this	Yes Yes Yes	No substances are present in the device that can leak under any circumstances The device is intended to administer foods. It is constructed entirely from non-carcinogenic and non-phthalate containing materials Device is deigned to overcome an existing risk in nasogastric feeding of infants.	Device description Risk Management File + Instructions For Use. Instructions For Use

	paragraph, within the technical documentation and, within the instructions for use, information on residual risks for these patient groups and, if applicable, on appropriate precautionary measures.			
7.6	Devices must be designed and manufactured in such a way as to reduce, as much as possible, risks posed by the unintentional ingress of substances into the device taking into account the device and the nature of the environment in which it is intended to be used.	Yes	The device is intended for use within the hospital ward or in the home on a single patient basis.	Instructions for use and user training
8	**Infection And Microbial Contamination**			
8.1	The devices and manufacturing processes must be designed in such a way as to eliminate or reduce as far as possible the risk of infection to the patient, user and third parties. The design must allow easy handling and, where necessary, minimise contamination of the device by the patient or vice versa during use	Yes	The product is for single patient use and is packed sterile and remains so up to the point of use.	Device description and Instructions For Use
8.2	Tissues of animal origin must originate from animals that have been subjected to veterinary controls and surveillance adapted to the intended use of the tissues. Notified Bodies shall retain information on the geographical origin of the animals. Processing, preservation, testing and handling of tissues, cells and substances of animal origin must be carried out so as to provide optimal security. In particular safety with regard to viruses and other transmissible agents must be addressed by implementation of validated methods of elimination or viral inactivation in the course of the manufacturing process.	No	The device does not incorporate any tissue	
8.3	Devices delivered in a sterile state must be designed, manufactured and packed in a non-reusable pack and/or according to appropriate procedures to ensure they are sterile when placed on the market and remain sterile, under the storage and transport conditions laid down, until the protective packaging is damaged or opened.	Yes	The device is manufactured, packed and sterilised in an MHRA approved facility.	See QMS SOPs 20 and 21 and Instructions For Use

8.4	Devices delivered in a sterile state must have been manufactured and sterilised by an appropriate, validated method.	Yes	The device is manufactured, packed and sterilised in an MHRA approved facility.	See QMS SOPs 20 and 21 and Instructions For Use
8.5	Devices intended to be sterilised must be manufactured in appropriately controlled (e.g. environmental) conditions.	Yes	The device is manufactured, packed and sterilised in an MHRA approved facility.	See QMS SOPs 20 and 21 and Instructions For Use
8.6	Packaging systems for non-sterile devices must keep the product without deterioration at the level of cleanliness stipulated and, if the devices are to be sterilised prior to use, minimise the risk of microbial contamination. The packaging system must be suitable taking account of the method of sterilisation indicated by the manufacturer.	No		
8.7	The packaging and/or label of the device must distinguish between identical or similar products sold in both sterile and non-sterile condition.	Yes	Packaging and labelling are in accordance with ISO13485:2003/2012	See QMS SOPs 20 and 21
9	**Construction And Environmental Properties**			
9.1	If the device is intended for use in combination with other devices or equipment, the whole combination, including the connection system must be safe and must not impair the specified performance of the devices. Any restrictions on use must be indicated on the label or in the instruction for use.	Yes Yes	All devices are considered as a system and are subject to regulatory compliance/clinical investigation. Device to be labelled as "Exclusively for clinical investigation" and accompanied by Instructions for Use.	Clinical investigation plan and device description and associated documentation Labelling/Instructions For Use.
9.2	Devices must be designed and manufactured in such a way as to remove or minimise as far as possible: • the risk of injury, in connection with their physical features, including the volume/pressure ratio, dimensional, and where appropriate the ergonomic features, • risks connected with reasonably foreseeable environmental conditions, such as magnetic fields, external electrical influences, electrostatic discharge, pressure, temperature or variations in pressure, and acceleration,	 Yes Yes	 The device is made in a range of sizes to allow appropriate selection for the size and type of patient and indication Susceptible elements such as the monitor have the internal parts shielded	 Instructions for use Risk Assessment File and Design History File

	• the risks of reciprocal interference with other devices normally used in the investigations or for the treatment given, • risks arising where maintenance or calibration are not possible (as with implants), from ageing of the materials used or loss of accuracy of any measuring or control mechanism.	Yes Yes	The operating parameters of the device are at values sufficiently low as to make reciprocal interference extremely unlikely. This is to be considered during clinical assessment.	Risk Assessment File Risk Assessment File and Assessment Report
9.3	Devices must be designed and manufactured in such a way as to minimise the risks of fire or explosion during normal use and in single fault condition. Particular attention must be paid to devices whose intended use includes exposure to flammable substances which could cause combustion.	No	Probably only involves the monitor battery – maintain liaison on topic with development partner I2I Ltd.	Risk Assessment File
10	**Devices With A measuring Function**			
10.1	Devices with a measuring function must be designed and manufactured in such a way as to provide sufficient accuracy and stability within appropriate limits of accuracy and taking account of the intended purpose of the device. The limits of accuracy must be indicated by the manufacturer.	Yes	The device is intended to provide a “Yes” or “no” indication of the position of the tube tip and not a quantitative measurement by visual and auditory means.	Instructions For Use and Risk Assessment File
10.2	The measurement, monitoring and display scale must be designed in line with ergonomic principles, taking account of the intended purpose of the device.	Yes	The device is intended to provide a “Yes” or “no” indication of the position of the tube tip and not a quantitative measurement by visual and auditory means.	Instructions For Use and Risk Assessment File
10.3	The measurements made by devices with a measuring function must be expressed in legal units conforming to the provisions of Council Directive 80/181/EEC.	No	The device does not make quantitative measurements	
11	**Protection Against Radiation**			
11.1	General			
11.1.1	Devices shall be designed and manufactured such that exposure of patients, users and other persons to radiation shall be reduced as far as possible compatible with the intended purpose, whilst not restricting the	No	The device does not emit radiation	Device description

	application of appropriate specified levels for therapeutic and diagnostic purposes.			
11.2	Intended Radiation	No	The device does not emit radiation	Device description
11.2.1	Where devices are designed to emit hazardous levels of radiation necessary for a specific medical purpose the benefit of which is considered to outweigh the risks inherent in the emission, it must be possible for the user to control the emissions. Such devices shall be designed and manufactured to ensure reproducibility and tolerance of relevant variable parameters.	No	The device does not emit radiation	Device description
11.2.2	Where devices are intended to emit potentially hazardous, visible and/or invisible radiation, they must be fitted, where practicable, with visual displays and/or audible warnings of such emissions.	No	The device does not emit radiation	Device description
11.3	Unintended Radiation	No	The device does not emit radiation	Device description
11.3.1	Devices shall be designed and manufactured in such a way that exposure of patients, users and other persons to the emission of unintended, stray or scattered radiation is be reduced as far as possible.	No	The device does not emit radiation	Device description
11.4	Instructions	No	The device does not emit radiation	Device description
11.4.1	The operating instructions for devices emitting radiation must give detailed information as to the nature of the emitted radiation, means of protecting the patient and the user and on ways of avoiding misuse and of eliminating the risks inherent in installation.	No		Device description
11.5	Ionising Radiation	No	The device does not emit radiation	Device description
11.5.1	Devices intended to emit ionising radiation must be designed and manufactured in such a way as to ensure that, where practicable, the quantity, geometry and quality of radiation emitted can be varied and controlled taking into account the intended use.	No	The device does not emit radiation	Device description
11.5.2	Devices emitting ionising radiation intended for diagnostic radiology shall be designed and manufactured in such a way, as to achieve appropriate image and/or output quality for the intended medical	No	The device does not emit radiation	Device description

	purpose whilst minimising radiation exposure of the patient and user.			
11.5.3	Devices emitting ionising radiation intended for therapeutic radiology shall be designed and manufactured in such a way as to enable reliable monitoring and control of the delivered dose, the beam type and energy and where appropriate the quality of the radiation.	No	The device does not emit radiation	Device description
12	**Requirements For Medical Devices Connected To Or Equipped With An Energy Source**			
12.1	Devices incorporating electronic programmable systems must be designed to ensure the repeatability, reliability and performance of these systems according to their intended use. In the event of a single fault condition (in the system) appropriate means should be adopted to eliminate or reduce as far as possible consequent risks.	No	The device contains no user-programmable elements	Device description. Also Instructions For Use (IFU) contains steps the user must take to verify correct functioning of the monitor prior to use.
12.1a	For devices which incorporate software or which are medical Software in themselves, the software must be validated according to state of the art taking into account the principles of development lifecycle, risk management, validation and verification.	No	The device contains only firmware in the monitor with no elements which may be accessed by users	Device description
12.2	Devices where the safety of the patients depends on an internal power supply must be equipped with a means of determining the state of the power supply.	Yes	The monitor contains a low-voltage battery and is provided with visual and audible battery status alarms/indicators	Device description and Instructions For Use
12.3	Devices where the safety of the patient depends on an external power supply must include an alarm system to signal any power failure.	No	There is no external power supply and the internal power supply (battery) cannot be recharged) or connected to an external power supply	Device description and Instructions For Use
12.4	Devices intended to monitor one or more clinical parameters of a patient must be equipped with appropriate alarm systems to alert the user of situations which could lead to death or severe deterioration of the patient's state of health.	Yes	The device is intended to provide a “Yes” or “no” indication of the position of the tube tip (but not a quantitative measurement) by visual and auditory means.	Device description and Instructions For Use
12.5	Devices must be designed and manufactured in such a way as to minimise the risks of creating electromagnetic fields which could impair the operation of other devices or equipment in the usual environment.	Yes	The operating parameters of the device are at values sufficiently low as to make the creation of electromagnetic fields capable of impairing the operation of other devices extremely unlikely.	EMC compliance assessment in the Risk Assessment File and Design History File

12.6	*Protection against electrical risks* Devices must be designed and manufactured in such a way as to avoid, as far as possible, the risk of accidental electric shocks during normal use and in single fault condition, provided that the devices are installed correctly.	Yes	The device is provided with a small external monitor which contains a single low-voltage battery.	
12.7	*Protection against mechanical and thermal risks*	Yes		
12.7.1	Devices must be designed and manufactured in such a way as to protect the patient and user against mechanical risks connected with, for example, resistance, stability and moving parts.	Yes	There are no moving parts. The device is flexible and smooth for easy introduction; the stability	Device description and Risk Assessment File; abrasion resistance of the Vitamin K1 tip will form part of the clinical investigation plan
12.7.2	Devices must be designed and manufactured in such a way as to reduce to the lowest possible level the risks arising from vibration generated by the devices, taking account of technical progress and of the means available for limiting vibrations, particularly at source, unless the vibrations are part of the specified performance.	No	The device does not produce vibrations and no scenarios have been identified where the device is likely to be subjected to vibration	Device description
12.7.3	Devices must be designed and manufactured in such a way as to reduce to the lowest possible level the risks arising from the noise emitted, taking account of technical progress and of the means available to reduce noise, particularly at source, unless the noise emitted is part of the specified performance.	Yes	The device does not produce any noise	Device description and
12.7.4	The terminals and connectors to the electricity, gas or hydraulic and pneumatic energy supplies which the user has to handle must be designed and constructed in such a way as to minimise all possible risks.	Yes	No connections to gas, hydraulic or pneumatic energy sources. Electrical connections have been the subject of risk assessments and have been designed in accordance with EN60601	Risk Management File + Instructions For Use contain a description of the connections
12.7.5	Accessible parts of devices (excluding any parts or areas intended to supply heat or reach given temperatures) and their surroundings must not attain potentially dangerous temperatures under normal use.	No	The device does not supply heat	Device description
12.8	*Protection against the risks posed to the patient by energy supplies or substances*	Yes		

12.8.1	Devices for supplying the patient with energy or substances must be designed and constructed in such a way that the flow rate can be set and maintained accurately enough to guarantee the safety of the patient and of the user.	Yes	The device does not supply energy and is used for enteral feeding or gastric decompression only	Instructions For Use
12.8.2	Devices must be fitted with the means of preventing and/or indicating any inadequacies in the flow-rate which could pose a danger. Devices must incorporate suitable means to prevent, as far as possible, the accidental release of dangerous levels of energy from an energy and/or substance source.	No No	The device is not intended to have a controllable flow rate The device does supply energy; selection of the device size (lumen) determines and limits overall flow rate of enteral feeds	Device description and Instruction For Use Device description and Instruction For Use
12.9	*The function of the controls and indicators must be clearly specified on the devices.* Where a device bears instructions required for its operation or indicates operating or adjustment parameters by means of a visual system, such information must be understandable to the user and, as appropriate, the patient.	Yes	The monitor which forms part of the device has an indicating function only and has no adjustment means. It provides "Yes/No" information concerning the position of the tube tip and is in an 'On' condition whenever connected.	Device description and Instruction For Use
13	**Information Supplied By The Manufacturer**			
13.1	Each device must be accompanied by the information needed to use it safely and properly, taking account of the training and knowledge of the potential users, and to identify the manufacturer. This information comprises the details on the label and the data in the instructions for use. As far as practicable and appropriate, the information needed to use the device safely must be set out on the device itself and/or on the packaging for each unit or, where appropriate, on the sales packaging. If individual packaging of each unit is not practicable, the information must be set out in the leaflet supplied with one or more devices. Instructions for use must be included in the packaging for every device. By way of exception, no such instruction leaflet is needed for devices in Class I or	Yes Yes	there is personal training provided by the manufacturer to the user, as well as comprehensive IFU for the system as a whole and its component elements. the IFU are included within the packaging of each supplied unit of the device	Instructions For Use; on-site training Instructions For Use

	Class IIa if they can be used completely safely without any such instructions.			
13.2	Where appropriate, this information should take the form of symbols. Any symbol or identification colour used must conform to the harmonised standards. In areas for which no standards exist, the symbols and colours must be described in the documentation supplied with the device.	Yes	symbols on labels conform to standards. Other symbols are explained in the IFU	Instructions For Use
13.3	The *label* must bear the following particulars:			
	a) the name or trade name and address of the manufacturer. For devices imported into the Community, in view of their distribution in the Community, the label, or the outer packaging, or instructions for use, shall contain in addition the name and address of the authorised representative where the manufacturer does not have a registered place of business in the Community;	Yes	Provided in Instructions for Use	Instructions for Use
	b) the details strictly necessary to identify the device and the contents of the packaging especially for the users	Yes	The device and its packaging are clearly marked as intended exclusively for clinical investigation.	Device description, packaging, and markings
	c) where appropriate, the word "STERILE";	Yes	Both inner packaging and outer cartons are clearly marked 'STERILE'.	Device description, packaging, and markings
	d) where appropriate, the batch code, preceded by the word "LOT", or the serial number;	Yes	Both inner packaging and outer cartons are clearly marked with a LOT number. Each monitor bears a LOT number and serial number.	Device description, packaging, and markings
	e) where appropriate, an indication of the date by which the device should be used, in safety, expressed as the year and month;	Yes	The device is intended for clinical investigation only and should be used for the duration of that investigation. The end date is to be reflected in the IFU	Clinical Investigation Plan and Instructions For Use. At the end of the clinical investigation the manufacturer will remove the devices from the investigation
	f) where appropriate, an indication that the device is for single use. A manufacturer's indication of single use must be consistent across the Community;	Yes	Both inner packaging and outer cartons are clearly marked with a 'FOR USE ON A SINGLE PATIENT' USE BY' label. Each monitor is marked 'FOR SINGLE PATIENT USE'.	Device description, packaging, and markings
	g) if the device is custom made, the words "custom made device";	No	The device is not custom made	

	h) if the device is intended for clinical investigations, the words "exclusively for clinical investigations	Yes	Both inner packaging and outer cartons are clearly marked 'EXCLUSIVELY FOR CLINICAL INVESTIGATION'.	Device description, packaging, and markings
	i) any special storage and/or handling conditions;	Yes	Both inner packaging and outer cartons are clearly marked 'STORE AWAY FROM EXTREMES OF HEAT AND COLD AND OUT OF DIRECT SUNLIGHT'.	Device description, packaging, and markings
	j) any special operating instructions;	Yes	The operation of the system is according to a specific protocol	see Instructions For Use and the Clinical Investigation Plan
	k) any warnings and/or precautions to take;	Yes	risk assessment has been carried out and documented, including this table and various warnings were generated that are reflected in the IFU	Risk Management File and Instructions For Use
	l) indicate year of manufacture of active devices other than those covered by e). This indication may be included in the batch or serial number;	No	an alternative requirement was covered in 13.3e above.	
	m) where applicable, method of sterilisation:	Yes	Both inner packaging and outer cartons are clearly marked with the method of sterilisation	Device description, packaging, and markings
	n) In the case of a device within the meaning of Article 1(4a), an indication that the device contains a human blood derivative.	No	The device does not contain a human blood derivative.	Device description.
13.4	If the intended purpose of the device is not obvious to the user, the manufacturer must clearly state it on the label and in the instructions for use.	Yes	Intended use is unambiguously described in Instructions For Use	Instructions For Use
13.5	Wherever reasonable and practicable, the devices and detachable components must be identified, where appropriate in terms of batches, to allow all appropriate action to detect any potential risk posed by the devices and detachable components.	Yes	Both inner packaging and outer cartons are clearly marked with a LOT number. Each monitor bears a LOT number and serial number.	Device description, packaging, and markings
13.6	Where appropriate, the instructions for use must contain the following particulars:			
	a) the details referred to in 13.3, with the exception of d) and e)	Yes	Instructions For Use contain information as stated below	See Instructions For Use
	b) the performances referred to in section 3 and any undesirable side effects;	Yes	name & address and contact details of manufacturer; Device name, model, serial number, and year of manufacture,	See Instructions For Use

	c) if the device must be installed with or connected to other medical devices or equipment in order to operate as required for its intended purpose, sufficient details of its characteristics to identify the correct devices or equipment to use in order to obtain a safe combination;	Yes	exclusively for clinical investigations, warnings, precautions and storage performance characteristics according to Section 3	See Instructions For Use
	d) all the information needed to verify whether the device is properly installed and can operate correctly and safely, plus details of the nature and frequency of the maintenance and calibration needed to ensure that the devices operate properly and safely at all times;	Yes	method of connection to enteral feed sources and decompression bellows or syringe	See Instructions For Use
	e) where appropriate, information to avoid certain risks in connection with implantation of the device;	No	The device is not implantable	See Instructions For Use
	f) information regarding the risks of reciprocal interference posed by the presence of the device during specific investigations or treatment;	No	Interference unlikely	
	g) the necessary instructions in the event of damage to the sterile packaging and, where appropriate, details of appropriate methods of re-sterilisation;	Yes	“Do not resterilise if packaging is damaged”	See Instructions For Use
	h) if the device is reusable, information on the appropriate processes to allow reuse, including cleaning, disinfection, packaging and, where appropriate, the method of sterilisation of the device to be resterilised, and any restriction on the number of reuses.	No	“SINGLE PATIENT USE”	See Instructions For Use
	Where devices are supplied with the intention that they may be sterilised before use, the instructions for cleaning and sterilisation must be such that, if correctly followed, the device will still comply with the requirements in Section I.	No	Device supplied sterile	See Instructions For Use
	If the device bears an indication that the device is for single use, information on known characteristics and technical factors known to the manufacturer that could pose a risk if the device were to be re-used. If in accordance with Section 13.1 no instructions for use are needed, the information must be made available to the user upon request;	No	“SINGLE PATIENT USE. Disapplication of Section 13.1 does not apply	See Instructions For Use

	i) details of any further treatment or handling needed before the device can be used (for example, sterilisation, final assembly, etc.);	No	Device is supplied ready for use	See Instructions For Use
	j) in the case of devices emitting radiation for medical purpose, details of the nature, type intensity and distribution of this radiation. The instructions for use must also include details, allowing the medical staff to brief the patient on any contraindications and any precautions to be taken. These details should cover in particular:	No	No radiation emitted	See Instructions For Use
	k) precautions to be taken in the event of changes in the performance of the device;	No	No radiation emitted	
	l) precautions to be taken as regards exposure, in reasonably foreseeable environmental conditions, to magnetic fields, external electrical influences, electrostatic discharge, pressure or variations in pressure, acceleration, thermal ignition sources etc.;	No	No radiation emitted	See Instructions For Use
	m) adequate information regarding the medicinal product or products which the device in question is designed to administer, including any limitations in the choice of substances to be delivered;	Yes	Delivery of enteral feed products only	
	n) precautions to be taken against any special, unusual risks related to the disposal of the device;	Yes	Safe disposal of batteries	
	o) medicinal substances, or human blood derivatives incorporated into the device as an integral part in accordance with Section 7.4;	No	No blood derivatives incorporated in device; presence of Vitamin K1 is addressed in IFU.	
	p) degree of accuracy claimed for devices with a measuring function;	No	Not a quantitative measuring device	
	q) date of issue or the latest revision of the instructions for use.		Addressed in IFU	

14	Where conformity with the essential requirements must be based on clinical data, as in Section I (6), such data must be established in accordance with Annex X	Yes	a clinical investigation is carried out to establish performance of the device	Clinical Investigation Plan (CIP)

	Requirements	Applies	Comment	Class
	MDD Definition of Purpose of a Medical Device			
	Diagnosis, prevention, monitoring, treatment or alleviation of disease,	Yes	This is a medical device for enteral feeding or gastric decompression which is intended to indicate that it has been correctly placed prior to the commencement of feeding or gastric decompression	
	diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,	Yes	As above on the basis that enteral feeding is only required when a patient cannot feed or be fed by other means	
	investigation, replacement, or modification of the anatomy or of a physiological process	No		
	control of conception	No		
CLASSIFICATION CRITERIA 1				
1	**DEFINITIONS 1: Definitions for the classification rules**			
1.1	**Duration**			
	Transient – Normally intended for continuous use for less than 60 minutes	No		
	Short term – Normally intended for continuous use for not more than 30 days	Yes		
	Long term – Normally intended for continuous use for more than 30 days	No		
1.2	**Invasive Devices:**			
	Invasive device A device which, in whole or in part, penetrates inside the body, either through a body orifice or through the surface of the body.	Yes		
	Body orifice Any natural opening in the body, as well as the external surface of the eyeball, or any permanent artificial opening, such as a stoma.	Yes		
	Surgically invasive device An invasive device which penetrates inside the body through the surface of the body, with the aid or in the context of a surgical operation. For the purposes of this Directive devices other than those referred to in the previous subparagraph and which produce penetration other than through an established body orifice, shall be treated as surgically invasive devices.	No		

	Implantable device Any device which is intended to be totally introduced into the human body; or	No	Only a tubular portion of the device is introduced	
	to replace an epithelial surface or the surface of the eye, by surgical intervention which is intended to remain in place after the procedure	No		
	Any device intended to be partially introduced into the human body through surgical intervention and intended to remain in place after the procedure for at least 30 days is also considered an implantable device.	No	The intention is that the device is introduced via a nursing or parental intervention into a natural body orifice.	
1.3	**Reusable surgical instrument** Instrument intended for surgical use by cutting, drilling, sawing, scratching, scraping, clamping, retracting, clipping or similar procedures, without connection to any active medical device and which can be reused after appropriate procedures have been carried out.	No		
1.4	**Active Medical Device** Any medical device operation of which depends on a source of electrical energy or any source of power other than that directly generated by the human body or gravity and which acts by converting this energy. Medical devices intended to transmit energy, substances or other elements between an active medical device and the patient, without any significant change, are not considered to be active medical devices.	No	The device is for enteral feeding and gastric decompression. The device has a low voltage battery but this is located outside the body and only serves to power monitoring means for a signal generated by a chemical change in the stomach caused by the effect of pH on a foodstuff.	
1.5	**Active Therapeutical Device** Any active medical device, whether used alone or in combination with other medical devices, to support, modify, replace or restore biological functions or structures with a view to treatment or alleviation of an illness, injury or handicap.	No		
1.6	**Active Device For Diagnosis** Any active medical device, whether used alone or in combination with other medical devices, to supply information for detecting, diagnosing, monitoring or treating physiological conditions, states of health, illnesses or congenital deformities.	No	The monitoring function serves only to indicate position of the device itself, not any function of the patient.	
1.7	**Central Circulatory System** For the purposes of this Directive, 'central circulatory system' means the following vessels: arteriae pulmonales, aorta ascendens, arteriae coronariae, arteria carotis communis, arteria carotis externa, arteria carotis interna, arteriae cerebrales, truncus brachicephalicus, venae cordis, venae pulmonales, vena cava superior, vena cava inferior	N/A	Not Applicable	
1.8	**Central Nervous System** For the purposes of this Directive, 'central nervous system' means brain, meninges and spinal cord.	N/A	Not Applicable	
II	**IMPLEMENTING RULES 2. Implementing rules**			
2.1	Application of the classification rules shall be governed by the intended purpose of the devices.		The device is intended for enteral feeding and gastric decompression	

2.2	If the device is intended to be used in combination with another device, the classification rules shall apply separately to each of the devices. Accessories are classified in their own right separately from the device with which they are used.			
2.3	Software, which drives a device or influences the use of a device, falls automatically in the same class.			
2.4	If the device is not intended to be used solely or principally in a specific part of the body, it must be considered and classified on the basis of the most critical specified use.			
2.5	If several rules apply to the same device, based on the performance specified for the device by the manufacturer, the strictest rules resulting in the higher classification shall apply.			
III	**CLASSIFICATION**			
1	**Non-invasive devices**			
1.1.	**Rule 1** All non-invasive devices are in Class I, unless one of the rules set out hereinafter applies.	No	The device is invasive (Definition 1.2 – Body orifice)	
1.2	**Rule 2** All non-invasive devices intended for channelling or storing blood, body liquids or tissues, liquids or gases for the purpose of eventual infusion, administration or introduction into the body are in Class IIa: - if they may be connected to an active medical device in Class IIa or a higher class, - if they are intended for use for storing or channelling blood or other body liquids or for storing organs, parts of organs or body tissues, in all other cases they are in Class I.	No	The device is invasive (Definition 1.2 – Body orifice)	
1.3	**Rule 3** All non-invasive devices intended for modifying the biological or chemical composition of blood, other body liquids or other liquids intended for infusion into the body are in Class IIb, unless the treatment consists of filtration, centrifugation or exchanges of gas, heat, in which case they are in Class IIa.	No	The device is invasive (Definition 1.2 – Body orifice)	
1.4	**Rule 4** All non-invasive devices which come into contact with injured skin: - are in Class I if they are intended to be used as a mechanical barrier, for compression or for absorption of exudates, - are in Class IIb if they are intended to be used principally with wounds which have breached the dermis and can only heal by secondary intent, - are in Class IIa in all other cases, including devices principally intended to manage the micro-environment of a wound.		The device is invasive (Definition 1.2 – Body orifice)	
2	**Invasive Devices**			

2.1	**Rule 5** All invasive devices with respect to body orifices, other than surgically invasive devices and which are not intended for connection to an active medical device: - are in Class I if they are intended for transient use, - are in Class IIa if they are intended for short-term use, except if they are used in the oral cavity as far as the pharynx, in an ear canal up to the ear drum or in a nasal cavity, in which case they are in Class I, - are in Class IIb if they are intended for long-term use, except if they are used in the oral cavity as far as the pharynx, in an ear canal up to the ear drum or in a nasal cavity and are not liable to be absorbed by the mucous membrane, in which case they are in Class IIa. All invasive devices with respect to body orifices, other than surgically invasive devices, intended for connection to an active medical device in Class IIa or a higher class, are in Class IIa.	No No No Yes	The device is a nasogastric tube for enteral feeding and gastric decompression, the tip of which is introduced into the stomach	IIa
2.2	**Rule 6** All surgically invasive devices intended for transient use are in Class IIa unless they are: - intended specifically to diagnose, monitor or correct a defect of the heart or of the central circulatory system through direct contact with these parts of the body, in which case they are in Class III, - reusable surgical instruments, in which case they are in Class I, - intended to supply energy in the form of ionizing radiation in which case they are in Class IIb, - intended to have a biological effect or to be wholly or mainly absorbed in which case they are in Class IIb, - intended to administer medicines by means of a delivery system, if this is done in a manner that is potentially hazardous taking account of the mode of application, in which they are in Class IIb.	No	Not a surgically invasive device	
2.3	**Rule 7** All surgically invasive devices intended for short-term use are in Class IIa unless they are intended: - either specifically to diagnose, monitor or correct a defect of the heart or of the central circulatory system through direct contact with these parts of the body, in which case they are in Class III, - or specifically for use in direct contact with the central nervous system, in which case they are in Class III, - or to supply energy in the form of ionizing radiation in which case they are in Class IIb, - or to have a biological effect or to be wholly or mainly absorbed in which case they are in Class III,	No	Not a surgically invasive device	

	- or to undergo chemical change in the body, except if the devices are placed in the teeth, or to administer medicines, in which case they are in Class IIb.			
2.4	**Rule 8** All implantable devices and long-term surgically invasive devices are in Class IIb unless they are intended: - to be placed in the teeth, in which case they are in Class IIa, - to be used in direct contact with the heart, the central circulatory system or the central nervous system, in which case they are in Class III, - to have a biological effect or to be wholly or mainly absorbed, in which case they are in Class III, - or to undergo chemical change in the body, except if the devices are placed in the teeth, or to administer medicines, in which case they are in Class III.	No	Not an implantable device	
3	**Additional Rules Applicable To Active Devices**			
3.1	**Rule 9** All active therapeutic devices intended to administer or exchange energy are in Class IIa unless their characteristics are such that they may administer or exchange energy to or from the human body in a potentially hazardous way, taking account of the nature, the density and site of application of the energy, in which case they are in Class IIb.	No	Not an active therapeutic device	
3.2	**Rule 10** Active devices intended for diagnosis are in Class IIa: - if they are intended to supply energy which will be absorbed by the human body, except for devices used to illuminate the patient's body, in the visible spectrum, - if they are intended to image in vivo distribution of radiopharmaceuticals, - if they are intended to allow direct diagnosis or monitoring of vital physiological processes, unless they are specifically intended for monitoring of vital physiological parameters, where the nature of variations is such that it could result in immediate danger to the patient, for instance variations in cardiac performance, respiration, activity of CNS in which case they are in Class IIb. Active devices intended to emit ionizing radiation and intended for diagnostic and therapeutic interventional radiology including devices which control or monitor such devices, or which directly influence their performance, are in Class IIb.	No	Not a diagnostic device	
	Rule 11 All active devices intended to administer and/or remove medicines, body liquids or other substances to or from the body are in Class IIa, unless this is done in a manner: - that is potentially hazardous, taking account of the nature of the substances involved, of the part of the body concerned and of the mode of application in which case they are in Class IIb.	Yes	The device is a nasogastric tubes, one primary intended use of which is for enteral feeding	IIa
3.3	**Rule 12** All other active devices are in Class I.	No	Rule 11 prevails. The device is invasive and Class IIa	IIa
4	**Special Rules**			

4.1	**Rule 13** All devices incorporating, as an integral part, a substance which, if used separately, can be considered to be a medicinal product, as defined in Article 1 of Directive 65/65/EEC, and which is liable to act on the human body with action ancillary to that of the devices, are in Class III.	No	The device incorporates microgram amounts of Vitamin K1 as a coating on its tubular tip; this substance is classified as a food substance under the applicable directive and also occurs naturally in the human body	
4.2	**Rule 14** All devices used for contraception or the prevention of the transmission of sexually transmitted diseases are in Class IIb, unless they are implantable or long term invasive devices, in which case they are in Class III.	No	Not applicable	
4.3	**Rule 15** All devices intended specifically to be used for disinfecting, cleaning, rinsing or, when appropriate, hydrating contact lenses are in Class IIb. All devices intended specifically to be used for disinfecting medical devices are in Class IIa. This rule does not apply to products that are intended to clean medical devices other than contact lenses by means of physical action.	No	Not applicable	
4.4	**Rule 16** Non-active devices specifically intended for recording of X-ray diagnostic images are in Class IIa.	No	Not applicable	
4.5	**Rule 17** All devices manufactured utilizing animal tissues or derivatives rendered non-viable are Class III except where such devices are intended to come into contact with intact skin only.	No	Not applicable	
5	**Derogation**			
	Rule 18 By derogation from other rules, blood bags are in Class IIb.	No	Not applicable	

Appendix 15: Quality Policy and Objectives

The Quality Management System of the UOHLINGT Project

The Quality Policy:

- is relevant to the organisational goals and the expectations and needs of the intended customers.
- communicates the organisation's commitments and aspirations to comply with requirements and maintain the effectiveness of the QMS and to define principal objectives for the QMS.
- provides a framework for establishing specific quality objectives and provides direction for the improvement effort to the QMS.
- facilitates continual improvement through the EMT by means of goals and objectives.
- is periodically reviewed through framework of Management Reviews to ensure its continual relevance and suitability.
- is understood, implemented and maintained at all levels in the UOHLINGT Project organisation.

The UoHLINGT Team Members provide evidence of their commitment to the implementation of an effective QMS by:

- Communicating to the organisation the importance of meeting customer, statutory and regulatory requirements through the Quality Policy, Quality Objectives, Quality Manual and corresponding training.

- Defining the purpose and objectives for the QMS in the form of the Quality Policy and Quality Strategic Objectives;

- Periodically reviewing the QMS to ensure its continuing suitability, adequacy and effectiveness.

- Ensuring the availability of adequate resources in consideration of the current scope of the organisation and any other needs for the QMS

- Continually improving the QMS and manufactured product. This activity is managed and measured by the Management Review process (Quality Management Review Group - QMRG) and by the provision of suitable technical resources;
- Maintaining compliance with the Essential Requirements of the Medical Devices Directive 93/42/EEC where it impacts upon QMS requirements.

The EMT and the QMC establishes Quality Objectives on an annual basis to:

- implement the Quality Policy;
- meet requirements for products and processes
- improve the QMS and Quality Performance
- define the direction and priorities for continual improvement
- enable the UoHLINGT team to achieve the functional strategic goals/outcomes
- each functional unit develops specific quality objectives as part of their own 'departmental' objectives.

Appendix 16: List of Standard Operating Procedures (SOP's)

V03 17 March 2014	
UOHLINGT SOP No.	**Title**
SOP 01	Document Control Procedure
SOP 02	Device Master Record Procedure
SOP 03	Quality Records Procedure
SOP 04	Design And Development Procedure
SOP 05	Risk Management Procedure
SOP 06	Management Review Procedure
SOP 07	Process Validation Procedure
SOP 08	Supplier Evaluation Procedure
SOP 09	Purchase Order Procedure
SOP 10	Inventory Management Procedure
SOP 11	Control of Instrumentation
SOP 12	Internal Quality Audit Procedure
SOP 13	Traceability - Trials Product
SOP 14	Outsourced Manufacturing Control Procedure for Trials Product
SOP 15	QMS Computer System Procedure
SOP 16	Translation Procedure
SOP 17	Staff induction, Skills Evaluation and Training Procedure
SOP 18	Control of Non-Conforming Product Procedure
SOP 19	Corrective And Preventive Action Procedure (CAPA)
SOP 20	Cleaning and Sterilisation Validation Procedure
SOP 21	Labelling And Instructions For Use Procedure
SOP 22	Analysis of Data Procedure
SOP 23	Quality Plan Procedure
SOP 24	EU Vigilance Reporting & Field Safety Corrective Action (FSCA) Procedure
SOP 27	Environmental Control - Work Environment Procedure
SOP 31	Customer Complaints And Feedback Procedure
SOP 32	Product Recall And Advisory Notices
SOP 34	Change Control Procedure

Appendix 17: List of Operating Procedure Forms (OPF's)

V05 –22 July 2014	
UOHLINGT OPF No.	**Title**
OPF 01	Document Approval Form
OPF 02	Distribution List
OPF 03	Revision History Form
OPF 04	Feasibility Review Form
OPF 05	Project Team Formation Form
OPF 06	Design Verification Table
OPF 07	Design Plan Form
OPF 08	Development Stage 1 Checklist
OPF 09	Design And Development Change Form
OPF 10	Project Decision Record Form
OPF 11	Development Stage 2 Checklist
OPF 12	Design Transfer Checklist
OPF 13	Management Review Agenda
OPF 13a	Management Review Minutes
OPF 13b	Project Team Meeting Agenda
OPF 13c	Project Team Meeting Minutes
OPF 13d	Quarterly Review Meeting Agenda
OPF 13e	Quarterly Review Meeting Minutes
OPF 13f	Quality Management Committee Meeting Agenda
OPF 13g	Quality Management Committee Meeting Minutes
OPF 13h	Risk Assessment Meeting Agenda
OPF 13i	Risk Assessment Meeting Minutes
OPF 13j	User Carer Advisory Group Meeting Agenda
OPF 13k	User Carer Advisory Group Meeting Minutes
OPF 14	Failure Mode Effect Analysis Form - Design And Process
OPF 15	Supplier Evaluation, Audit And Approval Form (SEAAF)
OPF 15 a -v	Supplier Evaluation, Audit And Approval Form (SEAAF)
OPF 16	Register Of Approved Suppliers
OPF 18	Inventory Check List

OPF 19	Inventory Management Worksheet
OPF 19a	Inventory Management Worksheet
OPF 19b	Inventory Management Worksheet
OPF 20	Quarantine/Reject Log
OPF 21	Reagent Log For -80°C Freezer
OPF 21	Reagent Log For Fridge/Freezer
OPF 22	Inventory Received Label
OPF 23	Annual Internal Audit Schedule
OPF 24	Internal Audit Plan Checklist
OPF 25	Internal Audit Report Incorporating Corrective And Preventive Action Report
OPF 26	New Employee Induction Form And Check List
OPF 27	Training Folder Requirements List
OPF 28	Training Requirements - Template
OPF 28.1 – 28.8	Training Requirements – Individual Completed Forms
OPF 29	Training Record - Template
OPF 29.1 – 29.8	Training Record - Individual Completed Forms
OPF 30	Register Of Attendance – Collective Training
OPF 31	Equipment Register
OPF 32	Identification And Status Label
OPF 33	Calibrated Equipment History Record Sheet
OPF 34	Equipment Calibration And Functional Status Chart
OPF 35	Verified Equipment Log Sheet
OPF 36	Non-Conformance Report/Returns Note
OPF 37	Non-Conformance Log
OPF 38	Customer Complaint/Satisfaction Form
OPF 39	Customer Complaints Log
OPF 40	Change Note Form
OPF 41	Change Note Register
OPF 42	Corrective And Preventive Action Request Form
OPF 43	University Of Hull – Faculty Of Science – Department Of Chemistry: Written Risk Assessment And COSHH Form
OPF 45	Biological Sciences Procedural Risk Assessment And Coshh Form
OPF 46	Purchase Order Request Form (PORF)

Appendix 18: Questions for Risk Assessment

Annex C Questions that can be used to identify medical device characteristics that could impact on safety

EN ISO 14971: 2007(E) Annex C		Applicable Yes/No	Characteristic
C2.1	What is the intended use and how is the medical device to be used?		The UoHLINGT comprises a modified nasogastric tube and monitor. The nasogastric tube is designed for the delivery of feeds to patients who cannot swallow and for the decompression of the stomach prior to gastrointestinal surgery. The monitor is connected in order to determine correct placement in the stomach The tube is available in sizes from 6Fg to 18 Fg
C2.2	Is the medical device intended to be implanted?		No. The tube is to be inserted through the nose or mouth into the stomach
C2.3	Is the medical device intended to be in contact with the patient or other persons		The UOHLINGT is designed to dwell in the stomach and the tip sit in gastric fluid. It is intended that it may be left in situ for up to 28 days During insertion the tube will pass through the nose, naso pharynx, oropharynx, oesophagus and so into the stomach. It will come into contact with the mucosal lining of the gastro-intestinal tract.
C2.4	What materials or components are utilise in the medical device or are used with or are in contact with the medical device?		Polyurethane Vitamin K1 Silver/silver chloride ink Vege – gel
C2.5	Is energy delivered to or extracted from the patient?	No	The vitamin K1 and vege-gel are such small quantities that any energy derived from and required for digestion is minimal.
C2.6	Are substances delivered to and/or extracted from the patient	Yes	VitaminK1 Vege gel Silver silver chloride Are inserted into the stomach and natural processes will try to dif
C2.8			Method of product sterilisation The impact of other sterilisation methods not intended by the manufacturer
C2.9	Is the medical device intended to be routinely cleaned and disinfected by the user?		Types of cleaning or disinfecting agents to be used Limitations on the number of cleaning cycles The design of the medical device can influence the effectiveness of routine cleaning and disinfecting The effect of cleaning and disinfecting agents on the safety or performance of the device
C2.10	Is the medical device intended to		Temperature Humidity

	modify the patient environment?		Atmospheric gas composition Pressure Light
C2. 11	Are measurements taken?		The variables measured The accuracy and precision of the measurement results
C2. 12	Is the medical device interpretative?		Whether conclusions are presented by the medical device from input or acquired data The algorithms used Confidence limits Special attention should be given to unintended applications of the data or algorithm
C2. 13	Is the medical device intended for use in conjunction with other medical devices, medicines or other medical technologies?		Identifying any other medical devices, medicines or other medical technologies that can be involved and potential problems associate with such interactions Patient compliance with the therapy
C2. 14	Are there unwanted outputs of energy or substances?		Energy-related factors: Noise and vibration Heat Radiation (including ionisation, non-ionisation, and ultraviolet/infrared radiation) Contact temperatures Leakage currents Electric or magnetic fields Substance-related factors: Substances used in manufacturing Cleaning or testing having unwanted physiological effects if they remain in the product Other substance-related factors: Discharge of chemicals Waste products Body fluids
C2. 24	Is the medical device intended for single use?		Does the medical device self-destruct after use? Is it obvious that the device has been used?
C2. 25	Is safe decommissioning or disposal of the medical device necessary?		The waste products that are generated during the disposal of the medical device itself: Does it contain toxic or hazardous material? Is the material recyclable?
C2. 26	Does installation or use of the medical device require special training or special skills?		The novelty of the medical device The likely skill and training of the person installing the device
C2. 27	How will information for safe use be provided?		Whether information will be provided to the end user by the manufacturer or will it involve the participation of third parties such as installers, care providers, health care professionals or pharmacists and whether this will have implications for training

			Commissioning and handling over to the end user and whether it is likely/possible that installation can be carried out by people without the necessary skills Based on the expected life of the device, whether re-training and re-certification of operators or service personnel would be required
C2.28	Will new manufacturing processes need to be established or introduced?		New technology New scale of production
C2.29	Is successful application of the medical device critically dependent on human factors such as the user interface?		
C2.29.1	Can the user interface design features contribute to use error?		User interface design features that can contribute to use error: Control and indicators Symbols used Ergonomic features Physical design and layout Hierarchy of operation Menus for software driven devices Visibility of warnings Audibility of alarms Standardisation of colour coding See IEC 60601-1-6 for additional guidance on usability and IEC 60601-1-8 for guidance on alarms
C2.29.2	Is the medical device used in an environment where distractions can cause use error		The consequence of use error Whether the distractions are commonplace Whether the user can be disturbed by infrequent distraction
C2.33	Is the medical device intended to be mobile or portable?		The necessary grips Handles Wheels Brakes Mechanical stability Durability
C2.34	Does the use of the medical device depend on essential performance?		Characteristics of the output of life-supporting devices The operation of an alarm See IEC 60601-1-1 for a discussion of essential performance of medical electrical equipment and medical electrical systems

Appendix 19: Failure Mode Effect Analysis (FMEA)

Risk Analysis & Assessment – Failure Mode and Effects Analysis (FMEA)						
1 Biological Hazards						
Hazard	**Failure Cause**	**Effect on Patient/Product/User**	**Initial Risk Estimation of Risk Index Number (RIN) Risk Severity x Probability**	**Initial Risk Priority Number (RPN) =RIN x detection**	**Control Measure**	**Residual Risk**
i) Toxicity of parts of the UOHLINGT tube	Use of inappropriate materials for the nasogastric tube, sensors, electrodes or wires or as packaging for the nasogastric tube	Systemic or local tissue reaction of patient or operator who come into contact with those materials	4 x 3 = 12 Unacceptable	12 x4 =48 Medium priority	Specification for quality and purity of components of UOHLINGT: • Polyurethane (medical grade) • vitamin K1 is already available as a drug and food supplement • Silver/silver chloride (medical grade) • The other parts of the nasogastric tube and packaging are the same as those currently in use in nasogastric tubes and are already CE marked and there have been no reports of such effects	4 x 1 = 4 ALARP Acceptable

					The chemicals used for the sensing tip of the UOHLINGT have been tested for toxicity and biocompatibility (Toxicology report Richard Reece Jones Oct 2013).	
	Breakdown of electrode chemicals by digestive processes	Systemic or local tissue reaction of patient	3 x 2 = 6 ALARP	6 x 3 = 18 Low priority	Toxicity report to review the evidence of harm caused by absorption of vitamin K1 and silver silver chloride Longevity studies to examine the digestion of vitamin K1 and silver silver chloride	3 x 1 = 3 ALARP
	Patient or user has an allergic reaction to any component of UOHLINGT	Allergic reaction (swelling of mucous membranes, rash, in rare instances anaphylactic shock) to tip coating or tube materials either once in the stomach or during passage through nose and oesophagus	5 x 2 = 10 Unacceptable	10 x 1 = 10 Low	Toxicology reports on tip coating found minimal evidence of sensitivity. Warning in package of potential sensitivity reaction. Nurse in User group had experienced 1 patient in 16 years who appeared to be sensitive to the silicone tubes in current use. This baby produced a lot of mucous with a silicone tube in situ but this improved once milk as well as tube had been changed.	5 x 1 = 5 ALARP
		Sensitivity to material used to secure the tube to the face	1 x 5 = 5	5 x 1 =5 Low	This is relatively common particularly with young babies and measures are taken to protect the skin with..... UOHLINGT will pose no additional risk as it will be secured in a similar way to current tubes	5x1 =5 ALARP

ii) Spread of Infection	Patient with undetected MRSA or Clostridium Difficile is treated with UOHLINGT and appropriate infection control measures not followed	Other patients are exposed to and therefore are infected by MRSA or Clostridium Difficile	3 x 3 = 9 Unacceptable	9 x 2 - 18	Screen all patients for MRSA or Clostridium Difficile and ensure appropriate infection control policies followed UOHLINGT tubes are single use only and will be disposed of after use. The indicator box will be cleaned thoroughly between patients and patients with known infection given personal indicator box.	3 x 2 = 6 ALARP
	A patient with an infection is treated and parts of the UOHLINGT come into contact with this infection	Infection is transmitted to other patients. An infection of a type other than above would be less severe if transmitted.	2 x 3= 6	6 x 2 = 12	The probability of a patient with UOHLINGT having an infection would be at least the same as that of having a normal nasogastric tube patients with infectious skin diseases must have their own individual indicator box. Instruct User to use disinfectant wipes to clean indicator box prior to each use. Use individual indicator box for patients with known infection.	2 x 3 = 6 ALARP

2 Mechanical Hazards						
Hazard	**Failure Cause**	**Harm - Effect on Patient/Product/User**	**Initial Risk Estimation of** **Risk Index Number (RIN) Risk** **Severity x Probability**	**Initial Risk Priority** **Number (RPN)** **=RIN x detection**	**Control Measure**	**Residual Risk**
i) Tip of tube not in stomach	Operator misplacement. vomiting, patient pulling on the tube etc	Tube becomes misplaced in the oesophagus or trachea and, if not detected prior to use, will cause poor absorption of feed or respiratory distress and possibly death	5 x 5 = 25	25 x 2 =50 High	The position of the tube must be checked after insertion and any episodes of coughing or vomiting or if it is suspected that the patient has accidently or deliberately tampered with the tube. This is normal practice for any ng tube and UOHLINGT should be treated within the same hospital protocols as for tubes currently in use. Thus the position of the tube will be checked before every administration of feed or medication. The method of detecting correct placement is easier and more certain than current methods.	5 x1 = 5 ALARP
ii)Abrasion to delicate mucosal lining of nasal passages, pharynx and oesophagus	Stiffness of tube and Elecrodes	Bleeding and ulceration of mucosal lining. Pain	4 x 1 = 4	4 x 2 = 8 Low	The UOHLINGT will be at least as soft and flexible as the best tubes in current use. The shore hardness will be assessed using a tip deflection test. Current tubes occasionally cause bleeding in babies and children when first passed. This usually resolves. Health Professionals are instructed to only have 3 attempts to place tubes and then refer the patient to more experienced/senior colleague. The electrodes will	4 x 1 = 4 ALARP

		Perforation of oesophagus or stomach			be created flush with the tube or within a current feeding port.	
iii) Feed does not flow through the tube	Tube may be kinked in the stomach Professional users consider that this is a rare occurrence. More likely to be curled in mouth on insertion but this is immediately identified and rectified	Feed will not flow freely through the tube Electric signal may be altered	2 x 2 = 4	4 x 2 = 8 Low	Markings on tube will indicate length inserted. Impairment of electrical signal due to kinking minimised	2 x 1 = 2 Acceptable
	Feeding ports and internal size of feeding lumen may be too small to allow free flow of feeds	Feed cannot be administered	2 x 2 = 4	4 x1 = 4 Low	Appropriate size of tube and feeding ports must be used for patient and type of feed to be administered.	2 x 1 = 2 Acceptable
	Tube may become blocked	Feed cannot be administered	2 x 2 = 4	4 x1 = 4 Low	Current tubes are flushed with cooled boiled water (for babies under 1 year sterile water is used) after every feed or administration of medicine. UOHLINGT tubes would be flushed in line with NPSA guidelines	2 x 1 = 2 Acceptable
iv) Tube cannot be inserted	Tube is too soft to allow insertion	Tube cannot be used and patient requires alternative device	1 x 2 =2	2 x1 =2 low	A number of tubes in current use require guide wires for insertion as they are too soft. The co-extruded wires will provide some rigidity to the tube to facilitate insertation, avoiding the use of guide wires	1 x 2 =2 Acceptable
V) Electrode becomes detached from connecting wire	Poor adherence of electrode to wire/tube.	The electrode ceases to function adequately and so does not correctly identify placement in the stomach	4 x 3 = 12 Unacceptable	12x3 = 36 Medium	Design of electrodes reviewed and decision to make electrodes out of conducting wire agreed (date). This results in electrodes being continuous with conducting wire and so no possibility of detachment.	4 x 1 = 4 ALARP

		Dislodged electrode may cause intestinal blockage or perforation				
vi) Tube cannot be connected to indicator box	Failure or detachment of connectors	Feed cannot be delivered/ stomach cannot be decompressed as it is not possible to confirm position with indicator box.	3 x 3 = 9 Unacceptable	9 x3 =27 medium	Design of tube reviewed to enable traditional detection methods (pH indicator paper and/or X Ray) to be used with UOHLINGT if connection to indicator box not possible. See design review xxx Risk therefore reduced to equivalent risk of current methods of placement detection.	3 x 2 = 6 ALARP
3 Electrical Hazards						
Hazard	**Failure Cause**	**Harm - Effect on Patient/Product/User**	**Initial Risk Estimation of Risk Index Number (RIN) Risk Severity x Probability**	**Initial Risk Priority Number (RPN) =RIN x detection**	**Control Measure**	**Residual Risk**
i) Excessive current	Malfunction of indicator box	Electric shock causing: fibrillation or death	5 x 1 = 5	5 x 1 = 5	The electrochemical signal is generated within the patient and no current is delivered to the patient. A p9 battery generates ..... Laboratory and ex-vivo testing demonstrate that the currents generated are in the range of ..... and therefore the probability of death from electric shock is The batteries used in the indicator box are AA which are.... and are external to the patient's body and thus risk of harm is reduced	5 x 1 = 5 ALARP

					The batteries in the indicator box cannot be accessed by the patient as they are secured within the device and the treatment is under supervision.	
ii)Electrical connection between tube and indicator box malfunctions	Poor design of connector	Electric shock to patient or carer causing fibrillation and death Overheating of connection causes burns to patient and/or user	5 x 1 = 5	5 x 1 = 5	Medical Device Designers involved in designing a robust and safe connection which is tested in accordance with	5 x 1 = 5 ALARP
iii)Failure of the electrical insulation within the system		Electric shock causing: Fibrillation or Death + Burns	5 x 1 = 5	5 x 1 = 5	The electrical current generated by the UOHLINGT system is…..and therefore no harm can be caused by contact with this current	5 x 1 = 5 ALARP
iv) Ingress of fluids		Electric shock causing: Fibrillation or Death.	5 x 1 = 5	5 x 1 = 5	The UOHLINGT is designed to dwell in the stomach and the tip sit in gastric fluid. However the tube is designed so that fluid cannot enter the electrical system.....	5 x 1 = 5 ALARP
v)Heat	Overheating of electrical equipment can cause burns and battery powered equipment are no exceptions	Serious burn	5 x 1 = 5	5 x 1 = 5		5 x 1 = 5 ALARP
vi) No current detected	Battery failure	System fails to detect correct placement	5 x 3 =15	15 x 1 =15	Low battery indicator light on indicator box identifies when battery is low but still operational and requires replacement before next feed. Indication when battery no longer functional also present. Batteries replaceable but not rechargeable	5 x1 = 5 ALARP

4 Environmental Hazards						
Hazard	**Failure Cause**	**Harm - Effect on Patient/Product/User**	**Initial Risk Estimation of Risk Index Number (RIN) Risk Severity x Probability**	**Initial Risk Priority Number (RPN) =RIN x detection**	**Control Measure**	**Residual Risk**
i)Inappropriate disposal of equipment and its components and batteries	Operators unaware of correct disposal methods	Adverse impact on the environment . The severity of harm to the environment can have a minor impact on the health of population The probability of this level of effect is well established and can be taken as frequent	2 x 5 = 10 Unacceptable	10 x 4 = 40	The device and its components as well as batteries are to be disposed of according to local and WEEE regulations. The instructions for use makes this abundantly clear. This can reduce the probability of inappropriate disposal.	2 x 3 = 6 ALARP
5 Radiation Hazards						
i)There are no identifiable radiation hazards either intrinsic or extrinsic	N/A	N/A	N/A	N/A	N/A	N/A

6 Chemical Hazards						
Hazard	**Failure Cause**	**Harm - Effect on Patient/Product/User**	**Initial Risk Estimation of Risk Index Number (RIN) Risk Severity x Probability**	**Initial Risk Priority Number (RPN) =RIN x detection**	**Control Measure**	**Residual Risk**
i)Electrode material (working electrode and/or reference electrode) is degraded or digested by the stomach acid	Digestive juices in stomach	The electrode ceases to function adequately and so does not correctly identify placement in the stomach. Products of digestion or degradation may be toxic to the patient	4 x 2 = 8	8 x 3 = 24 medium	Toxicity report to review the evidence of harm caused by absorption of vitamin K1 and silver silver chloride Laboratory tests on electrodes placed in gastric fluid for 30 days demonstrate that the amount of chemicals transferred to gastric fluid is negligible and functionality of electrodes continues. Toxicology reports clearly demonstrate that if digested electrode material is not harmful. Data sheets for vitamin K1 and Ag/AgCl	4 x 1 = 4 ALARP
ii)Electrode material is inactive or insensitive	Unsuitable materials used	Correct identification of placement in the stomach is not possible and alternative tube has to be used.	1 x 1 = 1	1 x 1 =1	Medical grade materials used and data sheets checked and stored. Laboratory experiments indicate no inactive materials encountered. Extensive laboratory testing has optimised the concentration and amount of vitamin K1 to be used in order to correctly and clearly identify placement in the stomach. Indicator box will not function if signal not generated.	1 x 1 =1 acceptable
iii)Electrode material may not adhere to the tube tip causing	Unsuitable materials used adherence to	Correct identification of placement in the stomach not possible due to	2 x 2 = 4	4 x 1 = 4	Tube designed to ensure that electrode surface is not in contact with nasal mucosa during insertion. Extensive testing of	2 x1 = 2

it to rub off during passage through the nose and oesophagus	electrode insecure	insufficient electrode material remaining. Damage to nasal and oesophageal mucosa by electrode material			adherence of vitamin K1 and Ag/Ag Cl to surgical stainless steel wires	acceptable
iv)Electrode material may be inactivated by exposure to sunlight, electric light, certain temperatures	Inappropriate packaging and storage	Correct identification of placement in the stomach not possible due to inactivated electrode material	2 x 2 = 4	4 x 1 = 4	Clear storage instructions and appropriate packaging materials	2 x1 = 2 acceptable
v)Chemicals in the UOHLINGT tube material may leach into the stomach and oesophagus	Use of inappropriate materials for manufacture	Plasticisers and phthalates have been known to cause toxic reactions	4 x 2 = 8	4 x 4 - 16	Tubes manufactured using medical grade polyurethane of a quality already used in the manufacture of NGT which has been demonstrated to not leach harmful products.	4 x 1 = 4 Acceptable
7 Human Factors Hazards						
Hazard	**Failure Cause**	**Harm - Effect on Patient/Product/User**	**Initial Risk Estimation of Risk Index Number (RIN) Risk Severity x Probability**	**Initial Risk Priority Number (RPN) =RIN x detection**	**Control Measure**	**Residual Risk**
i)Confusing or missing instructions for use	Poorly written IFU and labelling. IFU not enclosed with product	Placement of tube not determined so decompression not achieved OR feed not given or given in	4 x 3 = 12 unacceptable	12 x 4 = 48 High priority	The UOHLINGT system has very simple sequence of user instructions and controls developed in discussion with lay and professional users. IFU written in plain	4 x 1 = 4 ALARP

		incorrect location causing intolerance or respiratory failure.			English with clear schematic diagrams and translated as appropriate.	
ii)Complex or confusing control system	Poorly designed indicator box. Poorly written IFU		4 x 3 = 12 unacceptable	12 x 4 = 48 High priority	The indicator box was assessed by full team for ease of visualisation	4 x 1 = 4 ALARP
ii)Ambiguous or unclear device state			4 x 3 = 12 unacceptable	12 x 4 = 48 High priority	Instructions for use and user training are provided.	4 x 1 = 4 ALARP
iv)Ambiguous or unclear presentation of settings, measurements or other information			4 x 3 = 12 unacceptable	12 x 4 = 48 High priority	User advisory group involved in determining size, shape and layout of Indicator Box. Extensive discussion with clinicians and medical device manufacturers informed design of UOHLINGT system. User advisory group involved with writing IFU	4 x 1 = 4 ALARP
v)Insufficient visibility			4 x 3 = 12 unacceptable	12 x 4 = 48 High priority		4 x 1 = 4 ALARP
vi)Poor mapping of controls to actions, or of displayed information to actual state			4 x 3 = 12 unacceptable	12 x 4 = 48 High priority		4 x 1 = 4 ALARP
vii)Use by unskilled/untrained personnel	Lack of preparation	Damage to the UOHLINGT system + stoppage of treatment	4 x 3 = 12 unacceptable	12 x 4 = 48 High priority	The UOHLINGT system has been designed with the help of non-professional (unskilled) users to ensure that it is easy to use. Training and clear IFU will be provided for all users.	4 x 1 = 4 ALARP

viii)Inadequate warning of hazards associated with re-use of single-use medical devices	Poorly written IFU and labelling	Cross infection	See 2.1 – Biological hazards		Instruction For Use (IFU) + training	4 x 1 = 4 ALARP
ix)Insufficient warning of side effects	Poorly written IFU and labelling	Inappropriate use on patients. Inadequate treatment applied to patients	4 x 3 = 12 unacceptable	12 x 4 = 48 High priority	Toxicology Reports indicate that sensitivity reactions to components of UOHLINGT are extremely rare. Include warnings in the IFU + user training	4 x 1 = 4 ALARP
8 **Clinical Hazards**						
Hazard	**Failure Cause**	**Harm - Effect on Patient/Product/User**	**Initial Risk Estimation of Risk Index Number (RIN) Risk Severity x Probability**	**Initial Risk Priority Number (RPN) =RIN x detection**	**Control Measure**	**Residual Risk**
i)Patients with temporary feeding difficulties are given feeds via UOHLINGT for longer than necessary	Ease of feeding make UOHLINGT more attractive	Normal feeding patterns are not established or re-established	2 x 2 = 4	4 x 2 =8 low	Patients receiving nasogastric feeding through any type of tube are constantly reassessed and indicator boxed and normal oral feeding attempted once safe to do so.	2 x 1 = 2 acceptable

					Parents stressed desire to establish normal feeding as soon as possible no matter how easy ng feeding appeared. Instructions for use will clearly explain normal ng feeding practices to be adhered to.	
ii)Gastro-intestinal system of patient incorrectly diagnosed with feeding difficulties is exposed to the UOHLINGT	Mis diagnosis	Adverse physiological effect, impairing the normal gastro-intestinal system of the patient.	2 x 1 = 2 acceptable	2 x 2 = 4	None required but patients receiving treatment are clinically examined at regular intervals to monitor the progress of treatment	2 x 1 = 2 acceptable
iii)Exposure to the UOHLINGT feeding system	Ease of feeding make UOHLINGT more attractive	Patients and carers may become reliant on the reassurance given by UOHLINGT that adequate calorific intake is being delivered.	2 x 2 = 4	4 x 2 =8 low	In babies and recovering patients the natural development of the suck and swallow reflex will mean that oral feeding will become progressively important and UOHLINGT redundant. In patients with permanent feeding problems surgical insertion of PEG feeding tube will become necessary to replace UOHLINGT	2 x 1 = 2 acceptable
iv)Exposure to the UOHLINGT feeding system	Over feeding	Nausea and vomitting	2 x 2 = 4	4 x 1 =4 low	The rate, type and timing of feed delivery can be adjusted to eliminate or minimise nausea This is current practice for NGT in current use ie continuous feeding ceases for 2-4 hours per 24 hour cycle.	2 x 1 = 2 acceptable
v)Exposure to the UOHLINGT in a patient having undiagnosed cranial fracture or fractures to the nasoorbitoethmoid (NOE) complex.	Inappropriate use in vulnerable patients	Tube may be inserted through nose, via fracture in base of skull or nasoorbitoethmoid (NOE) complex into the brain	5 x 2 = 10	10 x 1 = 10	Instructions for Use clearly state that patients with head or frontal facial injuries must be X rayed before attempts at passing a feeding tube are made. Tubes must not be passed on patients with known or suspected skull or frontal facial fractures	5 x 1 = 5 ALARP

Appendix 20: GANT Chart

Task Mode	Task Name	Duration	Start	Finish
1	**MILESTONE: AWARD OF GRANT**			Mon 17/01/11
2	**DURATION OF WORK UNDER i4i FPD STREAM 2 GRANT**	916 days	Mon 04/07/11	Fri 03/07/15
3	**MILESTONE: POST-DOC RECRUITED**			Mon 04/07/11
4	**ENGINEERING/CHEMISTRY**			
5	Recruit PDRA chemist	87 days	17/02/11	MS commenced 4/7/11
6	Identify Manufacturing Partner Firms (Tubes; Elements of Chemical System	94 days	25/08/11	03/01/12 Arrotek for v 2 prototypes 24/01/14 INTERVENE v 3 prototypes
7	**LINGT Iteration v2 TUBE AND EXTERNAL MONITOR - Design; Construct; Test; Verify; Validate. For Gastric Mucosa Tasks include:-**			
8	**SURFACE CHEMISTRY**			
9	Investigate covalent vitamin K1 attachment to enhance sensor stability	100 days	11/07/11	Decision to abandon covalent attachment
10	Investigate olefin functionality in vitamin K1 side chain	100 days	11/07/11	completed
11	Investigate 2nd redox reference species (non pH affected) - elimination of 'drift' in observed response	100 days	11/07/11	Ag/AgCl agreed
12	**ENTERAL COATING CHEMISTRY**			
13	Investigate gastrically-degradable coating materials for improved service life	100 days	O6/01/12	Abandoned
14	Consideration of biocomaptibility issues	70 days	Oct 2013	Toxicology reports completed Oct 2014
15	**ELECTRODE DESIGN**			
16	Investigate embedded wires	170 days	06/01/12	2 designs from Arrotek evaluated. April 2013 coextruded wires possible but not commercially viable so 3 lumen tube agreed

17	**ELECTRONICS, SENSOR AND SYSTEM**			
18	Improve potentiostat inter-electrode current measurement as function of PD	70 days	Oct 2012	Image to Implant 27/01/14
19	Improve electronics for fast digital response	70 days	Oct 2012	Image to Implant 27/01/14
20	Progress system size and weight minimisation	70 days	Oct 2012	Image to implant 27/01/14
21	**HNGT PRODUCT INTEGRATION AND ERGONOMICS**			
22	Functional Monitor/Tube Interface Capture and Release	25 days		Agreed meeting 27/01/
23	PCB and Readout Means	25 days		Image to Implant
24	**PROTOTYPE MANUFACTURE AND TESTING**			
25	Further testing of early in vitro prototypes	15 days		LINGT iteration 2 completed
26	Serial prototype testing	15 days		LINGT iteration 2 completed
27	Commence process development and SOPs for LINGT commercial production conversion	20 days		ongoing
28	**MILESTONE: LINGT V2 TUBE AND MONITOR COMPLETED**			**Wed 18/04/12** Achieved
29	Feasibility/Functionality of Engineered Solution v2 Agreed As Basis for v3 Refinement	10 days		03/05/12
30	**LINGT Iteration v3 - TUBE AND EXTERNAL MONITOR: Rectify from v2: Redesign; Construct; Test; Verify; Validate. tasks include:-**			
31	**SURFACE CHEMISTRY**			
32	Refine application vitamin K1 attachment for improved sensor stability	70 days	03/05/12	
33	Refine reduction of 'drift' in observed response	70 days	03/05/12	
34	**ENTERAL COATING CHEMISTRY**			
35	Select gastrically-degradable coating material for improved service life	70 days	03/05/12	Decision to abandon gelatine coating
36	Biocompatibility studies	50 days	03/105/13	Toxicology Reports completed Oct 14
37	**ELECTRODE DESIGN**			
38	Refine embedded wires design	70 days		Co-extrusion considered but not commercially viable at Nov 2014

39	**ELECTRONICS, SENSOR AND SYSTEM**			
40	Refine current measurement as function of PD	150 days	27/01/14	Image to Implant
41	Refine electronics for fast digital response	150 days	27/01/14	Image to Implant
42	Progess system size and weight reduction	150 days	27/01/14	Image to Implant
43	**LINGT PRODUCT INTEGRATION AND ERGONOMICS**			
44	Refine Monitor/Tube Interface Capture and Release	25 days	Agreed meeting 21/08/14	Discussions with User Network
45	PCB Aspect Ratio Versus Readout	25 days	Agreed meeting 21/08/14	Image to Implant
46	**PROTOTYPE MANUFACTURE AND TESTING**			
47	Further prototype testing	15 days	Wed 06/06/13	Tue 26/06/13
48	Further process development towards HNGT commercial solution; progress SOPs	20 days	Wed 25/01/12	Tue 21/02/12
49	**MILESTONE: HNGT V3 TUBE AND MONITOR COMPLETED**			**December 2014**
50	Feasibility/Functionality of Engineered Solution v3 Agreed As Basis for v4 Finalisation	10 days	December 2014	
51	**LINGT FINAL ITERATION v4 - Rectify from v3: redesign; DESIGN FREEZE; Construct; Test; Verify; Validate. For Pilot Trials. Tasks include:-**			
52	**SURFACE CHEMISTRY**			
53	Finalise applicstion vitamin K1 for optimal sensor stability	110 days	Jan 2015	April 2015
54	Elimination of 'drift' in observed response	110 days		
55	**ENTERAL COATING CHEMISTRY**			
56	Optimise selected gastrically-degradable coating material for best service life			Abandoned
57	Biocompatibility studies	110 days		Complete Oct 2014
58	**ELECTRODE DESIGN**			
59	Finalise embedded wires/tube design	110 days		3 lumen tube agreed 21/08/14
60	**ELECTRONICS, SENSOR AND SYSTEM**			

61	Optimise/finalise current measurement	110 days		Feb 2015
62	Finalise/optimise electronics	110 days		Feb 2015
63	Optimise system size and weight	110 days		Feb 2015
64	**PROTOTYPE MANUFACTURE AND TESTING**			
65	Final prototype testing	30 days	Feb 2015	March 2015
66	Optimise process development for commercial application; finalise documentation	110 days		March 2015
67	**LINGT PRODUCT INTEGRATION AND ERGONOMICS**			
68	Finalise Monitor/Tube Interface Capture and Release	110 days		March 2015
69	PCB Aspect Ratio Versus Size and Style	110 days		March 2015
70	Optimise Final Aesthetics and User Issues	50 days		March 2015
71	**MILESTONE: LINGT V4 FINAL ITERATION TUBE AND MONITOR COMPLETED**			**Friday 17 April 2015**
72	IDENTIFY/ENGAGE: LINGT Packaging Development/Sterilisation Partner Firms	55 days		INTERVENE
73	ORDER/PRODUCE/RECEIVE PRE-PRODUCTION BATCH: For Pivotal Trials/Commercial Evaluation	25 days		
74	**MILESTONE: PRE PRODUCTION PRODUCT FOR PILOT TRIALS AND COMMERCIAL EVALUATION RECEIVED**			**Friday 17 April 2015**

75	**ETHICAL APPROVALS, TRIALS AND NOTIFIED BODY**			
76	PRE GRANT: FURTHER EX VIVO STUDY IN RESECTED HEALTHY STOMACHS (GASTRIC MUCOSA). Revise and ratify protocol. Apply for ethical clearance	55 days		23/02/11 extended for 1 year 23/02/12
77	IN VITRO evaluation in gastric fluid and sputum	25 days		May 2013
78	PILOT TRIAL - IN VIVO GASTRIC SURGERY. Draft and ratify protocol. Apply for ethical clearance	35 days		April 2015
79	PILOT TRIAL - IN VIVO ENTERAL FEEDING. Draft and ratify protocol. Apply for ethical clearance	35 days		April 2015
82	CONDUCT FURTHER EX VIVO HUMAN GASTRIC MUCOSA STUDY USING HNGT V2 (Ethical clearance granted). Collate and analyse results	110 days	October 2012	February 2013
83	**MILESTONE: EXTENDED EX VIVO GASTRIC MUCOSA STUDY COMPLETED**			**February 2013**
84	CONDUCT IN VITRO evaluation in gastric fluid and sputum	25 days	Feb 2013	July 2013
85	**MILESTONE: IN VITRO EVALUATION IN GASTRIC FLUID AND SPUTUM**			**July 2013**
86	TRIAL DATA AND ANALYSIS (X2) SUBMITTED TO/CONSIDERED BY NOTIFIED BODY: Cleared for Pilot Trials	45 days		Feb 2015
87	CONDUCT PILOT TRIAL - IN VIVO GASTRIC SURGERY USING HNGT V4. Collate and analyse results	65 days	April 2015	June 2015
88	**MILESTONE: IN VIVO PILOT TRIAL - GASTRIC SURGERY - COMPLETED**			**June 2015**
89	CONDUCT PILOT TRIAL - IN VIVO ENTERAL FEEDING USING HNGT V4. Collate and analyse results	75 days	? post doc and post award	
90	**MILESTONE: IN VIVO PILOT TRIAL - ENTERAL FEEDING - COMPLETED**		? post doc and post award	
101	**MILESTONE: REGULATORY CLEARANCE (CE MARK) GRANTED BY NOTIFIED BODY**		? post doc and post award	

102	**COMMERCIAL**			
103	Identify & Recruit Commercial Consultant (CC)	15 days	Wed 13/07/11	Tue 02/08/11 DY appointed for 3 years
104	Manufacturing Partner Evaluation and Selection	60 days	Wed 12/10/11 January 2014	Tue 03/01/12 Arrotek approved for v 2 Intervene approved v3
105	Potential major commercial partners (licensees) identified	80 days	April 2013	June 2013
106	Develop costed Bills of Materials (BOMs) for LIGNT v3	110 days	Feb 2015	June 2015
107	Develop costed Bills of Materials (BOMs) for LIGNT v3	110 days	Feb 2015	June 2015
108	Develop and Work-up Licensing Strategy/Deal	30 days	April 2015	June 2015
109	Develop Pricing Strategy	20 days	April 2015	June 2015
110	Negotiation of pre-commercial position with UoH	30 days	April 2015	June 2015
111	Approaches to/discussions with potential commercial partners/licensees	100 days	October 2013	January 2014 INTERVENE
112	**MILESTONE: SELECTED POTENTIAL COMMERCIAL PARTNERS DISCUSSIONS ADVANCED**			**Fri 04/07/15**

113	**QUALITY MANAGEMENT SYSTEM (QMS)**			
114	Identify & Recruit QMS Consultants (QMSC): Prepare Documentation to ISO 13485 and Train Team	50 days	Wed 14/12/11	Tue 21/02/12 DY prepared initial documentation – MS and BE initial training, team training 18/07/12
115	ISO 13485 basic implementation and training; Design History File live	45 days	Wed 22/02/12	Tue 24/04/12 ongoing
116	Documentation for QMS to ISO 13485: drafting and assembly; applicable electrical standards incorporated	110 days	Wed 28/03/13	Tue 28/08/13
117	**MILESTONE: QMS DOCUMENTATION DRAFTED AND ASSEMBLED**			**Wed 29/08/12** **Done in draft**
118	**MILESTONE: QMS BASIC IMPLEMENTATION**			Wed 29/08/12
119	QMS complete and fully implemented including electrical standards	75 days	Wed 29/08/12	Tue 11/12/12
120	**MILESTONE: QMS FULLY IMPLEMENTED**			**11/12/12**

121	**PATIENT/CARER/USER LIAISON GROUP**			
122	Patient/carer/user liaison group identified/recruited/established	60 days	Wed 21/09/11	Tue 13/12/11
123	**MILESTONE: PATIENT/CARER/USER LIAISON GROUP ESTABLISHED**			**Wed 14/12/11** achieved
124	Liaison group review meeting	1 day	Wed 18/01/12	Wed 18/01/12
125	Liaison group review meeting	1 day	Wed 28/03/12	Wed 28/03/12 Cancelled contact by phone and email
126	Liaison group review meeting	1 day	Thu 09/08/12	Thu 09/08/12
127	Liaison group newsletter	30 days		November 2012
128	Liaison group review meeting	1 day		March 2013
129	Liaison group newsletter	30 day		July 2013
130	Liaison group review meeting	1 day		December 2013
131	Liaison group review meeting	1 day		April 2014
132	Liaison group newsletter	30 day		Oct 2014
133	Liaison group review meeting	1 day		Jan 2015
134	Liaison group review evaluation meeting	1 day		June 2015
	QUARTERLY TEAM REVIEW MEETINGS			
	Kick-off team review meeting	1 day	Mon 18/07/11	Mon 18/07/11
	Quarterly team meeting	1 day	Wed 19/10/11	Wed 19/10/11
	Quarterly team meeting	1 day	Wed 25/01/12	Wed 25/01/12
	Quarterly team meeting	1 day	Wed 02/05/12	Wed 02/05/12
	Quarterly team meeting	1 day	Wed 18/07/12	Wed 18/07/12
	Quarterly team meeting	1 day	Wed 24/10/12	Wed 24/10/12
	Quarterly team meeting	1 day	Wed 16/01/13	Wed 16/01/13
	Quarterly team meeting	1 day	Wed 24/04/13	Wed 24/04/13
	Quarterly team meeting	1 day	Wed 24/07/13	Wed 24/07/13
	Quarterly team meeting	1 day	Wed 16/10/13	Wed 16/10/13
	Quarterly team meeting	1 day	Wed 15/01/14	Wed 15/01/14
	Quarterly team meeting	1 day	Wed 16/04/14	Wed 16/04/14
	Quarterly team meeting	1 day	Wed 25/06/14	Wed 25/06/14
	Quarterly team meeting	1 day	Wed 24/10/14	Wed 24/10/14
	Quarterly team meeting	1 day	Wed 21/01/15	Wed 21/01/15
	Quarterly team meeting	1 day	Wed 24/04/15	Wed 24/04/15
	Quarterly team meeting	1 day	Wed 25/06/15	Wed 25/06/15
	MILESTONE: END OF PROJECT	**0 days**	**Fri 03/07/15**	**Fri 03/07/15**

Appendix 22: Information sheet for User Advisory Group

NIHR Nasogastric Tube Project
Information for User Advisory Group

Feeding through a tube passed through the nose into the stomach is very widely used. It is the best method of feeding patients of all ages who temporarily cannot feed normally and the procedure may be taught to parents and carers. Such tubes are also used to increase patient safety during operations. However, making sure the feeding tube is in the right place is very difficult and has to be checked each time a tube is inserted and before every feed. Tubes used currently cannot indicate their position and determining this involves sampling stomach contents to test for acidity which can be difficult and uncertain.

A team of researchers at the University of Hull (the Team) are developing a new tube which can self-indicate its location within the human body. Handmade prototypes show that the new tube works. It is very soft and has a 'stripe' on the tip which is chemically sensitive to stomach contents. The 'stripe', sends a signal to an indicator outside the body which tells the carer whether or not the tube is in the stomach.

The Team has been awarded a grant from the NHS to fund a three year project to develop a manufactured prototype of the new tube. This prototype will be submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) for approval before testing on patients in pilot studies prior to licensing.

A User Advisory Group is being recruited to work with the Team to assist in developing the final product to ensure that it is easy to use and manipulate as well as being aesthetically pleasing. The User Advisory Group will also advise on the content and presentation of patient information sheets in the later stages of the project. It is intended that the User Advisory Group will include parents of children who receive or have received nasogastric feeds, adolescent and adult patients who administer their own feeds, carers and professional users including nurses. The group will be led by Barbara Elliott who is a nurse and the Principle Investigator on the project.

The User Group will meet at University of Hull 4 times a year over the course of the project. Meetings will last no more than 2 hours and refreshments will be provided. Travel and other costs will be reimbursed and there will be a small payment for time spent at the meetings.

If you are interested in participating in this group please contact:
Barbara Elliott on 01482 464518 or email b.e.elliott@hull.ac.uk

University of Hull
Faculty of Health and Social Care • July 2013

Bulletin

Information and Invitation Edition

Location Indicating Nasogastric Tube (LINGT) Project

Making it easier to use a nasogastric tube

The LINGT project is developing a nasogastric tube which self indicates its position to ensure greater patient safety and reduce distress for patients and carers.

What is a nasogastric tube?

A nasogastric tube is a fine tube which is inserted into the nose and gently pushed down the back of the throat, down the gullet (oesophagus) and into the stomach. The tube is sometimes inserted through the mouth, instead of the nose.

Why is it needed?

The tube has a number of uses, but it is mostly used for feeding. Anyone who cannot swallow in the normal way, such as premature babies, patients who are seriously ill or patients who have very recently had a stroke, can be given liquid food through a nasogastic tube directly into their stomach. Tubes are also used to drain the stomach before certain types of operations. Tubes may be used for a short time or over a period of weeks and sometimes months.

So, what is the problem?

Feeding cannot begin until it is certain that the tube is in the stomach.

The position can be checked with an xray, but that is not convenient or appropriate for many patients. So the recommended procedure is to withdraw a small amount of fluid from the stomach and test it with special paper. The paper changes colour depending on how acidic the fluid is. Stomach contents are acidic.

The problem can be in getting fluid from the stomach to do the test and interpreting the colour changes of the paper.

The LINGT Project is developing a special type of tube whose position is much easier and more certain to check. When this tube is inserted into the stomach, a sensor on the tip generates a tiny electric current which is detected by an indicator box attached to the other end of the tube, outside of the patient. A signal (light and/or sound) on the indicator box verifies correct placement. The design of both the tube and the box is underway.

What people have said so far.....

Feedback from meetings has emphasised the importance of involving carers and professionals. The information given has already been used in developing the risk assessment document, important for future patient safety, and highlighting the need to review the training and information available to users. People have also shared their ideas about the design of the indicator box which are listed below.

»»»»» Design of the indicator box «««««

What would be the appropriate size of the box?

- Mobile phone size or slightly larger
- Not small and fiddly
- Fit in a baby bag
- Fit in a pocket

And about the batteries

- Batteries might get lost
- Should not be able to use batteries for other devices

What needs to be included in the design

- On/off button and screen
- Date and time (useful to show battery is working)
- Low battery indicator
- Needs to be robust but lightweight and not drag on the tube
- Simple connector
- Enable parent-baby contact while feeding
- May be put on table while feeding, so non-slip
- As simple as possible - no need to interpret results
- More than one method to indicate the tube is in the right place
    - *words (yes/no)*
    - *colours (green=correct, red=stop)*
    - *tick/cross, sad/smiley face*
    - *vibration, useful for people with sight or hearing problems*
    - *buzzer*
    - *not sounds (hospitals are noisy places)*

»»»»» Who is involved in the LINGT Project? »»»»»

Some years ago, while working as a nurse on children's wards, Barbara Elliott recognised the problems of trying to check the position of nasogastric tubes. Barbara went on to work with a fellow nurse and other university and clinical colleagues to consider ways to solve these problems.

It has taken a number of years and achievements so far have been:

- LINGT research team formed
- Initial funding awarded by Yorkshire Concept
- Further funding awarded by National Institute for Health Research, Invention for Innovation (i4i) programme
- Initial prototype tubes developed and manufactured
- Links with professional and lay users established
- Indicator box developed
- Quality Management System established
- Patents applied for

Members of the LINGT research team come from a variety of backgrounds:

Barbara Elliott is the Principal Investigator (team leader) and is a Senior Lecturer in the Faculty of Health and Social Care, University of Hull.

Professor John Greenman is a Biomedical Scientist and Head of the School of Biological, Biomedical and Environmental Sciences and Director of Research.

Dr Jay Wadhawan is an Electrochemist and Senior Lecturer in the Department of Chemistry.

Dr Monika Schoenleber is a Chemist and Research Associate on the LINGT project.

Dr Robert Singh is the Commercial Development Officer, University of Hull.

Professor John MacFie is a Consultant Surgeon and Clinical Supervisor.

Professor David Young is an independent Business Consultant.

Professor Linda Shields is nurse advisor (now living and working in Australia).

Barbara Elliott, Robert Singh and Monika Schoenleber

Professor John Greenman

The project will come to an end in July 2014. At the end of the project, the aim is to have a self indicating nasogastric tube which is patented, ready for licencing by a commercial partner for large scale testing and manufacture.

The team cannot predict how long it will take before the new tubes will be available for patient use on the wards and in homes, but they are grateful to local people and professionals who have been helping to take this development project forward.

Latest news

Barbara Elliott and Monika Schoenleber have undertaken a series of clinical studies. Patients undergoing surgery for the management of obesity were asked if the LINGT tube could be tested on any stomach tissue removed during their operation. Nineteen patients agreed and results so far have been promising.

Expenses

Expenses are available and can be paid on the day of meetings. Payment for taxis, petrol, bus fares, childcare or other carer expenses can be organised. Please do not be 'out of pocket' as your help is important and valued.

Are you interested in helping?

The team want to ensure that people who have experience of, or who care for individuals using nasogastric tubes are involved with the project. They have already met with nurses and parents who have real experience of using nasaogastric tubes and have gathered information which will be used in the project.

If you have experience of using a nasogastric tube or caring for someone with a nasogastic tube, and are interested in getting involved with the project, please contact Barbara Elliott (contact details below).

The team plan to hold further meetings. However, group meetings are not for everyone and may not be convenient; so individual meetings or contact through letter, email or telephone can be arranged. Project Bulletins will be circulated regularly to keep participants notified of progress.

If you would like this information in a different format, please contact us.

»»»»» Contact details «««««

Faculty of Health and Social Care
Dearne Building
University of Hull
Hull
HU6 7RX

Barbara Elliott, Principal Investigator
LINGT Project

b.e.elliott@hull.ac.uk
01482 464518

www.hull.ac.uk/fhsc

This bulletin presents independent research funded by the National Institute for Health Research (NIHR) Invention for Innovation (i4i) Programme. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

University of Hull
Faculty of Health and Social Care

Bulletin 3 • October 2014

Location Indicating Nasogastric Tube (LINGT) Project

Welcome to the third bulletin

Clinical evaluation

A second round of clinical evaluation studies took place at the start of 2014. Twenty patients with nasogastric tubes in place kindly agreed to donate some gastric fluid. Samples were collected on the wards in Hull and Scarborough and Monika tested the prototype tubes in these samples in the laboratory.

These experiments helped to improve the functioning of the tube and we are very grateful to all the patients who took part.

A reminder about the project and how you can help

The LINGT project is developing a nasogastric tube which self indicates its position in the stomach.

By the end of the project, in July 2015, we aim to have a self indicating nasogastric tube which is patented, ready for licensing by a commercial partner for large scale testing and manufacture.

»»»»We will 'keep you posted' with further Bulletins»»»»

Awards

The LINGT project was shortlisted for two prestigious awards, the European Universal Biotech Innovation Awards and the Medipex NHS Innovation Awards. Unfortunately the project did not win but reaching the finals was a great achievement and good publicity for the project.

Monika and Barbara receiving the runner up prize in the Medical Devices and Diagnostics category at the Medipex Awards Dinner

How feedback from users and carers continues to be part of the work

Your comments and suggestions so far have helped us in designing the Indicator Box which will attach to the end of the nasogastric tube and show whether the tip of the tube is in the stomach. A company is now manufacturing the Indicator Boxes to be used in the next clinical evaluation studies.

Your comments will also be considered and used in the information and training packages for professionals, users and carers.

We will be needing your help to:

- Continue to tell us about procedures you use for inserting nasogastric tubes, care of the tube and feeding.
- Work with us on information for research participants for the next round of clinical evaluation studies.
- Review progress on the indicator box.
- Review how we are doing in our user and carer involvment work. What could we be doing better?

Thank you!

If you would like the Bulletin in a different format, please contact us.

Previous Bulletins can be obtained through the LINGT office (contact details below).

»»»»» *Contact details* «««««

Barbara Elliott, Principal Investigator, LINGT Project
Faculty of Health and Social Care
University of Hull, Hull HU6 7RX

b.e.elliott@hull.ac.uk • 01482 464518 • www.hull.ac.uk/fhsc

Design freeze

A company has been appointed to manufacture the new nasogastric tubes. This company already manufactures and supplies nasogastric tubes to the National Health Service and has considerable experience in developing new devices.

A special room has been created in the University where the special sensors can be applied to the prototype tubes before they are packaged and sterilised ready for testing on patients.

Jeanine Fisher working in the new lab with the final prototype tubes

Farewell to Rob and Monika

The team have sadly said goodbye to Dr Robert Singh who has a new job at the University of Essex. Rob's replacement is Dr Jeev Mantotta-Maxted who is already making a great contribution to the project. Dr Monika Schoenleber's work on the project was completed in July and she has joined her husband in Oxford. We wish both Monika and Rob every success for the future.

Your experiences and advice can help

Barbara Elliott and team have been meeting with nurses, patients and parents who have experience of using nasogastric tube.

If you know of someone who has experience of using nasogastric tubes and might be interested in hearing more, please get in touch with Barbara (contact details below).

Expenses to attend meetings are available and can be paid on the day. We can organise taxis, pay for petrol or bus fares. Payment can also be arranged for childcare or carer expenses. Just let us know. Please do not be 'out of pocket'. We value your help.

We hope to hold further meetings (group and individual meetings) or you can contact us by letter, email or telephone.

This bulletin presents independent research funded by the National Institute for Health Research (NIHR) Invention for Innovation (i4i) Programme. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

NHS National Institute for Health Research

Appendix 25: User Network Activity Table

Date of Report: 16 October 2013 Report Produced by:Barbara Elliott

	Team member	Aug 2013	Sept 2013	Oct 2013
Strategy	BE	Continue to review and monitor	Continue to review and monitor	Revise in view of comments
Bulletin	BE	NIHR i4i programme approved wording on Bulletin 2 and Information and Invitation Bulletin	Bulletin 2 and Information and Invitation Bulletin circulated to all members of the User network. Information and Invitation Bulletin given out at HEYTH Innovation Day 27 September 2013 Used for recruitment of patients to study 2 (gastric fluid and sputum)	Bulletins sent to Prof Watson for inclusion in FHSC information Develop Bulletin 3
Membership expansion	BE	Follow up 2 new members Explore the potential for a questionnaire for users/carers who would like to give feedback but do not want to join a group	Research Nurse from ICU recruited to User Network. Adult with experience of NG recruited	Meetings with new members arranged
Communications with members including meetings	BE	Letters sent to lay users with update and copies of Bulletins	Professional users sent email to arrange next meeting	Meetings to be held 24 Oct lay users

				7 Nov Professional users
Analysis of feedback	BE	Feedback included in URS		Ensure information from ongoing meetings is collated, analysed and fed into project and this process is fed back to the u/c network.
Identifying Resources and working towards publication	BE	ongoing	Ongoing Bibliography available on t drive in u/c folder	Continue to add to bibliography and save on refworks Commence work on paper for conf
Evaluation		ongoing	ongoing	Ongoing
Reflection on activity	Project Team	ongoing	Reflection file in filing cabinet in LINGT office –	Activity table included in Quarterly Review Meeting
Other				

Appendix 26: User Requirement Specification

DOCUMENT AUTHOR: **Barbara Elliott**

DOCUMENT APPROVAL

Approval: **Date**: 16 April 2014

MONIKA SCHOENLEBER

Controlling Manager

Approval: **Date**: 16 April 2014

BARBARA ELLIOTT

Project Leader

DISTRIBUTION LIST

Recipients:
Project Leader
Controlling Manager
Nominated Deputy Controlling Manager
Chief Electrochemist
Project Surgeon
Internal Auditor
Project Administrator

REVISION HISTORY			
Revision Level	**Reason For Change**	**Revision Initiated By**	**Issue Date**
0	**New Procedure**	**BEE**	**26.02.13**
1	Update	BEE	**26.07.13**

2	update	BEE	10.10.13
3	update	BEE	27.03.14
4	update	MS	10.05.14

CONTENTS

- **5.8** Mains/battery power
- **5.9** Warnings/alarms e.g. low power
- **5.10** Tests to relevant ISO standards e.g. ISO 60601
- **5.11** Ergonomics

6. Risk analysis

- **6.1** Key risk factors for existing and new product
- **6.2** Documentation of risk factors

7. Development

- **7.1** Product design for function and manufacture
- **7.2** Tooling and assembly jig design and validation
- **7.3** Development costs including engineering time
- **7.4** Materials
- **7.5** Tip form/hole punch/printing
- **7.6** Electrode/interface
- **7.7** Connectors/cabling/interface with box
- **7.8** Sterilisation validation

8. Project

- **8.1** Project scope/goals/objectives
- **8.2** Project deliverables
- **8.3** Project phases and milestones
- **8.4** Project team/communication etc

9. Regulatory requirements

- **9.1** Project file
- **9.2** Validation data
- **9.3** Sterilisation validation
- **9.4** Approvals to relevant ISO standards
- **9.5** Data required for CE mark

10. Clinical trial requirements

- **10.1** Proof of concept study
- **10.2** Target patients and study requirements

11. References

1. BACKGROUND/MARKET NEED/CLINICAL NEED

1.1 Current market practice

Tubes inserted into the stomach through the nose (nasogastric) or mouth (orogastric) are frequently used in clinical practice. Nasogastric tubes (NGT) are used in patients of all ages for the delivery of nutritional support and/or medication, decompression of the gastrointestinal tract or diagnosis and assessment. Orogastric tubes are less well tolerated and are used when the nasal passages are inaccessible for example after facial injury or surgery and most commonly in neonates who are obligate nose breathers.

1.2 Issues with current market practice

Verification of correct placement can be extremely difficult and must be undertaken after insertion and before each feed or administration of medication. Misplacement is common especially in children and has been reported in up 21% of patients (Ellett et al 2005). Misplacement in the oesophagus may cause intolerance of feeds and NGT erroneously placed in the respiratory tract can cause serious complications and death. Between 2005 and 2011 staff in England and Wales reported 21 deaths and 79 cases of harm resulting from feeding into the lungs through misplaced NGT (NPSA 2011).

1.3 Why is a new product required?

This harm is considered entirely preventable and in March 2011 misplaced nasogastric tubes not detected prior to feeding was confirmed by the Department of Health as being a “never event” and this problem remains on the 2012/2013 list of “Never Events” (DH 2012). Never events are serious avoidable events that cause patients harm and should never happen because there are guidelines in place to ensure that they are avoided. Current guidance states that stomach aspirate should be tested for pH using pH indicator paper and feeding only delivered if pH between 1 and 5.5 (NPSA 2011). The second line test is X-ray although this is an expensive and hazardous method and therefore not suitable for regular use. The NPSA (2011) found that the single greatest cause of harm was due to misinterpretation of X-rays with 45 serious incidents including 12 deaths being due to this resulting in the NPSA issuing a further safety alert in March 2011 focussing on the safe interpretation of X-ray images. **It is clear therefore that there is an urgent need for a safe, effective, bedside method for detecting the position of nasogastric tubes.**

1.4 Clinical Objective for the product

To fulfil an unmet clinical need by developing an effective, sensitive and reliable NGT which self-indicates its position thus ensuring greater safety with concomitant reduced distress both to patients and carers. Because it will be safer, easier and quicker to use than currently available techniques, the University of Hull Location Indicating Nasogastric Tube (UOHLINGT) will also be cost effective.

1.5 Evidence that there would be market requirement/acceptance of new product

The sections above describe the safety issues with conventional practice and this clinical problem was confirmed by the medical device manufacturers with whom we discussed the UOHLINGT. However, none would progress licensing discussions without clinical evidence of the effectiveness of UOHLINGT and hence the proposal for the current project funding was developed. Over time the UOHLINGT should become the first choice or mandatory for most cases as ‘best practice’ supplanting current recommendations. This will be justified on safety grounds reinforced by significant cost savings from reduced morbidity and shorter procedure (staff) times. Increased reliability with de-skilling will enable more lay carers to be taught the procedure facilitating earlier discharge and increased home care. Reduced anxiety and time savings are persuasive benefits and new medical device products offering such a profile have a good history of success.

Viasys’s Cortrak system for duodenal tube placement utilises an external scanner to detect placement of the tube. It has the disadvantage of requiring an additional high-value piece of equipment (the external scanner) and an experienced operative. It does not represent a competitor to the UOHLINGT but it does serve to indicate costs that the market will accept in order to mitigate risk of misplacement. Cortrak NGT’s cost in the region of $39 each (the scanner is usually supplied at additional cost >$10k). In the USA, this still represents a cheaper alternative to X-ray confirmation of placement and so can provide a saving for insurance companies reimbursing medical costs.

1.6 Potential market requirement for new product

Current UK usage of nasogastric tubes is estimated by to be 1-12m per annum based on discussions with individual hospitals, British Association of Enteral Nutrition and NHS Purchasing and Supply and 3 large NGT manufacturers. Extrapolation of these figures provided by hospitals indicate usage between 1-6 million tubes per annum in the UK although feedback from companies indicate that the market could be substantially greater. Sales of the tubes are often combined with oral nutrition supplements and so obtaining precise figures is not possible. This situation was confirmed by the UK Head of Marketing for a leading international healthcare company that manufactures NGTs who indicated that they alone sold in the range of £5-10 million of NGTs in the UK per annum.

Including Europe and USA usage is estimated at 69 – 154m NG tubes pa worth £60 – 120m. Figures often conflict. Although there will be additional materials and process costs with UOHLINGT, it is envisaged that in commercial production, any additional increase in price would be offset by the reduction in risk associated with use of the UOHLINGT (including reduced risk of litigation). The additional components are low-cost and the UOHLINGT is being designed with a view to reducing the manufacturing process costs. The commercialised UOHLINGT will significantly affect clinical practice.

A market survey for University of Hull identified UK NGT suppliers including Intervene Ltd, Medicina, Vygon, Corpack Medsystems, Pennine Healthcare, Fresenius Kabi, Covidien, and GBUK Enteral (most operate internationally). Low cost PVC NGT (av. £0.30) are used for less than 10 days as they become brittle after this: tubes for slightly longer term use cost on average £1; and Polyurethane (PU) tubes suitable for use up to 4-6 weeks cost £4 - £10 or even more. Higher value PU tubes are favoured in Europe due to concerns over the phthalate plasticisers used in PVC NGT. Similar products are available globally; all share risks of misplacement and detection.

According to Freedom Of Information Act request 3476 filed with the NHS Business Services Authority in April 2013 and answered on 15th May, the top 5 brands of NGT over financial years 2011 and 2012 are as follows:- GBUK Enteral, Corpak MedSystems Ltd, Intervene Ltd, Medicina Ltd and Vygon (UK).

2. TARGET AUDIENCE/KEY DECISION MAKERS

2.1 Users: i.e. nurses, clinicians, patients

Naso or orogastric feeding is used extensively with babies in neonatal units and is the preferred method for providing nutritional support for critically ill patients of all ages. Current clinical practice demands that anaesthetists pass nasogastric tubes prior to all gastrointestinal surgery to decompress the stomach. Passing nasogastric and orogastric tubes is a very common clinical procedure in a range of clinical areas and enteral feeding of patients by either the nasogastric or orogastric route is now a common practice in nursing. The procedure is often taught to parents and other carers so that they can give nasogastric feeds to their children at home. Some patients pass tubes on themselves to deliver feeding.

2.2 Decision Makers: clinicians, NHS, purchasing, committees

The current project is funded by NHS through National Institute for Health Research (NIHR) Invention for Innovation (I4I) programme and thus has the support of the NHS.

3. INTELLECTUAL PROPERTY

3.1 Ownership of design/IP

The UOHLINGT is protected by a portfolio of international patents/patent applications outlined in table 1 below. The scope of protection is based around use of the redox agent to form the sensing mechanism of the tube.

TABLE 1: PATENT PROTECTION FOR UOHLINGT

PatentTitle	Country	Application Number	Filing Date	Priority Date	Status

Catheter with a Sensing Region for Redox Reactions	EUROPE	EP07733747.5	03/12/2008	08/06/2006	Filed
Catheter with a Sensing Region for Redox Reactions	Patent Co-operation Treaty (PCT)	PCT/GB2007/050326	08/06/2007	08/06/2006	Now entered regional phase
Catheter with a Sensing Region for Redox Reactions	Australia	AU2007255153	04/12/2008	08/06/2006	Granted
Catheter with a Sensing Region for Redox Reactions	United States of America	US 12/303,427	04/12/2008	08/06/2006	Granted
Catheter with a Sensing Regios for Redox Reactions	Canada	CA 2,654,338	04/12/2008	08/06/2006	Filed

Another patent application is under discussion in order to further strengthen this position.
Preliminary freedom to operate searches have not identified any impediment to commercialisation of the UOHLINGT based on the current device concept.

3.2 Unique Selling Points

The UOHLINGT will not require aspiration of stomach fluid which can be a difficult and messy process particularly with young babies. Observing colour changes on pH indicator paper can also be difficult and subtle colour change can make the decision uncertain for professional and lay carers. The UOHLINGT system will be quick, clean and easy to use with a definite visual "yes" or "no" indication on the indicator box so avoiding the anxiety of decision making for practitioners and carers. The purpose of the UOHLINGT Project is to develop a simple means for indicating where the tube tip has been placed so that feeding, or any other use, is not attempted until and unless the tube tip is known with certainty to have been correctly placed in the stomach. It will be evident that this device, successfully developed, will have the potential to save lives, reduce patient morbidity and reduce anxiety in those passing the tubes and delivering feeds.
The UOHLINGT technology provides an opportunity to produce an NGT that has a competitive position that differentiates is from the generic feeding tubes currently on the market.

3.3 Design input from: Users, Doctors, Designers, Manufacturers

This project was developed from user carer feedback on the problems of identifying the location of nasogastric tubes and the project team include a consultant surgeon and two nurses. Two groups of users are advising the project team: a professional user group consisting of 6 healthcare professionals (1 doctor, 4 nurses and a dietician) and a group of 4 lay users consisting of 3 parents who have delivered nasogastric feeds to their children at home and one adult patient who has recently received nasogastric feeds. Group and individual meetings have been held on a regular basis with members of the User Advisory Groups. A user carer strategy has been produced and user carer involvement is discussed at every project meeting and a record maintained. Opinions of the group regarding the development and design of the indicator box have fed into discussion with external companies and their views will be sought on final design decisions and information sheets

for forthcoming clinical studies. Lay and professional users have signed confidentiality agreements to ensure that the design is protected for future licensing to companies.

Advice on design and development of initial prototypes was obtained from Arrotek medical Ltd. INTERVENE Group Ltd are manufacturing final prototypes for clinical trials and providing input into design of final iteration of UOHLINGT.

4. KEY REQUIREMENTS FOR NEW TUBE DESIGN:

The UOHLINGT is a Class IIa medical device. It is a nasogastric tube which is capable of indicating the location into which it is placed. It is to be inserted through the nose into the stomach and secured to the nose or face of the patient to prevent inadvertent removal as indicated in figure 1.

4.1 Materials (e.g. silicone/polyurethane)

The tube is to be made of medical grade extruded polyurethane of a quality and flexibility at least as good as NGT in current use (shore hardness in the range of 60-80 A). The initial prototype tubes will be transparent so that the presence and nature of fluid in the tube can be assessed visually. Future tubes used for feeding will be opaque to comply with current practice of only feeding through opaque (usually yellow, white or orange) tubes.

4.2 Wire tube, requirements for wiring, impedance etc

The 2 conducting wires are to be made of medical grade stainless steel. The effect of the wire on the stiffness of the tube needs to be minimised. Ideally wires will be coextruded so that they are embedded in the wall of the tube without any significant effect on the internal or external diameter (figure 2). Current prototypes utilise 0.25 mm diameter single core stainless steel wire but 0.1 mm diameter stainless steel wire is suitable in terms of resistance and conductivity. Braided wires may be preferred in order to lock into the polyurethane and reduce electrical “noise”.

4.3 Electrodes

Two different designs have been tested in the laboratory. Both utilise a prototype tube with 3 lumens; a large central lumen for feed and 2 additional smaller lumens at adjacent edges of the tube to contain wires (although co-extrusion would be a more desirable option for the reasons stated above).

The preferred design option which has been tested extensively in the laboratory in artificial gastric juice and human gastric fluid involves the exposure of the conducting wires by cutting away the outer layer of polyurethane (skiving) on both sides of the tube. The length of exposed wire is 6mm. A full drawing of the design is included in appendix 1.

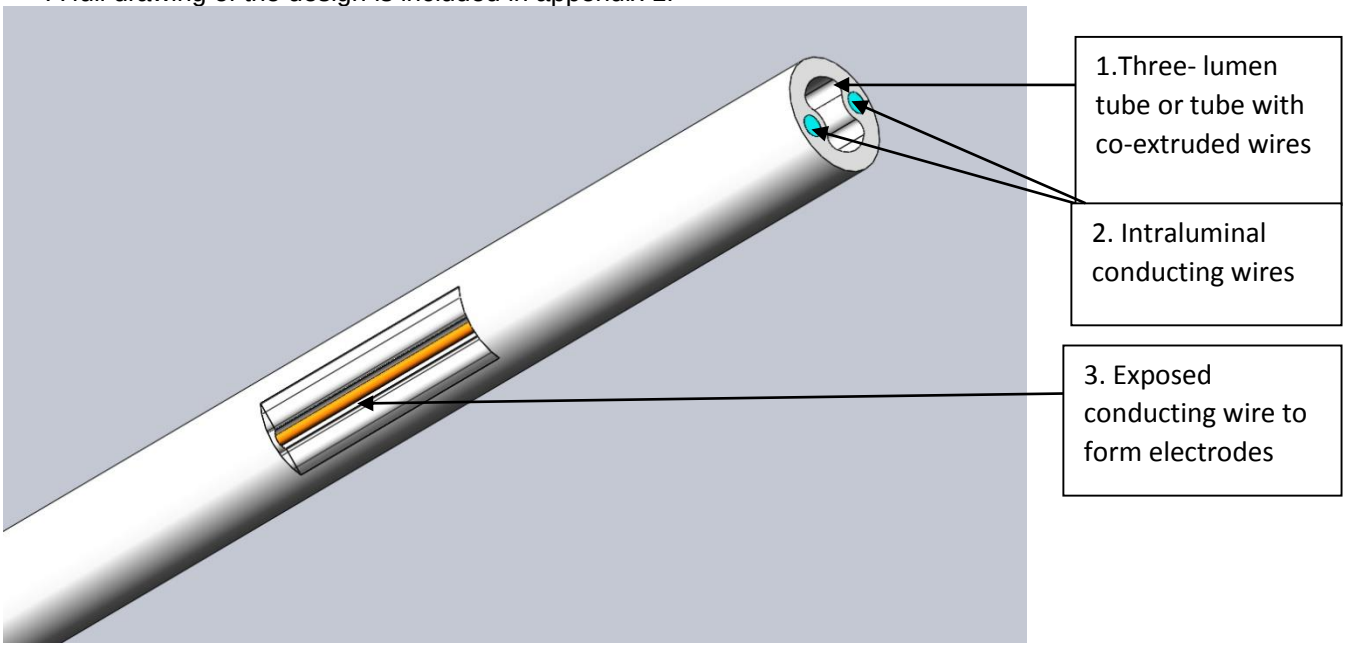


FIGURE 3: Tip of prototype UOHLINGT showing exposed wires which form electrodes

One electrode is the working electrode and the other acts as a reference electrode. The working electrode is coated with 288 µl of 10 mM vitamin K_1 dissolved in ethanol, which is air-dried. This is applied using a micro spotting machine that allows precise control of volumes used. The reference electrode is coated with medical grade silver-silver chloride paint which is cured in an oven set at +72ºC ±2 for 15 minutes.
It is desirable that the electrodes be 6mm in length and located 700 mm from the tip of a 12 Fr tube. In smaller tubes designed for feeding babies the electrodes will need to be only 100mm from the tip. Contact of the electrodes with the acidic environment within the stomach causes an electrochemical response which creates a small current which is passed along the wires.

4.4 Feeding ports

Four feeding ports are required for the initial prototypes, 2 on each side of the tube in the final 700 mm of the tube i.e. beyond the electrodes. As above these distances will be reduced when different sized tubes are manufactured. These feeding ports may be manufactured into a separately produced tube tip which is over moulded onto the body of the tube.

4.5 External connectors

The overall tube length may be up to 1200 mm but the length of tube outside the body varies. A luer lock connector with cap is over moulded to the external end of the tube to connect to a feeding syringe or pump. The conducting wires re-emerge from the tube wall near the external luer lock to enable connection to a suitable terminal point which will be linked to the indicator box. This may be immediately prior to the luer lock on a straight tube or a "Y" connection may be formed to allow one side for connection to feeding apparatus and one side for connection with the indicator box.

The indicator box must be capable of simple attachment, detachment and re-attachment to the tube as it is not left in situ during feeding but disconnected once a positive signal has been obtained. Because it is not desirable to increase the length of tubing outside the patient's body (for cosmetic and safety reasons i.e. risk of strangulation in babies) the design may require a flying lead from the indicator box that will be connected to the terminal on the UOHLINGT thus ensuring greater comfort and flexibility. However such a flying lead would add complexity and cost to the final product so a design avoiding such a requirement is the preferred option.

The connector requires development and the Team envisages a component somewhat similar in size and appearance to a Luer-lock connector, which will constitute a socket permanently attached to the tube. It will differ from an ordinary Luer-lock in requiring internal locating means so that physical and electrical connection between it (and thus the conductors in the tube wall) and the plug-end of the indicator box lead is easy, reliable and certain for unskilled users to achieve. The User Advisory Group has asked for a design which is as easy and simple as the connection to an Apple I-Pad charger which appears to use magnets. That precise design will, of course, be protected but a somewhat similar design approach, which is non-infringing, may be possible.
This development of the connector to the indicator box will require discussion and collaboration between manufacturers of the tube and indicator box.

4.6 Physical tests/requirements/e.g. pull tests/electrical tests

Testing of the physical qualities of the tube in terms of softness, strength, electrical conductivity will be required

4.7 Different sizes

It is intended that the UOHLINGT be supplied in a range of sizes from Fr 5 – Fr 18 but initial prototypes are required in Fr 12 as this is the size most commonly used for gastric decompression which is the next planned clinical investigation of the tubes.

4.8 Packaging/Sterilisation (ETO/Gamma?)/shelf life

The tube must be supplied sterile in clear, easy to peal packaging. Current NGT are sterilised using ethylene oxide and it is envisaged that this process be used for UOHLINGT. Tests have been conducted to determine that this process does not degrade the electrode coatings. Shelf life should be similar to tubes in current use to avoid wastage and unnecessary costs to the Health Service.

4.9 Length of time in body (hours/days)

From 1 hour to 30 days- one patient may receive several tubes, on a serial basis, during the course of treatment.

4.10 IFU

Under development with contributions from lay and professional users.

5. KEY REQUIREMENTS FOR SUPPORTING 'INDICATOR BOX'

The external indicator box of the UOHLINGT is an integral part of the system and it is essential that it is deployed on every occasion that a UOHLINGT is used. Development work on the indicator box is being carried out by a third party, Image to Implant, who have been contracted to develop the prototype indicator box for use in clinical evaluation.

5.1 Interface to tube

The indicator box is to be connected to the external end of the UOHLINGT after it has been inserted into the patient but before feeding commences. Once correct placement has been verified the indicator box can be removed and kept by the patient's bedside. As detailed above a flying lead from the indicator box may be necessary to connect to the terminal on the UOHLINGT but if direct connection is possible this would be preferred.

5.2 Size and shape

Whilst the indicator box does not have to be miniaturised, it is desirable that it is small enough and light enough to be held comfortably in one hand – quite possibly with the other hand and arm supporting the patient, especially in the case of small babies. By way of example only, we envisage the physical dimensions as being desirably similar to those of other commonly used hand-held electronic devices.

115 x 55 x 35 mm 118 gm Logitech mouse
115 x 60 x 10 mm 100 gm Blackberry phone
75 x 53 x 16 mm 40 gm Optimum Exceed diabetic glucose indicator

Information gained from our User Advisory Group suggest that they would like an indicator the size of a mobile phone or TV controller. They suggest that anything smaller could be lost but anything bigger could prove cumbersome if taking the child out or feeding them away from the home.

5.3 Signal output from tube/limit values

Voltammetric output in form of zero current potential using linear sweep is from a sensor at the tip of the tube. The aim is for a nurse or carer to place the tip of the tube in the stomach. The purpose of the indicator box is to indicate that this has been achieved or not achieved Linear sweep voltammetry (LSV), set to run from +0.4V to -0.4V with a scan rate of 0.1V/s; Estep 0.005V is utilised to obtain the potential at which the current reaches zero value (Ezcp). Experimental values obtained for output from the sensor are such that any value below +0.30V (Ezcp) is considered to be pH 5 or less (so we would assume in the stomach) and any value above +0.34V is considered to be pH 6 or over (so assumed not to be in the stomach). The detection range for the NGT to measure pH 5 or less and so verify stomach placement at Ezcp up to +0.32V ±0.02.

5.4 Indicator box display and Interpretation of indicator box display

The purpose of the indicator box display is to indicate that placement of the tip of the tube in the stomach has been achieved or not achieved. This needs to be as simple and clear as possible with no requirement for interpretation of numbers by the operator, for instance 'green' light when in stomach and 'red' light for tube elsewhere. Consideration of colour blindness must be made. In most Caucasian societies red/green colour blindness occurs in 10% of men; in Asians and Africans the figures are 5% and 4%, respectively. For these reasons the indicator will require appropriate flashing and continuous light signals.

For clinical trials it would be useful to also have a display and record of the current generated but this would not be required in the final device.

5.5 Storage of data

The final indicator box will not require data storage but if this is possible to include and relatively cheap to manufacture it would be desirable for clinical trials.

5.6 Compatibility to other electrical equipment

It is necessary to demonstrate that the UOHLINGT tube and indicator box system is safe to use in patients with other electrical device implants such as pacemakers and in operating theatres where electronic devices will be in use such as patient monitoring equipment and diathermy.

5.7 Mains/battery power

The UOHLINGT indicator box is powered by a battery which is a primary (disposable) Lithium ANSI/NEDA 1604LC of typical capacity 1,200 mAh having a nominal voltage of 9.6V from three 3.2V cells. This type of battery is generally referred to by lay persons as a PP9 battery. The battery is rectangular: are height 48.5 mm, length 26.5 mm, width 17.5 mm (or 1.9" x 1.0" x 0.68"). Both terminals are at one end and their centres are 12.7 mm apart. Because the UOHLINGT is powered

by a low voltage battery there are no issues relevant in respect of earth leakage current, enclosure leakage (touch) current or the quality of electrical insulation. The battery should have a duty life sufficient to provide readings on a 1-4-hourly basis for up to 6 months and which is user-replaceable. The battery is non-rechargeable and no means of connection to an external charging source is provided. An on/off switch is needed and to conserve battery life the indicator box will need to be provided with an "Auto-off" after a no-signal condition for 20 minutes. It is desirable that a duty life of 12 months for each indicator box meaning 270 hours battery life is desirable.

5.8 Warnings/alarms e.g. low power

The indicator box is provided with a visual indicator of battery condition which will also act as an indication that the system is working when switched on. A visual low battery indicator is essential.

5.9 Tests to relevant ISO standards e.g. ISO 60601

Image to Implant, the manufacturer of the Indicator Box, will ensure that the design and implementation of the design in the prototype units of the Indicator Box are verified, validated and tested by a suitable recognised Testing House accredited to ISO 13485;2012, IEC 60601 and any other applicable standards prior to its use in patients and will thereafter inform the University of Hull of the outcome.

5.10 Ergonomics

The indicator box needs to be:-

- Smooth with no sharp corners;
- Resistant to fluid ingress (say IP54/circa NEMA 3) as it will be used near liquid food;
- Easy to clean;
- Easy push button or surface moulded switching with no ventilation openings;
- Non slip under surface
- Overall intuitive use design for persons of only average intelligence.

6. RISK ANALYSIS

6.1 Key risk factors for existing and new product

The entire UOHLINGT Project was conceived as a risk containment and mitigation response to the risk issues intrinsic to the use of conventional NGT and the known limitations of prior risk containment strategies associated with them (Puntervoll et al 2002, NPSA 2011).

In current clinical practice, the Minor Risks (harms or injuries) identified for the UOHLINGT are acceptable in return for the benefits of reliable and known correct location which overcomes the risks and problems of conventional NGT.

A toxicologist has prepared reports on the risks associated with the materials used for the tube sensor and it is not envisaged that there will be any concerns regarding these.

6.2 Documentation of risk factors

A Risk Management file is under preparation with information prepared and analysed by the Quality Management Committee of the UOHLINGT Project Team including its BS EN ISO 13485:2012 compliant QMS Controlling Manager. These persons are identified below.

Risks have been analysed and assessed by the following:

The Quality Management Committee of the UOHLINGT Project Team comprising Barbara Elliott, Project Manager, Dr Monika Schoenleber, Controlling Manager, Dr Robert Singh, Knowledge Exchange (replaced by Dr Jeev Mantotta- Maxted on 1 April 2014), Professor David Young, External consultant to UOHLINGT Project Team (retired on 1 April 2014) and Prof John MacFie, Professor of Surgery/Consultant Surgeon, Academic Surgical Unit, Castle Hill Hospital, Hull.

7. DEVELOPMENT

7.1 Product design for function and manufacture
7.2 Tooling and assembly jig design and validation
7.3 Development costs including engineering time
7.4 Materials/
7.5 Tip form/hole punch/printing/
7.6 Electrode/interface
7.7 Connectors/cabling/interface with box
7.8 Sterilisation validation

All required for UOHLINGT tube as described in section 4. Number of units required 300 for clinical evaluation.

8. PROJECT DESCRIPTION

8.1 Project scope/goals/objectives

The overriding milestone for the end of the 48 month project is a pre-production UOHLINGT product, pilot trialled in preparation for regulatory clearance (CE marking), ready for licensing to a medical device company with appropriate manufacturing capability and global marketing and distribution.

8.2 Project deliverables

The principal deliverable is pilot batches of sufficient pre-production product to allow potential licensees to evaluate it with a view to their licensing marketing rights from University of Hull.

8.3 Project phases and milestones

This is a four year project which commenced in July 2011.

Milestones achieved so far:

Post-Doctorate Research Assistant (PDRA) recruited
Patient/carer/user liaison group established
HNGT v3 tube and indicator box completed
QMS documentation drafted and assembled
QMS basic implementation completed
Extended ex vivo gastric mucosa study completed on resected healthy stomachs to verify the chemistry in a manufactured prototype. 20 patients recruited 15 studies completed.
UOHLINGT v4 tube and indicator box completed

Next milestones to be achieved

QMS fully implemented and certified
UOHLINGT v5 final iteration tube and indicator box completed
MHRA clearance to conduct trials on patients
In vivo pilot trial – anaesthetised patients (in essence healthy volunteers)
In vivo pilot trial - enteral feeding
Pre production product for pivotal trials and commercial evaluation completed

Future Milestones

Regulatory clearance (CE mark) submission made to notified body
Overriding milestone: confirmation of regulatory clearance (CE mark) received
Potential commercial partner discussions advanced

8.4 Project team/communication

Mrs. Barbara E Elliott -Principal Investigator
Dr. Monika Schoenleber -Postdoctoral Research Associate
Dr Jeev Mantotta- Maxted - Knowledge Exchange Officer -Patent and Commercialisation
Professor John Greenman – Professor of Tumour Immunology, Biological scientist
Dr Jay Wadhawan – Chief electrochemist
Professor John MacFie – Consultant Surgeon
Prof Linda Shields – Nurse Advisor based in Australia

9. REGULATORY REQUIREMENTS

9.1 Project file
9.2 Validation data
9.3 Sterilisation validation
9.4 Approvals to relevant ISO standards
9.5 Data required for CE mark

10. CLINICAL TRIAL REQUIREMENTS

10.1 Proof of concept study

Extended ex vivo gastric mucosa study conducted October 2012 – January 2013 on resected healthy stomachs to verify the chemistry in a manufactured prototype. 20 patients recruited 15 studies completed. Laboratory testing of tube in 7 samples of human gastric fluid and 3 samples

of sputum conducted Sept – October 2013. Further studies on 5 samples of gastric fluid conducted March 2014.

10.2 Target patients and study requirements

Adult patients who require NGT for gastric decompression pre surgery where NGT are routinely passed in anaesthetised patients by an anaesthetist working under direct vision which ensures correct routing. The surgeon is able to confirm that the UOHLINGT is in the stomach by tactile means and as the tube is removed at end of surgery the patient has no discomfort. **One hundred patients on 2 hospital sites are to be recruited.** Ethical approvals currently being sought

The above study is to be followed by a ward-based enteral feeding pilot study will follow in 20-25 patients using very experienced specialist nutrition nurses familiar with passing NGT, to establish ease and speed of use. Informal agreement of the respective Trust managements for site use (as distinct from ethical clearance) has been reached and is currently being formalised. Separate US trials are not required under the 510k system for regulatory clearance.

11. REFERENCES

Department of Health (2012) Updated never events policy framework and data http://www.dh.gov.uk/health/2012/10/never-events/

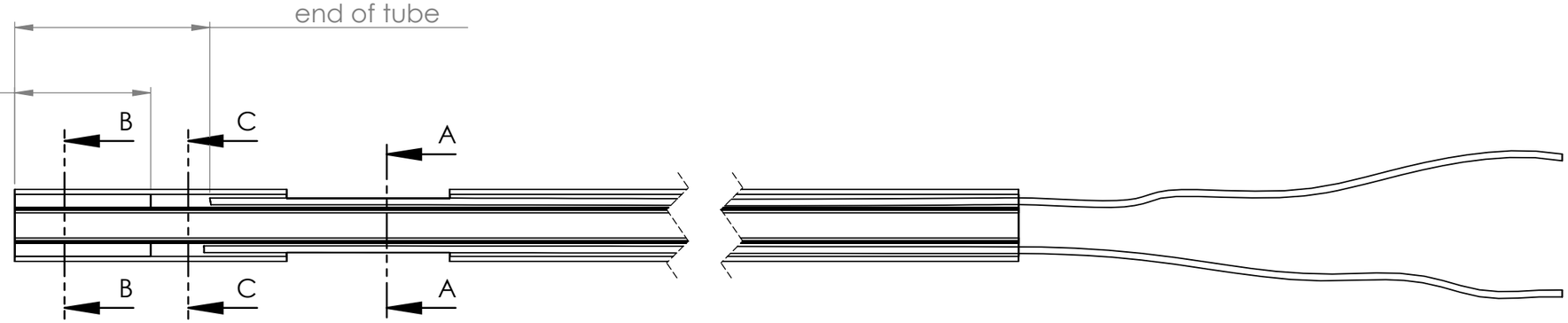
Ellett et al (2005) Gastric Tube Placement in Young Children, Clin. Nurs Res., 14, 238-252

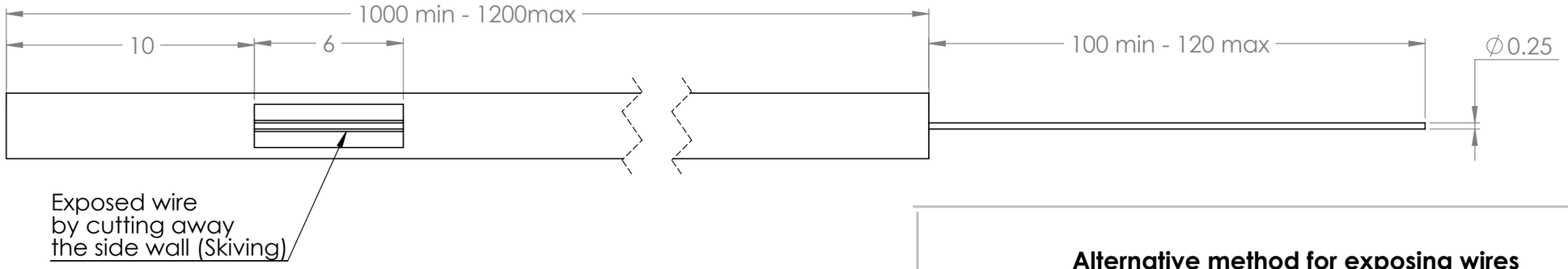
National Patient Safety Agency (2011) Reducing the harm caused by misplaced nasogastric feeding tubes in adults, children and infants http://www.nrls.npsa.nhs.uk/resources/type/alerts/?entryid45=129640&q=0%c2%acnasogastric+tube%c2%ac

Puntervoll SA, Soreida E, Jacowicz W, Bjelland E (2002) Rapid Detection of Oesophageal Intubation: take care when using colorimetric capnometry, Acta Anaesthesiol Scand. Vol 46 pp 455-7

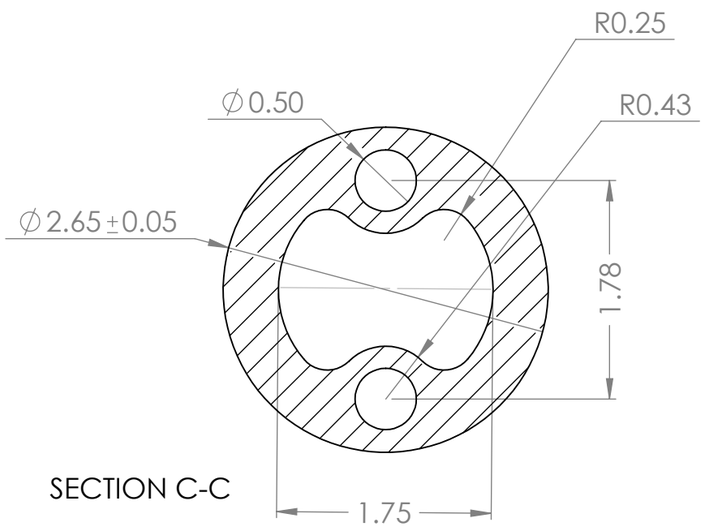
OPTIONAL
2x End Bungs
0.5 dia x5 long
push fit or glued with
aproved substance

Wire termination
6-8mm from
end of tube





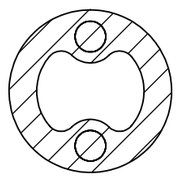
ALL DIMENSIONS in mm
and are REPRESENTATIVE
of a PROTOTYPE SAMPLE



SECTION C-C

SCALE 20 : 1

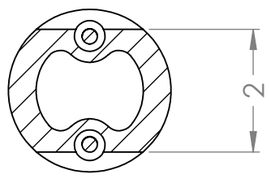
TUBE ONLY



SECTION B-B

SCALE 10 : 1

TUBE + END BUNGS

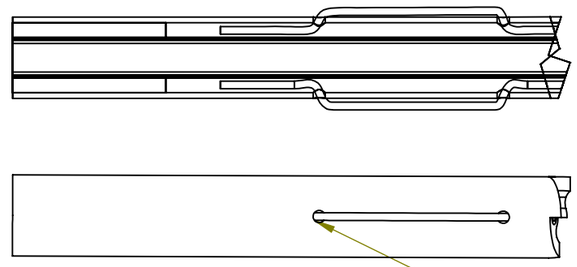


SECTION A-A

SCALE 10 : 1

TUBE + WIRES

Alternative method for exposing wires



All other dimensions
as per main drawing

Rev.	Date	Resp.	CO no. / Comment	Approved by
0	26/02/2014	B Elliott	First release	B Elliott

Drawn by: K Seward	Date Drawn: 26/02/2014	UNIVERSITY OF Hull	
Material	Alternative method for exposing wires	General linear tolerance	
First used in		General angular tolerance	
Item to be		Colour	Format: A3 / Scale: 5:1 / Unit: mm
Description: Location Indicating Nasogastric Tube (LINGT) -Option 1			Item no.-Rev.: 1001 - 0