UNIVERSITY OF HULL

A proof-of-concept study evaluating the role of emerging ultrasound technologies in the active surveillance of localised prostate cancer

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by

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Dedication

I dedicate this thesis to my husband and best friend, Trevor. You taught me to reach to the moon and back, and I did.

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"Success is not final; failure is not fatal: it is the courage to continue that counts."
Winston Churchill

Publications and Conferences

During the course of my PhD, I have co-authored the following articles, book chapter and e-learning for health session (listed in date order).

Parker, P. (2020) Sonographer-led contrast-enhanced ultrasound services. *RAD Magazine*, 47(549):11-12.

Parker, P. (2021) The world of medical ultrasound – A President's perspective. Available online: https://hospitalhealthcare.com/latest-issue-2021/radiology-and-imaging/the-world-of-medical-ultrasound-a-presidents-perspective/

Parker, P., Twiddy, M., Whybrow, P., Rigby, A. & Simms, M. (2021) The role of diagnostic ultrasound imaging for patients with known prostate cancer within an active surveillance pathway: A systematic review. *Ultrasound*, 30(1):4-17

Freeman S.J. & Parker, P.C. (2022) Ultrasound of the testes and male pelvis. In Davidson N, (4th ed) *Abdominal ultrasound. How, why and when*. United Kingdom: Elsevier, 229-264

Smith S, Parker T, Parker P. (2022) The justification of non-obstetric ultrasound referrals: A safe and effective practice. *Ultrasound*, 30(1):52-61

Parker, P., Edwards, H., Twiddy, M., Whybrow, P. & Rigby, A. (2023) Embedding new technology into clinical ultrasound practice: Is role extension for sonographers the key to improving patient pathways? *Ultrasound*, 31(2):84-90.

Parker, P.C., Patel, U., Britland, L. (2023) e-Learning for health. Session 17_03 Men's Health Ultrasound: TRUS and Transperineal Biopsy of the Prostate Gland https://portal.e-lfh.org.uk/

Schaer, S., Rakauskas, A., Dagher, J., La Rosa, S., Pensa, J., Brisbane, W., Marks, L., Kinnaird, A., Abouassaly, R., Klein, E., Parker, P., et al. (2023). Assessing cancer risk in the anterior part of the prostate using micro-ultrasound: validation of a novel distinct protocol. *World Journal of Urology*, 41(11):3325-3331.

Parker, P., Twiddy, M., Rigby, A., Whybrow, P. & Simms, M. (2024) Evaluating the Role of Ultrasound in Prostate Cancer trial – phase 1: Early experience of micro-ultrasound in the United Kingdom. *Ultrasound*, 1742271X231226302.

Conference and study event presentations

I have attended and presented as an invited speaker at the following conferences and study events (listed in date order)

British Medical Ultrasound Society (BMUS) Annual Scientific Meeting (ASM) December 2019. Harrogate

- Principles of extended ultrasound practice
- Prostate ultrasound
- Sonography as a profession. Where are we now?

University College Dublin and BMUS Study event, February 2020. Dublin

- New techniques in ultrasound imaging
- Top tips for testicular ultrasound

BMUS ASM (Online event), December 2020

- Covid-19 & The ultrasound department

Bracco Contrast Enhanced Ultrasound (online event), May 2021

- Contrast Enhanced Ultrasound Service in the workplace - The Hull University Teaching Hospital NHS Trust experience.

Humber and North Yorkshire Cancer Alliance, Prostate cancer study day, July 2021, Hull

- Changing Practice – How LATP Biopsy Works for Us

Australasian Society of Ultrasound in Medicine (ASUM), ASM (online event), November 2021

- Rapid Diagnostic Pathways: Challenges and Opportunities

Australasian Sonographers Association (ASA) ASM, (online event), April 2022

- Ultrasound around the world: What the profession looks like in the UK.

BMUS Professional Issues Study Day, May 2022, London

- Advanced and consultant level practice: the manager's perspective

University College Dublin and BMUS Study event, October 2022. Dublin

- Ultrasound Workforce: Tackling the challenges ahead.

BMUS ASM December 2022. Cardiff

- Presidents Welcome
- Interventional Ultrasound & Prostate Cancer: Is it more than a shot in the dark?
- Supporting Advanced and Consultant Practice
- ❖ Poster presentation: Early experience of micro-ultrasound prostate imaging

European Radiology Conference (ECR), February 2023, Vienna

- The appendix and the role of ultrasound

Australasian Sonographers Association, ASM, May 2023, Brisbane

- Career development opportunities for sonographers – is regulation a barrier?
- Innovations in ultrasound prostate cancer diagnosis and assessment

British Society of Uro-Radiologists and British Association of Urological Surgeons, Transperineal biopsy study day, September 2023, Harrogate

- Training in LATP as a sonographer
- Hands on workshop faculty member

Humber and North Yorkshire Integrated Care System, Primary Care practice, teaching and learning event, October 2023, Hull

- Ultrasound in cancer pathways

BMUS ASM December 2023. York

- Micro-ultrasound in prostate cancer. What? Why? So what?
- Addressing the challenges of recruitment of non-CASE accredited practitioners
- Hands on workshop faculty member – interventional ultrasound guided procedures

Canon Medical Ultrasound (online event), February 2024

- Innovations in interventional Ultrasound & Prostate Cancer

Society of Diagnostic Medical Sonography (SDMS - USA) (online event), June 2024

- Innovations in interventional Ultrasound & Prostate Cancer – the UK perspective

Abstract

Background

Although one in eight men will develop some form of prostate cancer (PCa) within their lifetime, not all PCa is of high-risk of progression. In such cases active surveillance (AS) provides an alternative to radical treatment (Hamdy et al., 2023; Wilt et al., 2020). However, inconsistencies in AS regimes exist (Merriel et al, 2019), and capacity for surveillance magnetic resonance imaging (MRI), required to identify progression, is limited. Novel high frequency ultrasound (microUS) potentially offers an alternative imaging solution in AS.

Aims

This proof-of-concept trial aimed to determine if there was a role for emerging ultrasound technologies in the monitoring of PCa in men on AS, and to better understand how this technology could be implemented and embedded into clinical practice.

Method

This prospective single-centre trial was undertaken in two discreet studies. Study 1 comprised of a cross-sectional study of 100 patients presenting with suspected PCa who underwent MRI and ultrasound (US) guided biopsy (phase 1), and a longitudinal study of 10 patients with low-risk disease managed on an AS pathway (phase 2). All patients underwent transrectal US imaging using both standard and microUS transducers. Images were retrospectively analysed by two reviewers and risk stratified. Agreement rates between reviewers, MRI, and histological outcomes post biopsy were calculated.

Study 2 was a longitudinal study of practitioner experience of the new technology, informed by normalisation process theory (NPT). Data was collected at three points during the study and analysed narratively.

Results

Study 1, phase 1: Agreement between individual reviewers and histology was poor and ranged from 26.7% to 56.7% for standard ultrasound and 25.9% to 56.7% for microUS. Sensitivity of standard ultrasound was calculated to be 48% with a specificity of 75%. A kappa value of 0.21 was determined by assessing the inter-rater reliability (IRR). Retrospective review of microUS had a sensitivity and specificity of 77% and 40%

respectively with a higher, but only fair, IRR kappa score of 0.31. Performance of microUS was improved when scored in real-time by two practitioners, with sensitivity and specificity of 73.3% and 53.8% respectively identified, and an improved IRR of 0.38 was determined when calculated as a weighted kappa.

Study 1, phase 2: Twenty follow-up scans were performed across 10 patients. Change in appearances at microUS was noted by one reviewer in one follow-up scan, but this change remained within the low-risk stratification. Little consistency between scores of the monitoring scans and the baseline assessment was identified, and a lack of clinical confidence in this test curtailed this study phase.

Study 2: Data from the initial survey identified positive engagement and support for microUS. However, findings from the subsequent surveys indicated that microUS was difficult to use and interpret. Evidence from this study suggests that microUS is not currently normalised into routine practice.

Conclusion

A role for ultrasound within the prostate cancer AS pathway has not been identified during this trial. However, study 1, phase 1 findings suggest that microUS could be used for screening in patients in whom MRI is contraindicated. Further research in this area is required.

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Abbreviations, acronyms, and glossary of technical terms

Abbreviation	Short descriptor	Description
Aplio i700	Canon Medical Systems, Crawley, UK	The standard ultrasound system supplied by Canon Medical Systems
AS	Active surveillance	Active surveillance is an aspect of deferred active treatment and is now the preferred term. The term is used to mean monitoring the organ of interest closely, with a plan to treat it if tests indicate that any cancer is developing or increasing in size. Active surveillance for prostate cancer can also be known as expectant management.
ASAP	Atypical small acinar proliferation	ASAP isn't a medical condition but is a term used to describe changes to prostate cells seen under the microscope, which are suggestive but not definitive for cancer. ASAP occurs at a rate of up to 5% on prostate biopsies. 30-40% of patients with ASAP may develop prostate cancer (PCa) within a 5-year period.
CAI	Computer assisted imaging	Vis-à-vis Artificial Intelligence: the ability of a computer or computer-controlled robot to perform tasks commonly associated with intelligent beings.
CEUS	Contrast enhanced ultrasound	Ultrasound imaging performed following intravenous injection of an ultrasound contrast agents. These are gas-filled microspheres, which reflect sound waves and enhance the ultrasound image, particularly useful to assess differences in perfusion within an organ.
csPCa	Clinically significant prostate cancer	Malignant change within the prostate gland with a Gleason score of 3+3 or 3+4 with a core length of less than 6 mm
DAT	Deferred active treatment	A pathway for patients who are suitable for curative treatment but in whom this can be safely delayed until such time the disease demonstrates signs of progression
Endocavity	Endocavity transducer	An ultrasound transducer specifically designed to be inserted into a body cavity such as the rectum.
ERUP Trial	Evaluating the role of ultrasound in prostate cancer trial	Acronym for the research trial undertaken for this PhD.

ExactVu™	Exact Imaging™ Markham, Canada	The micro-ultrasound platform supplied by Exact Imaging™.
FoP	Fear of progression	Describes the fear patients experience that the cancer will progress or return. It noted to be an appropriate response, although elevated levels can become dysfunctional, affecting well-being, quality of life, and social functioning.
gain	Overall gain	A method to alter the amount of amplification applied to all the ultrasound signals from any depth in the field of view.
GIRFT	Getting it right first time	A national programme designed to improve the treatment and care of patients through in-depth review of services, benchmarking, and presenting a data-driven evidence base to support change
Gleason Score	Histology assessment of the prostate	Gleason is a commonly used grading system for prostate cancer. The Gleason score examines the pattern of cancer cells in the prostate tissue, and how they look and act, compared with normal cells. There are 5 different patterns, graded from 1 to 5. Grades 1 and 2 look like normal prostate tissue.
HUTH	Hull University Teaching Hospitals NHS Trust	The hospital site which hosted and sponsored the ERUP trial research project.
IRR	Inter-rater reliability	The extent to which two or more raters (or reviewers) agree.
ISUP	International Society of Urological Pathologists	The ISUP Grade Group system which grades prostate cancer from 1 (least aggressive) to 5 (most aggressive).
LA	Local anaesthetic	Used in association with prostate biopsy procedures, typically LATP Biopsy.
MHz	Megahertz	Unit of sound frequency measurement
microUS	Micro-ultrasound	Micro-ultrasound is a novel high resolution ultrasound technology aiming to improve prostate imaging. It uses imaging frequencies of between 22 - 29 MHz
mL	millilitre	Volume measurement
mpMRI	Multiparametric MRI	Combining several different MRI techniques into a single scan session.
mpUS	Multiparametric Ultrasound	The use of different US parameters in combination in a bid to increase the accuracy of cancer diagnosis.

MRI	Magnetic resonance imaging	A diagnostic imaging modality that uses strong magnetic fields and radio waves to produce detailed images of the inside of the body.
ng/mL	nanograms (ng) per millilitre (mL)	Density of a PSA protein within a mL of blood
NoMAD tool	**N**ormalisation **M**e**A**sure **D**evelopment tool	A questionnaire of 23 survey items for assessing implementation processes from the perspective of professionals directly involved in the work of implementing complex interventions in healthcare.
NPT	Normalisation process theory	A conceptual framework for understanding and evaluating the processes (implementation) by which new health technologies and other complex interventions are routinely operationalised in everyday work (embedding) and sustained in practice (integration).
NPV	Negative predictive value	The ratio of subjects truly diagnosed as negative for a disease compared to all those who had negative test results.
PACS	Picture archiving and communication system	A medical imaging technology used to securely store and digitally transmit electronic images and associated radiology reports.
PAS	Patient administrative system	An electronic system for recording patient demographics and all patient encounters within the hospital organisation.
PCa	Prostate cancer	Malignant change within the prostate gland of any grade
PIN	Prostatic intraepithelial neoplasia	A condition defined by neoplastic growth of epithelial cells within pre-existing benign prostatic acini or ducts. It can be reported as high or low grade. As PIN satisfies almost all the requirements for a premalignant condition, high-grade PIN (HGPIN) is accepted as a precursor to prostate cancer. The incidence of isolated high-grade PIN averages 9% (range 4–16%) of prostate biopsies.
PI-RADS v2	Prostate Imaging–Reporting and Data System	A structured reporting scheme for multi-parametric prostate MRI in the evaluation of suspected prostate cancer in treatment naive prostate glands. Version 2 is currently widely adopted.

PSFU	Personalised stratified follow-up	A programme for moving follow-up care of patients from outpatient clinics to remote monitoring
PPV	Positive predictive value	The ratio of patients truly diagnosed as positive for a disease compared to all those who had positive test results.
PRI-MUS™	**P**rostate **R**isk **I**dentification-using **M**icro-**U**ltra**S**ound	An evidence-based protocol for identifying sonographic features of the prostate under micro-ultrasound to help direct and target biopsies.
PSA	**P**rostate **S**pecific **A**ntigen	A protein, produced by the prostate, elevated levels of which may indicate the presence of cancer. Reported as ng/mL.
PSAD	PSA density	A calculation performed at diagnostic imaging, usually MRI, and is the serum prostate specific antigen (PSA) level (ng/mL) divided by the volume of the prostate gland (mL), resulting in a value with the units, ng/mL
RP	Radical prostatectomy	A surgical procedure performed to remove the prostate gland and seminal vesicles (and adjacent lymph nodes if indicated at staging imaging) after a prostate cancer diagnosis
Standard US	Standard ultrasound	Diagnostic imaging with ultrasound emitted in the range of between 7 - 11 MHz
TCG	Time gain compensation	A method to normalise the ultrasound signal amplitude with time whilst compensating for depth.
TP Biopsy	Transperineal biopsy	A procedure undertaken using ultrasound guidance to take samples of the prostate. Access to the prostate is achieved via needle puncture of the perineum. It has a higher safety profile than that of transrectal biopsy.
TRUS Biopsy	Transrectal biopsy	A procedure undertaken using ultrasound guidance to take samples of the prostate. Access to the prostate is achieved via needle puncture of the rectum and is associated with a post procedure infection risk of approximately 4%.
US	Ultrasound	A diagnostic imaging modality that uses sound waves to create an image of part of the inside of the body.

Chapter 1 Introduction

1.1 Foreword

This thesis is an exploration into how patient care for men with low grade prostate cancer can be improved. The main theme relates to men being managed under an active surveillance regime and whether the inclusion of ultrasound in that pathway could bring any benefit. This thesis investigates whether the introduction of ultrasound may bring positive changes to outcomes and considers the impact on professionals delivering the service when transformations to diagnostic provisions are made.

The research study is entitled:

A proof-of-concept study evaluating the role of emerging ultrasound technologies in the active surveillance of localised prostate cancer.

With a short title of:

"Evaluating the Role of Ultrasound in Prostate Cancer (ERUP) trial."

The purpose of this research was to broaden the knowledge of ultrasound imaging in active surveillance and to investigate the role of the sonographer within the multidisciplinary team delivering this important prostate cancer pathway.

This chapter provides the context of the study and the background from which the research purpose has emerged. The target population is explained and a brief rationale for the study is presented.

1.2 Background

The detection of prostate cancer is increasing in the United Kingdom (UK) as well as globally (Merriel et al., 2019). This increase is led, in part, by prostate serum antigen (PSA) selective screening in the USA (Vasarainen et al., 2015) and the efforts to increase awareness of prostate cancer (PCa) by The Movember Foundation (Bruinsma et al., 2018) and Prostate Cancer UK (2024b) charities. High profile celebrities in the UK who have been diagnosed with PCa, such as Stephen Fry and Bill Turnbull, have

highlighted the prevalence of this common disease to men and their families leading to an improved understanding of the need to seek assessment (Kirby, 2018). The impact on the publics' awareness of PCa when prominent public figures publicise their own health status cannot be underestimated. Indeed, King Charles III's prostate diagnosis in January 2024, despite being benign in nature, resulted in a "1000% increase in visits to the NHS advice website" (NHSE, 2024b).

Despite the fact that one in eight men will develop some form of PCa within their lifetime, and that around 52,000 men in the UK will be diagnosed with PCa per year (Bruinsma et al., 2018; Prostate Cancer UK, 2024b), screening for PCa remains controversial. Measuring the prostate specific antigen (PSA) level within the blood stream is a good indicator of a prostate abnormality, but a raised PSA level alone is a poor predictor of what that pathology may be (Dasgupta & Kirby, 2012). Whilst there has been a global increase of three-times the incidence of PCa (Merriel & Gnanapragasam, 2019), the cancer specific mortality rate remains low at ≤ 1.5% (Dalela et al., 2017). It is reassuring to know that, despite this increase in incidence, up to two thirds of men now have low-risk cancer when newly diagnosed (Vasarainen et al., 2015).

1.3 Diagnosis and detection

The diagnosis of PCa is histological following a biopsy procedure. This procedure usually involves a transrectal ultrasound (TRUS) examination, which guides where appropriate biopsies of the prostate are taken, and, at the time of this PhD commencing, a TRUS guided biopsy via the rectum was the predominate investigation. TRUS biopsy is not without complications and is associated with serious post procedure infection and / or haemorrhage in between 0.5 -6.9% of cases (Drost et al., 2019). Given the high complication rate, there is a move towards safer, but more complex, transperineal prostate biopsies (Pilatz et al., 2021; Newman et al., 2022). Serious consideration of the implications of the invasive test and subsequent diagnosis should be given prior to PSA testing. Prior to PSA testing, men should be counselled so that they are aware of the range of possible outcomes, both from the investigations and the histology, and are consequently able to make an informed choice of

treatments available to them before embarking on a prostate cancer pathway (Merriel et al., 2019). As the Prostate Cancer UK charity (2024b) discusses, there are disadvantages to having a PSA test, particularly in isolation and they advise men, prior to being tested, to carefully consider their position:

> "If I was diagnosed with slow-growing prostate cancer that might never cause any problems, would I still want to have treatment, even though it could cause side effects? Or would I be comfortable having my cancer monitored instead?" (Prostate Cancer UK, 2024b)

Although low grade cancer can be monitored (NICE, 2021), high grade PCa does progress, metastasising to the bone (84%), distant lymph nodes (10.6%), liver (10.2%), and thorax (9.1%) (Gandaglia et al., 2014) and therefore the seriousness of a PCa diagnosis cannot be overlooked. Risk of disease progression, as well as stage of cancer upon diagnosis, are all important factors in managing patients and treatment choices. Treatment is varied with an emphasis on patient centred care, that is care focussing on individuals' health needs (Reynolds, 2009), rather than cancer staging to ensure a best fit for both patients and their families. PCa, however, is known to have a long lead time of 9.9 – 13.3 years before progression commonly occurs (Dasgupta & Kirby, 2012). Therefore, in men with low grade disease, consideration as to the side effects of treatment over risk of disease progression is required in the decision making process (NICE, 2021).

1.3.1 Classifying clinically significant cancer

Traditionally, PCa grades were described according to the Gleason Score, a system named for the pathologist who developed it in the 1970s (Gleason, 1977). Gleason identified that malignant cells could be categorised into 5 distinct patterns as they change from normal cells to poorly differentiated malignant cells (as depicted in Figure 1.1 below). The cells are graded on a scale of 1 to 5. Grade 1 cells resemble normal prostate tissue; those closest to 5 are considered "high-grade" and have mutated so much that they barely resemble normal cells. Gleason patterns 1 and 2 are no longer recorded and are considered normal. The Gleason score is composed of a primary (most predominant) grade plus a secondary (highest non-predominant) grade; the range for a primary or secondary grade is from 3 to 5. Prostate cancer is reported

as the sum of the Gleason grades followed, by the primary and secondary scores, and ranges from 6 to 10. For example, Gleason 8 (4 + 4) with higher scores indicating a more aggressive form of PCa (Kasivisvanathan et al., 2018).

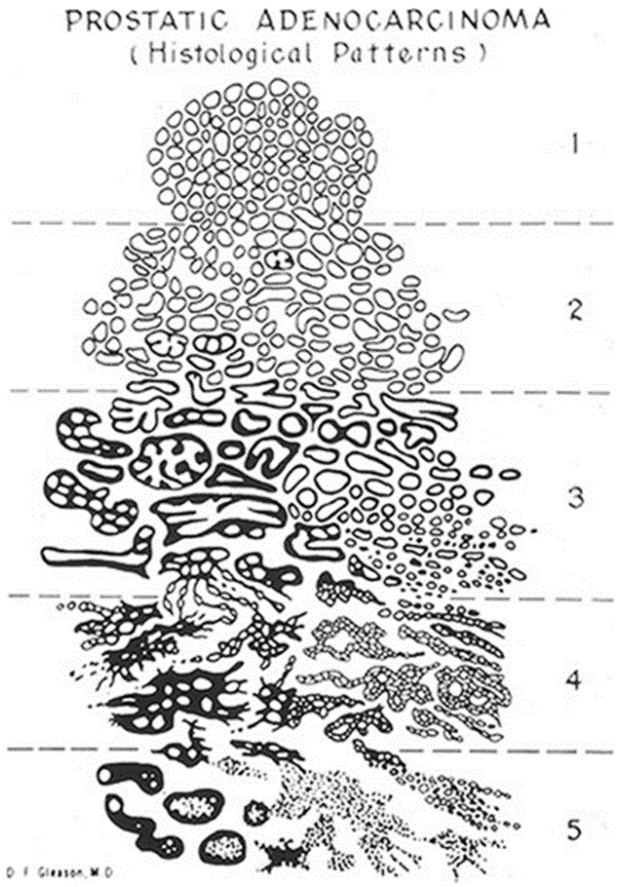

Figure 1.1 Differentiated prostate cells. 1 & 2 are normal, 3, 4, & 5 demonstrating increasing malignant change. (Gleason 1977)

In this context (Kasivisvanathan et al., 2018), clinically significant prostate cancer (csPCa) is defined as the presence of a single biopsy core indicating disease of Gleason 6 (3 + 3) or Gleason 7 (3 + 4) - both with a positive core length of more than 6 mm - or ≥ Gleason 7 (4 + 3) on histological analysis. Clinically insignificant cancer is defined as a biopsy sample with a Gleason score of 6 (3 + 3) or Gleason 7 (3 + 4) with a positive core length of less than 6 mm. Gleason grading does identify different patterns of prostate cells but creates overlap between scores, particularly of Gleason 7, which may be a combination of 3 + 4 cells or 4 + 3 cells. Given that Gleason pattern 4 cells comprise a heterogenous group of tumours with a greater risk of poor survival rates than Gleason pattern 3 (van Leenders et al., 2020) the International Society of Urological Pathology (ISUP) reached a consensus to group Gleason patterns relative to

the risk of progression or relapse (Epstein et al., 2016). The risk groups aim to simplify PCa grading and are defined by the PSA, the PSA density (the PSA level compared to prostate volume), the number of positive cores, and the stage of the tumour, as well as the Gleason score. Table 1.1 below provides an overview of the ISUP group classification and descriptors used.

Table 1.1 ISUP Prostate cancer grade group system (Epstein et al. 2016, Kasivisvanathan et al. 2013)

Risk Group	Grade Group	Gleason Score	Descriptor
Low / very low	Grade Group 1	Gleason ≤ 6 (3 + 3) (single core length < 6mm)	**Insignificant prostate cancer**
Intermediate (favourable)	Grade Group 2	Gleason 6 (3 + 3) (single core length ≥ 6mm)	**Significant prostate cancer (csPCa)**
	Grade Group 2	Gleason 7 (3 + 4) (single core length < 6mm)	**Insignificant prostate cancer**
Intermediate (unfavourable)	Grade Group 3	Gleason 7 (3 + 4) (single core length ≥ 6mm)	**Significant prostate cancer (csPCa)**
	Grade Group 3	Gleason 7 (4 + 3)	**Significant prostate cancer (csPCa)**
High-risk	Grade Group 4	Gleason 8 (4 + 4)	**Significant prostate cancer (csPCa)**
Very high-risk	Grade Group 5	Gleason 9 – 10 (4 + 5, 5 +4, 5 + 5)	**Significant prostate cancer (csPCa)**

1.4 Treatment options

The common treatment for PCa is either radical prostatectomy or external beam radiotherapy, usually combined with hormone therapy. Other, less common, treatments such as brachytherapy and high intensity focussed ultrasound (HIFU) are available, although the outcome is similar; all treatment options pose a high-risk of morbidity with complications such as urinary incontinence and erectile dysfunction commonly occurring (Kirby, 2018).

Deferred treatment with curative intent is a model that was explored in the DETECTIVE trial in 2019 (Lam et al., 2019). Also known as deferred active treatment (DAT), this is a pathway for patients who are suitable for curative treatment, but in whom this can be safely delayed until such time the disease demonstrates signs of

progression. This delays any intervention, which may have significant side effects, thereby preserving normal urinary and sexual function for as long as is possible in most men.

1.5 Side effects and complications

As Nam et al (2014) discuss, bowel & urinary symptoms, tiredness, and fatigue, as well as erectile dysfunction can occur after radical treatment. The complications of intervention are often coupled with the unpleasant side effects of hormone therapy treatment of prostate cancer such as hot flushes, strength & muscles loss, loss of libido and weight gain (Prostate Cancer UK, 2020). Such side effects and complications are not rare. Indeed, a study by Johansson (2011), with a median follow-up of 12.2 years evaluated the long-term quality-of-life outcomes in men with histologically proven PCa. This study demonstrated the prevalence of erectile dysfunction and urinary leakage following surgery as 84% and 41%, respectively. Peri-operative complications can also occur and can be early (≤ 30 days post radical prostatectomy) or late (> 30 days post radical prostatectomy) events (Rodrigues et al., 2012). Complications, as either early or late events, include lymphocele, urine leak, urinary tract infection, bladder neck contracture, deep vein thrombosis / pulmonary embolism, and myocardial infarction (Johansson, 2011; Nam et al., 2014). These significant immediate and long-term complications require careful risk benefit analysis between the patient and physician prior to intervention with all available options, which may include the option to delay active treatment, appraised (Bill-Axelson et al., 2013).

What is of key interest is that no differences in the 10-year and 15-year mortality outcomes between patients who delayed active treatment and underwent monitoring, and those who received radical treatment were demonstrated in the recently ProtecT (Hamdy et al., 2016; Hamdy et al., 2023) and PIVOT (Wilt et al., 2017) trials. The National Institute for Health and Care Excellence (NICE, 2021) managing prostate cancer guidance (CG131), first published in 2019 but updated in 2021, recommended DAT as a method of safely managing men with low-risk prostate cancer with an aim of reducing unnecessary radical treatment (Merriel et al., 2019). However,

despite active surveillance DAT being a proposed option, risk stratifying men who would be suitable, and when any active treatment is required, has for many years, and continues to be, a conundrum in urological medicine (de Vos et al., 2023).

1.6 Risk stratification

In 1998, D'Amico et al first proposed criteria, which could be used as a system to evaluate the risk of recurrence following localised treatment of PCa (D'Amico et al., 1998). This has since been known as the D'Amico criteria. Measures of PSA levels, Gleason grades determined from the histology of the biopsy core, and the tumour stage score are used to categorise patients into three risk-based recurrence groups: low, intermediate, and high-risk, (Gabriele et al., 2016). The D'Amico risk group classification system was developed to estimate the likelihood of recurrence for any patient using a given set of parameters, (Rodrigues et al., 2012). Whilst the D'Amico criteria was initially devised as a tool to aid interventional treatment choice decision making, it is now a widely accepted method of determining risk factors prior to any treatment being proposed, including stratifying onto an DAT programme.

Data published by Dall'Era et al in 2012 suggested that 36% of men diagnosed with PCa in the United States of America (USA) are considered low risk by the D'Amico criteria (Dall'Era et al., 2012). However, data of the same year from the British Association of Urological Surgeons (BAUS) Cancer Register demonstrated that only 9% of newly diagnosed PCa in the United Kingdom (UK) between 2000 and 2006 met the criteria for low-risk disease (McVey et al., 2010). It is proposed that the difference is likely to be due to the low rate of PSA screening in the UK compared to the USA given the differing health economies of both countries. It is recognised that a higher rate of PSA screening does lead to an increased number of biopsies in asymptomatic patients, resulting in the detection of a higher rate of low-risk disease (Iremashvili et al., 2017) in the USA compared to the UK.

1.7 Active Surveillance

Active surveillance (AS), as a method of DAT for PCa, is described in the literature from around 2005 onwards. A common interchangeable term also employed is "watchful waiting" and in the early literature both terms were frequently used to describe

similar cohorts of patients. However, differentiation between these terms is now more widely defined. Watchful waiting (WW) is a passive strategy (Dahabreh et al., 2012). It is a term to describe the management approach in men diagnosed with PCa but with significant co-morbidities that would prevent a good outcome for curative treatment. This group includes men with a life expectancy of ≤ 10 years and is often regardless of the D'Amico risk classification. A WW programme will include a follow-up strategy, but any treatment will be for palliative care and to relieve symptoms rather than to provide a cure, (Dasgupta & Kirby, 2012; Rittenmeyer et al., 2016).

AS, however, forms the vast majority of the cohort of men on a DAT programme. AS presents a feasible alternative to radical intervention for patients diagnosed with low grade PCa and in whom the risk of progression is low. The aim of AS is to intervene with curative treatment should the disease progress either biologically (PSA changes) or histologically (Gleason score changes on repeat biopsy) (McVey et al., 2010) and is appropriate for indolent disease in younger men who can cope with, and will benefit from, curative treatment at an indeterminate future date, (Dahabreh et al. 2012). Careful selection of men on to an AS programme is required and the critical window for curative intervention has to be identifiable where disease progresses, (Iremashvili et al., 2017). The timing of intervention is crucial; early unnecessary intervention may result in life changing complications for little benefit, but treatment options are limited with significant disease progression. Therefore, appropriate monitoring is essential on an AS programme so that treatment can be delivered in the curative stage of the disease, (Dockray et al, 2012) (Dasgupta & Kirby, 2012).

1.8 Biopsy technique

The prevalence of disease progression has been reviewed as AS became a more commonplace option. It is noted that at least 33% of cases are reclassified and upgraded following a second biopsy and this has caused some doubt as to the value of AS (Schoots et al., 2015). Understanding the reason why reclassification occurs is an important factor in the consideration of selected men for an AS strategy to PCa treatment. Reclassification of disease may be misconstrued as rapid disease progression when it is most likely due to the original biopsy technique. The process of

obtaining biopsy samples of the prostate usually involves a procedure of placing an ultrasound probe into the rectum to image the prostate and guide where the biopsy needle can be safely inserted. This procedure is known as a transrectal ultrasound guided prostate biopsy (TRUS Biopsy).

Ultrasound is used in this context primarily to guide the needle and adds very little diagnostic information. Ultrasound imaging is an extremely operator dependent technique (Deslandes et al., 2024) although, in expert hands, diagnostic information regarding the prostate can be obtained (Harvey et al., 2012; Correas et al., 2021). However, as Dall'Era et al (2008) identified, there is a known inconsistency of ultrasound interpretation, predominantly due to apparent fluctuations in lesion appearance and inter-operator variability in the assessment of the prostate. These limitations have resulted in an apparent limited diagnostic value of ultrasound in the identification of prostate cancer and, therefore, an extended sextant biopsy procedure has been widely used in an attempt to capture an optimum histological assessment of the prostate. This involves obtaining 12 cores from throughout the prostate taken in a semi-random pattern (Mustafa & Pisters, 2015) rather than relying on ultrasound imaging alone to identify possible target areas. Using this approach, PCa is detected in around 60% of patients, which includes all grades ranging from clinically insignificant Gleason 3 + 3 (22%) through to highly invasive Gleason 5 +5 (<1%) (Kasivisvanathan et al., 2019). It is, however, documented that the standard 12 core approach can fail to detect up to 20% of csPCa (Kirby, 2004). The PRECISION trial (Kasivisvanathan et al., 2018) identified that the use of MRI prior to biopsy can assist with targeting high-risk areas for increased sampling, but a targeted approach alone would result in 9% of potentially csPCa remaining undetected (Paulino Pereira et al., 2023). With this knowledge, a repeat biopsy to ensure the prostate has been adequately sampled, and any cancer present correctly characterised, is recommended for all patients with low-risk localised prostate cancer at initial diagnosis (Iremashvili et al., 2017; NICE, 2021). An approach to AS which increases the confidence of the initial biopsy grade, and which can identify prostate disease and potentially progression using imaging alone, would reduce the re-biopsy burden and associated risk of post procedure morbidity.

1.9 Criteria for AS

The proportion of men opting for AS as a treatment choice increased from 0% in 2000 to 39% in 2006 (McVey et al., 2010). Despite this growth in adoption, and AS being described frequently in the literature, criteria for selection on to an AS programme has been debated since being first described as an option (de Vos et al., 2023). Dall'Era et al (2008) concluded that, despite AS being a feasible option, specific criteria should be developed to aid the selection of patients and to monitor disease progression (Dall'Era et al., 2008). Eleven years later those criteria remain varied, and with little consensus, despite evidence to suggest the adoption of AS is growing globally (Bruinsma et al., 2018; Lam et al., 2019; Merriel et al., 2019).

The D'Amico criteria to classify low-risk PCa were specified as a PSA < 10 ng/mL, Gleason sum of ≤6 and clinical tumour stage T1/ T2a (Dall'Era et al., 2008). The criteria were further refined by Epstein in 2004 to include the volume and length of tumour within the biopsy core (Dall'Era et al., 2012). The introduction of the ISUP grade groups has further streamlined the identification of histological outcomes suitable for consideration of AS, and the current NICE guidance (NG131) (2021) for the diagnosis and management of prostate cancer recommends that men with grade group 1 are offered AS and to consider radical treatment only if AS is not suitable or acceptable to the patient. For men with grade group 2 localised PCa, NICE (ibid.) recommends that a choice between AS, radical prostatectomy or radical radiotherapy is offered if radical treatment is suitable for the patient.

1.10 Patient selection

The overwhelming evidence suggests that AS provides a treatment option for patients in whom delayed curative treatment is appropriate (Wilt et al., 2017; Hamdy et al., 2023). Nonetheless, there are key elements to be considered prior to adopting an AS strategy, which include the risk of misclassification at initial biopsy, and the impact on the individual should this occur (McVey et al., 2010). The 2021 NICE Guidance (NG131) recommends that men with a low-risk PCa electing for AS will need to be informed a risk that csPCa is present remains, and that the risk is higher if any of the following are present:

- The initial biopsy demonstrated high grade prostatic intraepithelial neoplasia (HPIN)
- The biopsy demonstrated atypical acinar proliferation (ASAP)
- There is an abnormal digital rectal examination.

Whilst AS can delay intervention, it is recognised that patient preference influences the decision to treat to a significant degree, and at a rate twice that of cancer staging progression (Klotz et al. 2015). The psychological impact of having the knowledge of a positive diagnosis of cancer without undertaking any curative treatment has to be considered (Dasgupta & Kirby, 2012). Within a long-term follow-up study of men on AS by Klotz et al (2015), 6% of patients elected to have radical treatment despite no evidence of disease progression and this affects the success of an AS strategy. Bruinsma et al (2018) found similar with 9.1% of patients within their follow-up cohort discontinuing AS due to patient or clinician choice despite no evidence of disease progression (ibid.).

Although underlying patient anxiety and distress should not initiate radical and potentially life limiting treatment, it is recognised that this will influence management. To optimize adherence to an AS strategy psycho-oncology support will be required to help minimise distress (Briganti et al., 2018). Clinicians are aware that there is a cohort of patients that are comfortable with uncertainty and, therefore, able to tolerate an AS strategy compared to the more health anxious who tend to self-select into curative treatment (Loeb et al., 2017). In addition to the psychological considerations, socio-economic factors also influence treatment decisions. McVey et al (2010) reported a disparity between men from affluent areas and deprived areas electing for AS. Only 23% of men from affluent areas elected for AS compared to 36% from less affluent areas in their study based in the United Kingdom (UK). Progression to radical prostatectomy was also higher in the affluent group with 34% electing for surgery compared to only 19% of men from areas of deprivation (ibid.). The reasons for this disparity are not easily explained, but one possible explanation is because the less affluent have lower health coverage, particularly in the USA where a lot of research

has been undertaken, or due to men having jobs where they cannot afford time off to recuperate so opt to delay radical treatment (Catto et al., 2021).

1.11 Monitoring of AS

Monitoring of patients on AS is clearly essential; early detection of disease progression allows curative treatment to be undertaken at an appropriate time rather than the delayed application of palliative treatment due to significant and incurable disease progression (Heidenreich et al., 2014). Significant variation across the UK and internationally exists with both selection criteria and monitoring regimes. Bruinsma et al (2018) demonstrated varying criteria for selection and subsequent monitoring of patients on AS in their study and, in response to this, Merriel et al (2019) set out to develop a consensus statement on the current best practice of AS in the UK. This consensus statement (ibid.) has since been complemented by the NICE (NG131) (2021) publication, with additional guidance from the Movember Foundation (Bruinsma et al., 2018) also offering recommendations for an AS regime. Table 1.2 below provides an overview of current monitoring protocols published by these authors.

Table 1.2 Overview of current monitoring protocols

Author	Timing	Tests [a]
NICE NG131 (NICE, 2021)	Year 1 of active surveillance	Every 3 to 4 months: measure prostate-specific antigen (PSA)[b] Throughout active surveillance: monitor PSA kinetics [c] At 12 months: digital rectal examination (DRE) [d] At 12 to 18 months: multiparametric MRI
	Year 2 and every year thereafter until active surveillance ends	Every 6 months: measure PSA [b] Throughout active surveillance: monitor PSA kinetics [c] Every 12 months: DRE [d]
	a If there is concern about clinical or PSA changes at any time during active surveillance, reassess with multiparametric MRI and/or re‑biopsy. b Could be carried out in primary care if there are agreed shared-care protocols and recall systems. c Could include PSA density and velocity. d Should be performed by a healthcare professional with expertise and confidence in performing DRE.	
Prostate Cancer UK 2019 (Merriel et al.)	Year 1	Men receive personalised AS plan. Repeat PSA at recommended intervals within plan influenced by PSA history, mpMRI results and PSAD. At 12 months repeat mpMRI DRE if mpMRI contraindicated. Repeat biopsy only if progression noted on mpMRI or PSA changes
	Year 2 +	Repeat PSA at recommended intervals within plan influenced by PSA history, mpMRI results and PSAD. mpMRI if PSA changes (individualised threshold is breeched) Repeat biopsy only if progression noted on mpMRI. DRE on individual basis
Movember Foundation 2018 (Bruinsma et al.)	Year 1 onwards	Every 6 months: measure PSA Every 12 months: DRE Repeat biopsy at intervals of 3 – 5 years. mpMRI may be considered but data lacking as to its effectiveness. To be considered on local level

There are key components in each of these AS recommendations with the PSA blood test being the central monitoring test. In the publications by NICE (2021) and Merriel et al (2019) there is recommendation for multi-parametric magnetic resonance imaging (mpMRI) at 12 months, and at subsequent time points should there be changes to PSA. Both of these guidelines are UK based and it is noted with interest that the Movember Foundation (Bruinsma et al., 2018) recommendations, which have a global perspective, have less reliance on mpMRI but recommend repeat biopsy. This reflects the continued global variation in the approach to AS, which Loeb et al (2017) recognised resulted in a lack of confidence in this management pathway. As Merriel (2020) discussed in a review paper, there are key questions related to AS that remain unanswered:

- *"How can progression for localised prostate cancer be accurately predicted?*
- *What is the best protocol to use for men undergoing active surveillance?*
- *What is the role of mpMRI in follow-up for patients on active surveillance?" (ibid.)*

1.12 Diagnostic capacity

These questions must be placed in context with the real-world clinical settings, particularly here in the UK. Despite recommendations for the regular and repeated use of mpMRI from both NICE (2021) and the Prostate Cancer UK consensus statement (Merriel et al. 2019), a feature of diagnostics services within the National Health Service (NHS) of the UK is the lack of imaging capacity and the ever-increasing demand. This was particularly evident as this PhD research project commenced in 2019 (NHS England & NHS Improvement, 2020; NHSE, 2020a). Pressure for meeting diagnostic pathways and key performance indicators (NHSE, 2022) resulted in a bias towards using available imaging capacity for primary diagnostic investigations rather than for surveillance imaging, particularly when there are alternative monitoring tools, such as PSA available. In addition, there are reported limitations to the use of mpMRI, such as increasing acquisition time of the scan, as well as the safety issue of

gadolinium as a contrast agent (Zhen et al., 2019) alongside issues related to false negative MRI results due to spatial resolution, and relatively low reproducibility between different radiologists that O'Connor et al (2020) discuss.

The major pressure for diagnostic capacity however, is the need to deliver the timed prostate cancer diagnostic pathway (NHSE, 2022). At the time of devising this ERUP research proposal, performance in urology across the UK indicated that the NHS cancer targets (NHSE, 2018) were not being met. For the one month (31-day) wait from diagnosis to first definitive treatment plan, only 91.0% of people treated for urological cancers had a plan within 31 days of receiving their diagnosis (the target is 96%). More concerning was the two month (62-day) wait from urgent referral to first definitive treatment where only 48.6% of people treated for urological cancers (excluding testicular cancer) received first definitive treatment within 62 days of being urgently referred for suspected cancer (the target is 85%). The waiting time for MRI under the timed pathway (NHSE, 2022) should be no more than 5 days, but in 2019, within a large proportion of NHS Trusts, a wait of over 14 days existed (NHSE, 2020a). Adding routine surveillance MRI into the demand was not a realistic option at this time and an alternative solution was sought.

1.13 Advances in ultrasound technology

In 2014, Pavlovich et al, published the first study investigating a novel technique for imaging PCa. In this pilot study, a new ultrasound machine operating at 29 megahertz (MHz) (21 MHz centre frequency) compared to the 8 to 12 MHz of conventional, standard, clinical prostate ultrasound systems and the term "micro-ultrasound" (microUS) was coined. The pilot study by Pavlovich et al (2014) suggested that microUS offered superiority to standard ultrasound for the visualisation of prostate cancer, and it identified that a clinical trial with confirmatory biopsy was indicated. A randomised controlled trial was registered in 2016 (ClinicalTrials.gov NCT02079025) and 400 participants from this trial were recruited by Ghai et al (2016) to create the prostate risk identification using micro-ultrasound (PRI-MUS^{TM}) protocol and risk scale. The authors identified that by pairing PRI-MUS^{TM} with the high resolution microUS there was promise that this modality could be used for real-time visualisation

of suspicious lesions within the prostate. The first study comparing the diagnostic accuracy of microUS to mpMRI in an active surveillance population was released in 2019 by Eure et al. This feasibility study demonstrated that microUS could be as sensitive to csPCa as mpMRI, but it had many limitations including a small sample size, single institution, and single microUS reader with no inter-reader variability assessment. However, the study by Eure et al (2019) concluded that a within-patient comparison of the prostate was feasible, and promise was seen for this new technology in an AS pathway. Alongside advances in high frequency ultrasound imaging, a systematic review by Postema et al (2015) found evidence that by using a multi-parametric approach, namely combining different ultrasound parameters, significant improvements in the diagnostic performance of standard ultrasound machines for the detection of cancer could be attained.

1.14 Rationale for the ERUP trial

It is identified that an AS regime is a safe alternative to radical treatment (Hamdy et al., 2016; Wilt et al., 2017), which is advocated as a management option by NICE (2021) and has been adopted in the management of the local population of Hull and East Yorkshire. However, the numbers of men presenting with prostate cancer is rising (Prostate Cancer UK, 2024b) and real pressures on MRI capacity existed (NHSE, 2020a), coupled with a need for faster pathway delivery (NHSE, 2022). Capacity pressures within the local ultrasound service in 2019 were much lower than national levels, with performance standards in non-obstetric ultrasound being routinely met (NHSE, 2020a). The systematic review by Postema et al, (2015), together with the emerging evidence of the potential diagnostic performance of microUS, indicated that ultrasound imaging may have a role in the active surveillance of prostate cancer.

To be of value, any new diagnostic test needs to be feasible in the context in which it will be used. With support from the local urologists and radiologists, both pivotal to a monitoring pathway, a cohort of patients in whom low grade prostate cancer could be present was identified and the rationale for the ERUP trial was agreed. It was postulated that if ultrasound could identify disease progression in this cohort of men,

then this may reduce the burden on MRI, and the need for repeat biopsy, and offer a different form of imaging surveillance as a means of monitoring low grade PCa.

1.15 Thesis plan

This chapter has provided the context and rationale for my research. A systematic review of published literature related to the use of ultrasound in AS follows in the next chapter. A review of evidence regarding men's experience of AS is presented in, and Chapter 3. Chapter 4 considers how new technologies are embedded into clinical practice. I discuss the methodological considerations made in the research design, including a discussion of ultrasound parameters, in Chapter 5.

Chapter 6 outlines the multiphase research design, and provides the methods used to collect and analyse data of study 1, phase 1. The results of study 1, phase 1 are presented and discussed in Chapter 7, with study 1, phase 2 and study 2 of the ERUP trial presented in Chapter 8 and Chapter 9 respectively. The ERUP trial, in its entirety, is discussed in Chapter 10 and the thesis finishes with a reflective chapter (Chapter 11) outlining the impact this research has had on the local prostate cancer pathway and the wider clinical community.

Chapter 2 The role of diagnostic ultrasound imaging for patients with known prostate cancer within an active surveillance pathway in the United Kingdom: a systematic review

In this chapter, a systematic review of literature related to the use of ultrasound in the active surveillance of prostate cancer is presented. The purpose of this review was to better understand the role of ultrasound and to identify any gaps in knowledge that could be explored during this research project.

This chapter was initially completed in September 2020 and the evidence gleaned was used to inform the research study design. An abridged version of this chapter was published online in April 2021 and in print in February 2022:

Parker, P., Twiddy, M., Whybrow, P., Rigby, A. & Simms, M. (2021) The role of diagnostic ultrasound imaging for patients with known prostate cancer within an active surveillance pathway: A systematic review. *Ultrasound*, 30(1):4-17

A secondary literature search was conducted in February 2024 and any relevant new publications are included as an addendum to this published chapter.

2.1 Background to the review

Despite the fact that active surveillance (AS) has been advocated as a useful, safe and effective pathway in the management of prostate cancer for over 10 years (Klotz et al., 2015; Da Silva et al., 2017), the publications by Merriel (2020) and Bruinsma et al (2018) both highlighted a lack of consistency in AS monitoring protocols. The overview of key published AS monitoring protocols, described earlier in Chapter 1. Table 1.2 demonstrates that there is little consistency in the recommended use of multiparametric magnetic resonance imaging (mpMRI) (Bruinsma et al., 2018). The Prostate Cancer UK Consensus statement (Merriel et al., 2019) highlighted that the application of this imaging modality for monitoring disease is evolving, but also acknowledged that there are significant gaps in the literature surrounding the best use of mpMRI in AS, despite mpMRI being included with the NICE guideline 131 (NICE, 2021). An editorial review by Kasivisvanathan et al (2020) describes the use of mpMRI and mpMRI targeted biopsies of the prostate to better predict long term outcome for men on an AS pathway. However, it is noted that regular access to high quality

mpMRI, in terms of both imaging protocols and reporting standards is required for this to be a valuable asset to an AS programme (Eure et al., 2019). There is known variability between the reporters of mpMRI despite the use of a standardised reporting (Vargas et al., 2012; Vargas et al., 2016; Padhani et al., 2019). This variability, coupled with the challenges that present on mpMRI due to the poor visualisation of equivocal and / or mpMRI inconspicuous lesions that present in patients on AS, has resulted in a reduced sensitivity of mpMRI as an imaging modality for low grade disease, being reported (Branger et al., 2016). To improve diagnostic accuracy of mpMRI, in 2014, the European Society of Urogenital Radiology (ESUR) developed consensus-based guidelines for prostate mpMRI, known as the Prostate Imaging and Reporting and Data System (PI-RADS). This was later refined, and improved, with the PI-RADS v2 published in December 2014. PI-RADS v2 (Vargas et al., 2016) has since been updated again to simplify and standardise the terminology and content of mpMRI reports, and to reduce variability in imaging interpretations, with the overall aim of improving patient outcomes (Barentsz et al., 2016; Padhani et al., 2019).

Despite the reported limitations of mpMRI in AS, there is emerging recent data that supports its role in selecting and monitoring men on such a pathway (Glass & Dall'Era, 2019; Klotz et al., 2020). Although, formalising this into routine practice, given the very real variation in AS programmes (Merriel et al., 2019), and in the variable access to imaging, is a significant challenge (RCR, 2017; Davies et al., 2019). mpMRI has been demonstrated to detect prostate cancer (PCa) in asymptomatic patients, as published in the PROMIS trial, with authors documenting a sensitivity of mpMRI for clinically significant cancer of 93% (95% CI 88–96%) and a negative predictive value of 89% (95% CI 83–94%) (Ahmed et al., 2017). Further publications describe the benefits of mpMRI in an AS programme, (Glass & Dall'Era, 2019) although there is a recognition by the authors of the persistent and on-going multiple barriers to the widespread use of mpMRI for AS, including quality, cost, and capacity. It is therefore timely to review the options that modern, alternative imaging modalities present to this cohort of patients.

2.1.1 Ultrasound Technology:

Ultrasound imaging comprises different modes; the most common is B-Mode imaging, which produces an image on a screen made up of different intensity echoes returning from interactions with tissue boundaries within the area under examination. This standard B-Mode US imaging can assess the appearance of the prostate as a whole and regions of interest (ROI) within the gland; these ROI's are usually described in levels of density of returning echoes with the terms echoic or echogenicity (hypo- for dark areas; hyper- for bright areas and iso- for equal areas) commonly used. Tissue perfusion is assessed using technology that measures the Doppler shift in the frequency of echoes returning to the probe face. The Doppler shift can be displayed as either a colour map or a trace representing vascular flow. Perfusion can also be assessed by ultrasound using an intravenously injected contrast agent, which enhances areas of high blood flow within an organ, commonly seen in abnormal tissue (Sidhu et al., 2018). The stiffness of tissue is measured using elastography (Cosgrove et al., 2013); this technique measures the sonographic elasticity of tissue under pressure from either manual agitation (strain elastography) or an ultrasound pulse causing tissue agitation (sheer wave elastography). The elastogram produced is a map of differing areas of stiffness within the ROI and surrounding tissue (Hoskins et al., 2019).

Early publications related to imaging of patients on a monitoring programme do mention ultrasound in the diagnosis of PCa (Hruby et al., 2001), but the technological capabilities of the early machines available precluded this modality as having a useful role. Technological advances within the last two to five years have potentially changed that and there is now limited evidence that the use of ultrasound may now have a useful role in the identification of PCa (Bevilacqua et al., 2019; Eure et al., 2019; Maffei et al., 2019). A meta-analysis by Zhang et al (2019) assessed the sensitivity and specificity of micro ultrasound detection of PCa. Micro-ultrasound (microUS) utilises a transducer emitting a scanning frequency of 29MHz compared to the 7 – 9 MHz employed in most standard frequency endo-rectal ultrasound probes. This scan frequency has been widely utilised in ultrasound imaging of superficial structures (Lockwood et al., 1996) but is a relatively new technique in the field of transrectal imaging (Ghai et al., 2016). The depth to which ultrasound imaging is diagnostic at this

high frequency is limited to just a few centimetres, with a consequent limitation to the depth of the prostate that can be examined (Hoskins et al., 2019). There are, however, promising results from published studies (Ghai et al., 2016; Eure et al., 2019) supporting the use of microUS in PCa. The meta-analysis published by Zhang et al (2019) demonstrated microUS has a high sensitivity (91%) but only fair specificity (49%). Whilst a good detection ability was demonstrated, the possibility of misdiagnosis was high; potentially due to the learning curve of a new technique not commonly employed in the diagnosis of PCa. In conclusion, the authors suggested that microUS is a more convenient and cost-effective method of imaging and detecting clinically significant prostate PCa although additional clinical data and comprehensive evaluation remain a necessity (ibid.).

The lack of clarity regarding the use of imaging, either mpMRI or ultrasound, hinders clinician choice in pathway selection. Given the earlier technological limitations of standard frequency ultrasound it is, perhaps, understandable why clinicians may not have the confidence to use this modality in the monitoring of patients in such a sensitive and crucial pathway. If ultrasound imaging cannot identify the critical window (Iremashvili et al., 2017) where intervention is required its use within a surveillance pathway is significantly restricted. However, the improvements in ultrasound imaging described may lead to this modality being a useful adjunct to the monitoring of PCa and consequently relieve demand on mpMRI (Staerman, 2019; Lughezzani et al., 2020). Encouragingly, recent publications (Eure et al., 2019; Press et al., 2019) have identified a good correlation between mpMRI detected PI-RADS v2 lesions of ≥ 3 and identifiable features on ultrasound. A range of ultrasound parameters to assess PCa, including standard frequency ultrasound imaging (Press et al., 2019), tissue perfusion assessment with Doppler (Mischi et al., 2014), elastography (Boehm et al., 2015) and the emerging high frequency imaging (Ghai et al., 2016), have also been investigated independently, leading to the suggestion that there may be a useful role for multi-parametric ultrasound (mpUS) imaging in PCa, (Postema et al., 2015) other than as a tool to guide tissue sampling biopsy procedures.

2.2 Aim

The aim of this systematic review was to better understand the role of diagnostic ultrasound imaging within the active surveillance pathway of PCa and to clearly identify where gaps in knowledge and data exist.

2.3 Review Question

What is the role of diagnostic ultrasound imaging for patients with known prostate cancer within an active surveillance pathway?

This question has been framed within the PEO model (Boland 2017):

Population: Patients with known prostate cancer being managed under an active surveillance protocol or pathway

Exposure: Ultrasound Imaging recommended within the protocol or pathway which is used for diagnostic purposes

Outcomes: Identify the role that diagnostic ultrasound imaging has played within an AS protocol or pathway.

2.4 Methods

Prior to performing a systematic search of the literature, a search for previously published systematic review protocols was undertaken. A search of the PROSPERO database of the National Institute for Health Research was undertaken; no relevant systematic review protocols were identified (National Institute of Health Research, 2020). The literature search was conducted between April and June 2020. Ten databases were systematically searched for eligible articles: AMED, BNI, CINAHL, EMBASE, EMCARE, HMIC, Medline, PsycINFO, Web of Science and Google Scholar. Both forward and backward reference searching was undertaken. Publications dated between January 2000 and June 2020 were included in the search. PEO-based search terms were used with Medical Subject Headings (MeSH) to ensure keyword synonyms of these terms were acquired in each database search to increase the likelihood of identifying the location of relevant articles (Baumann, 2016). Truncation (*) was used to include different forms of the word in the search (Volpato et al., 2014). The Boolean

operator “OR” was used to include alternative keywords to broaden the search and the operator “AND” was used to combine search terms making the search more precise (Mahobia et al., 2019). “NOT” was used to ensure articles, which may use the search term ultrasound for guided biopsy rather than diagnostic procedures, were excluded given the extensive use of this search term within literature. The results were filtered to include only English language abstracts. This refined the search so that the articles obtained could be understood by the researcher. Search terms were based on the PEO framework, as presented in Table 2.1, to ensure the research question could be adequately answered. (Boland et al., 2017).

Table 2.1 Search Terms

Population	**AND**	Exposure		**AND**	Outcomes
Patients with prostate cancer		**Diagnostic Ultrasound Imaging**			**Active Surveillance**
1st term		2nd term	3rd term		4th term
prostate cancer **OR** cancer of the prostate **OR** prostate gland cancer **OR** prostate tumo* **OR** Prostat* neoplasm		diagnostic imaging **OR** Ultrasou* **OR** Ultrasonography **OR** sonograp* **OR** sonogram **OR** ultrasound diagnosis **OR** ultrasound scanning **OR** trans-rectal ultrasou* **OR** TRUS	**NOT** Biops*		active surveillance **OR** watchful waiting **OR** expectant management

Little evidence was expected to be found during the evidence search therefore no restrictions were placed upon type of articles included. Evidence has been sourced from:

- NICE Guidelines
- Previous systematic reviews of AS
- Single and multi-centre trials
- Case reports
- Published expert opinion and grey literature including conference abstracts.

A PRISMA flow process was followed to identify relevant publications (Moher et al., 2009), illustrated in Figure 2.1 below. After duplication removal, two reviewers independently screened all titles and abstracts to exclude irrelevant publications. Once potentially relevant titles had been identified, the remaining articles were independently screened by three reviewers. This second step of screening publications continued with each full text article or abstract assessed for relevance using the predetermined inclusion and exclusion criteria described in Figure 2.1 below. The rationale behind the inclusion and exclusion criteria is to better understand whether ultrasound can play a useful role in the AS of PCa and act as an adjunct or replacement to alternative imaging such as MRI.

Table 2.2 Inclusion and exclusion criteria for study eligibility

Inclusion Criteria	**Exclusion Criteria**
Any article related to the active surveillance of prostate cancer *and* Any article related to the use of ultrasound in the diagnosis or monitoring of prostate cancer. Any article with evidence of clinical utility of ultrasound in AS	Conference abstracts which do not provide information suitable for extraction. Abstracts with subsequent full articles and / or articles containing duplication of data. Articles describing the monitoring of PCa via other modalities; for example, MRI. Articles using US in PCa patients but for reasons other than diagnosis or monitoring; for example, to guide surgical planning or to guide biopsies. Articles related to the use of diagnostic US for men high-risk of PCa. Untraceable or unrelated articles Commentaries, editorials, or opinion articles Articles with no evidence of clinical utility (unless related to outcomes of interest within this review) Studies in languages other than English

Articles included with the review were required to contain data related to the role of ultrasound in AS or WW, as described in Chapter 1.7. A large range of exclusion criteria were required to avoid overlap between articles related to alternative imaging modalities or regarding the use of ultrasound purely used as a guide to target biopsy sampling of the prostate. Whilst conference abstracts were included within the literature search, these were excluded from the review if the methodology was of a poor quality or if the data was of insufficient detail to confidently judge the quality. Where there was close proximity of the conference abstract publication dates to the literature search, the primary authors were contacted directly to seek information regarding potential full paper publication, which should be consider and integrated into the systematic review at a later date.

2.4.1 Quality Assessment (QA)

It is essential to assess the methodological robustness of included studies to ensure that areas of bias are highlighted; this potentially increases the accuracy and relevance of the systematic review (Higgins et al., 2019). To evaluate the robustness of

the eligible papers, and as recommended by the Agency for Healthcare Research and Quality, Cochrane Collaboration, and the U.K. National Institute for Health and Clinical Excellence, a risk of bias assessment was performed according to the Quality Assessment of Diagnostic Accuracy Studies version 2 (QUADAS-2) tool (Whiting et al., 2011). This validated tool is recommended for assessing quality of healthcare studies for critical reviews and provides a qualitative assessment of the methodological quality and applicability of diagnostic accuracy studies. The primary reviewer undertook the risk of bias assessment, and any uncertainties were resolved by a second reviewer (TP).

Four domains were reviewed and subsequently scored:

1. patient selection, which describes the method for patient selection and the patients included,
2. index test, which describes the test being studied and how it was conducted and interpreted,
3. reference standard, which describes the reference standard used and how it was conducted and interpreted,
4. flow and timing, which describes the flow of patient inclusion and exclusion and the interval between the index test and the reference standard.

In this context the following applies:

Patients: Patients with low-risk PCa

Index Test: Diagnostic Ultrasound Imaging

Reference Standard: Patients on an active surveillance pathway

Target Condition: Histopathology proven progression or upgrade of PCa

Each domain was reviewed in terms of risk of bias and applicability of the study scored. Each item was scored as either “yes,” “no,” or “unclear.” The concerns of applicability of the individual studies were scored as either “yes,” “no,” or “unclear.” Zero points were awarded to each criterion where the concern of applicability was

deemed low; one point was awarded for criteria with high or unclear risks; Table 2.4 provides an overview of the QUADAS-2 tool scoring matrix.

Total applicability scoring interpretation:

> 0 – 1 point indicates a low concern of applicability for inclusion of the publication in the systematic review,
>
> 2 points indicates a moderate concern of applicability for inclusion of the publication,
>
> 3 – 4 points indicate a high concern of applicability for inclusion of the publication in the systematic review.

The inter-reviewer agreement was assessed using the Cohen Κ coefficient. Any disagreements were discussed and agreed by consensus. A standardise form was utilised to extract relevant data from the eligible articles. The following data were extracted from each eligible article:

- Year of publication,
- type of study described,
- the cohort size,
- the criteria used to describe clinically significant prostate cancer,
- the criteria used to describe disease progression,
- the modality of imaging used within the study,
- the mode of ultrasound imaging used within the study.

Given the limited number of full text original research articles available for review, and the heterogeneity of the study designs and outcomes, a meta-analysis of findings was not possible. A narrative review of the data was completed.

2.5 Results

The PRISMA diagram (Moher et al., 2009) was used to summarise the literature search, illustrated in Figure 2.1.

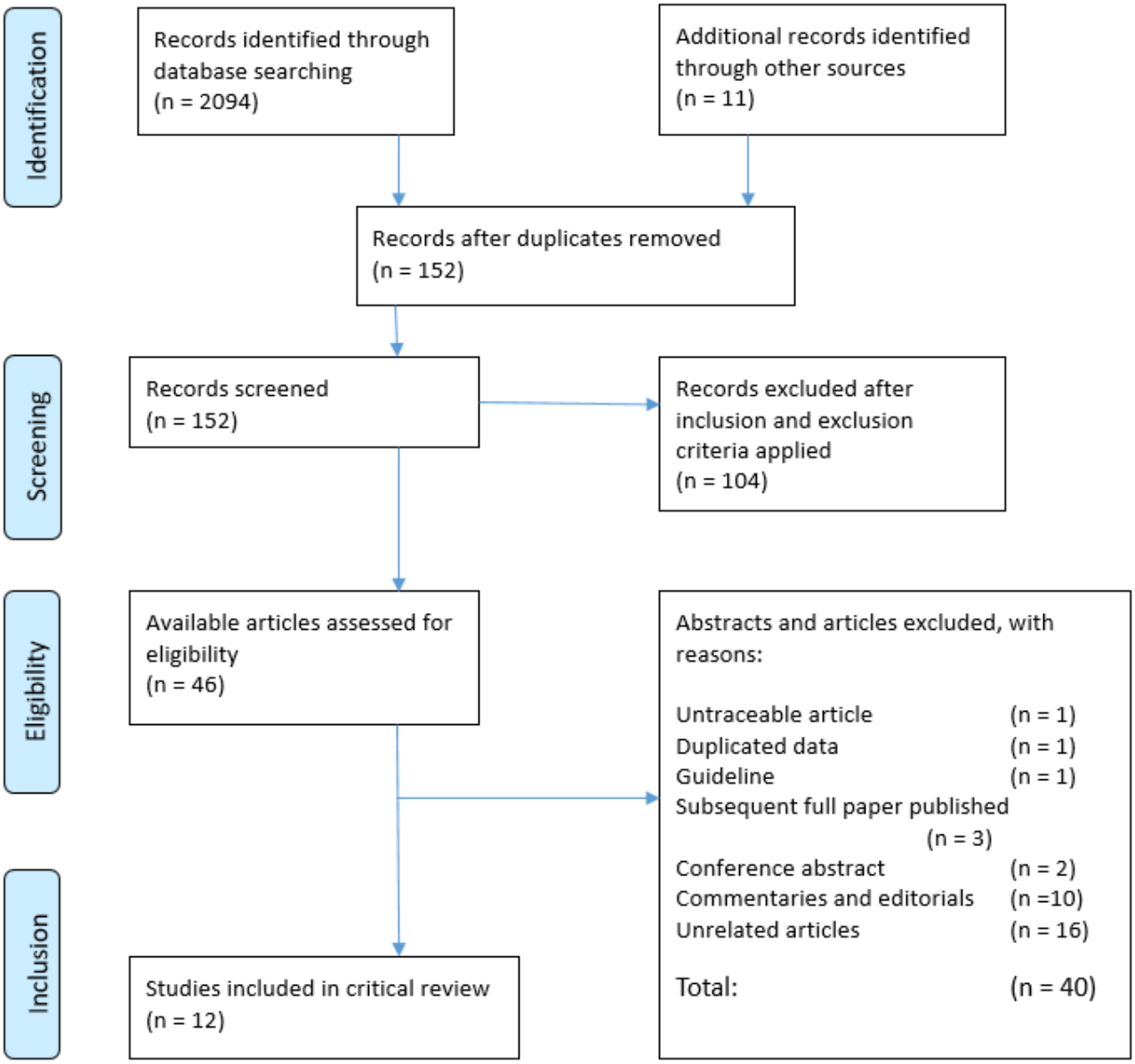

Figure 2.1 PRISMA diagram (Moher et al., 2009)

The range of evidence sourced, which included non-peer reviewed grey literature, is an indication that diagnostic ultrasound imaging is not in widespread use within AS protocols and few randomised control studies, or peer reviewed multicentre trials exist. Primarily, articles included described the clinical utility of the use of ultrasound in AS. Clinical utility studies assess the ability of the test to influence patient outcomes and management decisions (Olleik et al., 2018). In relation to this review, the role of

ultrasound and its impact on patient management is being assessed; therefore, including articles related to the clinical utility of ultrasound was required.

The initial search identified 2094 titles. A further 11 papers were found by forward backward reference searching of bibliographies during the preliminary search. Duplicates were identified and excluded using EndNote's (Clarivate Analytics) Author/Title/Year duplicate checker, followed by a manual verification by the primary reviewer. This yielded 152 potentially eligible articles that used ultrasound in AS of PCa. Of these, 106 articles were excluded on primary screening because ultrasound was used solely to guide biopsy procedures and had no role in the assessment of PCa. The remaining 46 abstracts were reviewed for eligibility and inclusion in the analysis and articles sourced; 23 available articles were reviewed by reviewer 1 (PP) and 2 (MT) and 23 available articles reviewed by reviewer 1 (PP) and 3 (PW).

2.5.1 Inter-reviewer agreement

The Cohen K coefficient (Glen, 2020) was calculated between reviewer 1 and 2 and reviewer 1 and 3. The Cohen K coefficient for inter-reviewer agreement between reviewer 1 and 2 was 0.82 and between reviewer 1 and 3, 0.75. This demonstrated near perfect and substantial agreement respectively between the reviewers. Despite the substantial agreement between reviewers 1 and 3 there were six publications in which these reviewers disagreed about their inclusion. A second review of these publications was made by reviewer 2 and a consensus agreement made regarding inclusion and exclusion based entirely on the review question.

The Cohen K coefficient are presented in Table 2.3 below.

Table 2.3 Cohen K coefficient calculations. a: reviewer 1 & 2; b: reviewer 1 & 3

a: Reviewer 1 and 2		
Po	Agreement to include = 3 /23 Agreement to exclude = 19 /23	22/23 = 0.95
Probability of inclusion agreement	Reviewer 1 = 3 /23 Reviewer 2 = 4 /23	0.13 * 0.17 = 0.02
Probability of exclusion agreement	Reviewer 1 = 20 /23 Reviewer 2 = 19 /23	0.87 * 0.82 = 0.7
Pe	0.02 + 0.7 = 0.72	
K = (Po – pe) / (1 – pe) = (0.95 – 0.72) / (1 – 0.72) = 0.82		K = 0.82 Near perfect agreement

b: Reviewer 1 and 3		
Po	Agreement to include = 8/23 Agreement to exclude = 11 /23	19/23 = 0.83
Probability of inclusion agreement	Reviewer 1 = 14 /23 Reviewer 2 = 10/23	0.60 * 0.43 = 0.26
Probability of exclusion agreement	Reviewer 1 = 11 /23 Reviewer 2 = 15 /23	0.48 * 0.65 = 0.31
Pe	0.22 + 0.26 = 0.48	
K = (Po – pe) / (1 – pe) = (0.83 – 0.31) / (1 – 0.31) = 0.75		K = 0.75 Substantial agreement

Po = the relative observed agreement among reviewers.

Pe = the hypothetical probability of chance agreement

2.5.2 Quality Assessment (QA)

From this final review, 12 eligible articles were taken forward to the quality assessment stage. The eligible articles were scored using the defined matrix and agreed parameters. The QUADAS-2 tool scoring matrix used in this review is presented in Table 2.4. The QUADAS-2 tool demonstrated heterogenity within the articles selected as eligible. Three articles discussed the technology of ultrasound and its use in the diagnosis of prostate cancer, rather than the role of ultrasound specifically in AS (Murciano-Goroff et al., 2014; Perez, 2019; Press et al., 2019) but were included as the potential role of ultrasound could be inferred from the data extracted from these

publications. Conference abstracts were included when no full text article was available. (Ko et al., 2011; Martel et al., 2019; Staerman, 2019; Maffei et al., 2020) despite the limited information that could be gleaned from such publications and the quality of the study could not be assessed. It was recognised that clinical studies are presented at conferences by clinicians, but these do not go on to become full text published articles; however, these abstracts provided information related to the clinical utility of US in AS and were worthy of analysis.

Table 2.4 Result summary of the QUADAS-2 Tool (Whiting et al. 2011)

Review Question **Patients:** Patients with prostate cancer

Index Test: Diagnostic Ultrasound Imaging

Reference Standard: Patients on an active surveillance pathway

Target Condition: Histopathology proven progression or upgrade of PCa

Checklist Questions	**Lead Author**	Hrurby, 2001	Ko, 2011	Sauvain, 2013	Weiss, 2013	Murciano-Goroff, 2014	Shoji, 2015	Eltemamy, 2016	Eure, 2019	Perez, 2019	Press, 2019	Staerman, 2019	Maffei, 2020
1) Patient Selection	Was a consecutive or random sample of patients enrolled?	yes	no	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
	Was a case control design avoided?	no	no	no	no	no	no	no	no	no	no	no	no
	Did the study avoid inappropriate exclusions?	yes	unclear	yes	unclear	yes	yes	yes	yes	unclear	no	unclear	yes
Concerns of applicability	*Is there concern that the included patients do not match the review question?*	No (0)	Yes (1)	No (0)	Yes (1)	Yes (1)	No (0)	No (0)	No (0)	Yes (1)	Yes (1)	Yes (1)	No (0)

Checklist Questions	**Lead Author**	Hrurby, 2001	Ko, 2011	Sauvain, 2013	Weiss, 2013	Murciano-Goroff, 2014	Shoji, 2015	Eltemamy, 2016	Eure, 2019	Perez, 2019	Press, 2019	Staerman, 2019	Maffei, 2020
2) Index Tests	Were the index test results interpreted without knowledge of the results of the reference standard?	yes	yes	yes	no	no	no	yes	yes	unclear	unclear	unclear	yes
	If a threshold was used, was it pre-specified?	yes	unclear	yes	yes	no	yes	yes	yes	unclear	yes	unclear	unclear
Concerns of applicability	*Is there concern that the index test, its conduct, or interpretation differ from the review question?*	No (0)	No (0)	No (0)	No (0)	No (0)	No (0)	No (0)	No (0)	Yes (1)	No (0)	No (0)	No (0)
3) Reference Standard	Is the reference standard likely to correctly classify the target condition?	yes	yes	yes	yes	no	yes	yes	yes	yes	no	yes	yes

	Lead Author	Hrurby, 2001	Ko, 2011	Sauvain, 2013	Weiss, 2013	Murciano-Goroff, 2014	Shoji, 2015	Eltemamy, 2016	Eure, 2019	Perez, 2019	Press, 2019	Staerman, 2019	Maffei, 2020
	Were the reference standard results interpreted without knowledge of the results of the index test?	yes	yes	yes	yes	unclear	yes	yes	yes	unclear	no	unclear	unclear
Concerns of applicability	*Is there concern that the target condition as defined by the reference standard does not match the review question?*	No (0)	No (0)	No (0)	No (0)	No (0)	No (0)	No (0)	No (0)	Yes (1)	Yes (1)	No (0)	No (0)
4) Flow and Timing	Was there an appropriate interval between index test and reference standard?	yes	unclear	yes	no	no	yes	unclear	yes	unclear	yes	unclear	yes
	Did all patients receive a reference standard?	yes	no	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes

	Lead Author	Hrurby, 2001	Ko, 2011	Sauvain, 2013	Weiss, 2013	Murciano-Goroff, 2014	Shoji, 2015	Eltemamy, 2016	Eure, 2019	Perez, 2019	Press, 2019	Staerman, 2019	Maffei, 2020
	Did all patients receive the same reference standard?	yes	unclear	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
	Were all patients included in the analysis?	no	unclear	yes	yes	yes	yes	yes	yes	unclear	yes	no	yes
Concerns of applicability	*Could the patient flow have introduced bias?*	No (0)	Yes (1)	No (0)	Yes (1)	Yes (1)	No (0)	Yes (1)	No (0)	Yes (1)	No (0)	No (0)	Yes (1)
	Lead Author	Hrurby, 2001	Ko, 2011	Sauvain, 2013	Weiss, 2013	Murciano-Goroff, 2014	Shoji, 2015	Eltemamy, 2016	Eure, 2019	Perez, 2019	Press, 2019	Staerman, 2019	Maffei, 2020
Total		0	2	0	2	2	0	1	0	4	3	1	1

2.5.3 Study Quality:

The studies were not weighted as there was large variation between the type of article reviewed, the type of studies performed, the type of technology used, and the range of patient numbers involved in each study. As the weighting applied to a study does not decrease greatly for studies with a small number of patients, an equal weighting has been assumed (Ahn & Kang, 2018). This does not reflect the quality of the study, or assume each is of equal quality, but resulted in each study being included in the review with equal importance.

The quality of the studies included in the QA varied greatly. This was due to the type of article included, the type of study performed, and the paucity of original research published which met the PEO question. The type of article included is presented in Table 2.5 to provide an understanding of the range of material reviewed.

Table 2.5 Type of article eligible for review

Article Type	**Number of articles available**	**Total Number of Patients included**
Full text original research – Prospective data collection	5	1044
Full text original research – Retrospective data collection	3	1811
Conference Abstract	4	470
Total	**12**	**3325**

In addition to the three publications in which the study design did not explicitly include patients on an AS pathway, (Murciano-Goroff et al., 2014; Perez, 2019; Press et al., 2019), a further publication by Weiss et al (2013) used a study cohort that did not meet the patient population criterion. There was a risk of bias within these publications due to lack of compliance with the PEO question. However, given the lack of original research papers related directly to the role of ultrasound in AS reviewers agreed to include these articles given that data presented could be extracted and extrapolated within this narrative review.

The quality of the study does, however, impact on the applicability of the published article to be included in the review. Seven publications had a low concern of

applicability for inclusion (Eltemamy et al., 2016; Eure et al. 2019; Maffei et al., 2020; Sauvain et al., 2013; Shoji et al., 2016; Staerman, 2019; Hruby et al., 2001), three had a moderate concern of applicability for inclusion (Ko et al., 2011; Murciano-Goroff et al., 2014) and two had a high concern of applicability for inclusion (Perez, 2019; Press et al., 2019) within the review. The cause of concern in the moderate and high categories related to the reference standard: patients on an active surveillance pathway, or in relation to how the index test: diagnostic ultrasound imaging, was used within the study (Table 2.4).

2.5.4 Characteristics of the studies

In response to the concerns regarding the studies complying with both the reference standard and index test, and the heterogeneity of the studies identified in the literature search, the characteristics of the studies were reviewed to assess the inclusion criteria for the study cohort. The design of the study, how disease was determined, including identification of disease progression if applicable, and the modality and mode of imaging used was also assessed. Study design, patient and inclusion characteristics are presented in Table 2.6; disease and imaging characteristics are presented in Table 2.7.

Table 2.6 Study, patient, and inclusion characteristics

Author and Year	**Study Design**	**Number of patients**	**Inclusion criteria**	**Study cohort inc. AS**
(Eltemamy et al., 2016)	Retrospective	875	PSA ≤20 ng/mL Clinical stage** ≤ T2 Biopsy Gleason score ≤ 3 + 4	Yes
(Eure et al., 2019)	Prospective	9	Age ≥ 40 < 80 years. Indication of biopsy required under AS protocol PSA ≤20 ng/mL Clinical stage <c T2c	Yes
(Hruby et al., 2001)	Retrospective	180	PSA ≤15 ng/mL Clinical stage T1b – T2N0M0 Biopsy Gleason score ≤ 7	Yes
(Ko et al., 2011)	Retrospective (Conference Abstract)	253	Patients in an active surveillance pathway	Yes

Author and Year	Study Design	Number of patients	Inclusion criteria	Study cohort inc. AS
(Maffei et al., 2020)	Prospective (Conference Abstract)	118	Indication of biopsy required under PRIAS*** protocol for AS of low-risk cancer	Yes
(Murciano-Goroff et al., 2014)	Prospective	70	Prostate Volume ≥ 20 ≤ 60 mL PSAD**** ≤ 0.15 ng/mL/cc	Yes
(Perez, 2019)	Prospective (Conference Abstract)	55	PSA between 4.2 – 40 ng/mL	Yes
(Press et al., 2019)	Prospective	672	Patients who had an MRI-US fusion targeted biopsy TRUS grade possible Standard MRI performed. MRI suspicion score of > 1 (findings suspicious of PCa)	No
(Sauvain et al., 2013)	Prospective	243	PSA ≤ 10 ng/mL Normal DRE	Yes
(Shoji et al., 2016)	Prospective	50	Age ≥ 40 < 80 years Life expectancy of >10 years PSA ≤20 ng/mL	Yes
(Staerman, 2019)	Prospective (Conference Abstract)	44	Biopsy proven PCa with Gleason score = 3+3	Yes
(Weiss et al., 2013)	Retrospective	756	Localised PCa treated with radical prostatectomy. TRUS and endorectal MRI performed	Yes

* PSA – prostate specific antigen

** TNM staging system – T = tumour; N = node involvement and M = metastastic spread

*** PRIAS - Active Surveillance for Low-Risk Prostate Cancer Worldwide: The PRIAS Study (Bul et al., 2013)

**** PSAD - prostate specific antigen density = PSA / prostate volume

***** DRE – digital rectal examination

The study characteristics were widely varied; in six studies, the prostate specific antigen (PSA) was an indicator for inclusion (Hruby et al., 2001; Sauvain et al., 2013;

Eltemamy et al., 2016; Shoji et al., 2016; Eure et al., 2019; Perez, 2019); in three studies the Gleason score provided an inclusion criterion (Hruby et al., 2001; Murciano-Goroff et al., 2014; Eltemamy et al., 2016; Staerman, 2019); as did the clinical stage and whether radical treatment was planned in three other studies (Hruby et al., 2001; Eltemamy et al., 2016; Eure et al., 2019). Other inclusion criteria included patient's age, the outcome of the digital rectal examination (DRE) and the prostate volume. Overall, however, it was difficult to draw direct comparisons between publications due to the heterogeneity of inclusion criteria applied. The target condition defined for this review was the histopathology proven progression or upgrade of PCa. In all studies, the cohort of patients had histologically proven PCa; the variability of inclusion criteria reflects the lack of consistency of practice within this clinical field. This variation is a challenge for clinicians and patients when planning care pathways and when radical intervention is required (Bruinsma et al., 2018).

2.5.5 Imaging: Identifying disease & progression

Each of the publications were reviewed to determine how disease was defined and to ascertain the imaging modality and mode employed to identify disease, identify disease progression, or monitor disease. Table 2.7 describes the disease characteristics described within the publications.

Table 2.7 Definition of disease, imaging modality and mode characteristics

Author and Year	**Definition of disease on imaging (or progression if applicable)**	**Imaging modality & mode utilised**
(Eltemamy et al. 2016)	Increase in: number of hypoechoic lesions demonstrated. ≥ 50% increase in lesion volume Gleason upgrade following biopsy.	TRUS* - Standard frequency B-Mode
(Eure et al., 2019)	Lesions identified on imaging warranting biopsy. Gleason upgrade following biopsy	MpMRI TRUS Standard frequency B-Mode High frequency B-Mode (29MHz)
(Hruby et al., 2001)	New or enlarging hypoechoic peripheral zone nodule. Increase in gland volume of ≥ 30%.	TRUS - Standard frequency B-Mode
(Ko et al., 2011)	Prostate volume Changes in the PSAD	TRUS - Standard frequency B-Mode

Author and Year	Definition of disease on imaging (or progression if applicable)	Imaging modality & mode utilised
(Maffei et al., 2020)	Upgrade of PRI-MUS™** score with confirmatory biopsy with Gleason upgrade	TRUS - High frequency B-Mode (29MHz)
(Murciano-Goroff et al., 2014)	n/a	MRI with endorectal coil TRUS - Standard frequency B-Mode
(Perez, 2019)	Lesions identified on imaging warranting biopsy.	MpMRI TRUS - High frequency B-Mode (29MHz)
(Press et al., 2019)	Presence of a demarcated or poorly demarcated hypoechoic ROI*** warranting biopsy	MpMRI TRUS - Standard frequency B-Mode
(Sauvain et al., 2013)	TRUS - Suspicious lesions described as: hypo-echogenic, weakly hypo-echogenic or subtle, heterogenic Focal if under 5 mm; Nodular if over 5 mm PDUS**** - Suspicious lesions described as: hypo-echogenic avascular lesion. **or** weakly hypo-echogenic or hyper-vascularised lesion **or** hyper-vascularised heterogenous or hyper-vascularised hypo-echogenic lesion	TRUS PDUS
(Shoji et al., 2016)	TRUS: Diameter of suspicious lesion Rate of change of the suspicious lesion Doppler grading (comparison with the normal anatomical blood supply (NABS) in the other unsuspicious parts of the prostate: 0: no flow 1: low - flow present but weaker or less than NABS. Downgrade 2: moderate: flow equal or similar to NABS. Stable 3: high: flow stronger or greater than the NABS. Upgrade	TRUS Doppler (not specified if colour or power)
(Staerman, 2019)	Suspicious areas	mpMRI TRUS - High frequency B-Mode (29MHz)
(Weiss et al., 2013)	n/a	MRI TRUS - Standard frequency B-Mode

* TRUS – Transrectal ultrasound
** PRI-MUS™ - prostate risk identification using micro-ultrasound
*** ROI – Region of interest
**** PDUS – power Doppler ultrasound

Whilst MRI was a ubiquitous imaging modality within the studies, the use and mode of ultrasound varied between the publications. Most commonly, in eight studies, standard TRUS was utilised (Hruby et al., 2001; Ko et al., 2011; Sauvain et al., 2013; Weiss et al., 2013; Murciano-Goroff et al., 2014; Eltemamy et al., 2016; Shoji et al., 2016; Press et al., 2019); three studies investigated microUS (Perez, 2019; Staerman, 2019; Maffei et al., 2020) and one study employed both standard and microUS (Eure et al., 2019). Defining or identifying disease with the differing ultrasound modes, however, is less varied. Lesion identification, using either standard transrectal ultrasound (TRUS) or microUS was the primary diagnostic feature in all studies. The authors used features inherent in ultrasound imaging, such as changes to the echogenicity of the suspected lesions, changes to the size of lesions or whether lesions were well demarcated. Identifying changes on ultrasound imaging is challenging in all studies, but data suggests that microUS has improved sensitivity and specificity over standard TRUS (Eure et al., 2019).

The next most frequent ultrasound mode employed within the studies reviewed was Doppler used to assess the perfusion of the prostate and suspected lesions (Sauvain et al., 2013; Shoji et al., 2016). Perfusion characteristics were assessed in addition to standard TRUS imaging in both studies. Doppler changes were not quantified in either study with both authors using qualitative assessments of perfusion to stratify any significant change. Doppler assessment is an operator dependent technique (Hoskins et al., 2019) and, as Sauvain et al (2013) identified, probe pressure may compress microvasculature within small peripheral lesions, thereby compromising the accuracy of this mode of imaging. However, Shoji et al (2016) found that an upgrade in the Doppler signature of a lesion was significant risk factor for biopsy-proven disease progression. Perfusion imaging remains an imaging mode that may add value to the ultrasound assessment of patients on AS.

2.5.6 Sensitivity and Specificity:

To gain a better understanding of the sensitivity and specificity of each ultrasound mode in the detection of clinically significant PCa, data was extracted from each study where there was a confirmatory reference standard documented within the study. The reference standard was either histopathological confirmation of PCa or, as in the two papers evaluating the reliability of prostate volume calculations with TRUS, MRI (Ko et

al., 2011; Murciano-Goroff et al., 2014). An overview of the study outcomes, including the sensitivity and specificity of each imaging mode where given, is documented in Table 2.8.

Table 2.8 Sensitivity & specificity of US modes utilised within each study

Author and Year	**Ultrasound mode utilised**	**Study outcomes &/or Sensitivity and Specificity of PCa detection**
(Eltemamy et al., 2016)	Standard frequency B-Mode	Evidence of TRUS progression: 49% agreement at biopsy No evidence of TRUS progression: 66% agreement at biopsy. TRUS independently associated with biopsy upgrade of disease. (OR 1.8, 95% CI 1.3 – 2.5, p <0.01)
(Eure et al., 2019)	Standard frequency B-Mode[A] High frequency B-Mode [B]	[A] Sensitivity 11%; specificity 93% [B] Sensitivity 89%; specificity 45%
(Hruby et al., 2001)	TRUS - Standard frequency B-Mode	25% of cohorts with biopsy proven progression had changes on TRUS. 3.5% had an increase in volume size.
(Ko et al., 2011)	TRUS - Standard frequency B-Mode	Coefficient of Variation calculated with Pearson correlation coefficient of 0.04. Variability in volume measurements does not adversely affect PSAD calculations.
(Maffei et al., 2020)	TRUS - High frequency B-Mode	Sensitivity 88.5%; specificity 30%
(Murciano-Goroff et al., 2014)	TRUS - Standard frequency B-Mode MRI	Standard TRUS & MRI prostate volume calculations appear to overestimate prostate volume by 9.34% & 16.57% respectively
(Perez, 2019)	TRUS - high frequency B-Mode[c] mpMRI[d]	[c] Sensitivity 93.3%; specificity 27.5% [d] Sensitivity 86.7%; specificity 40.0%
(Press et al., 2019)	TRUS - Standard frequency B-Mode	The overall cancer detection rates were 46.2%, 58.6% and 76.0% for USG 0, 1 and 2, respectively (P < 0.001). A well-defined ROI had a significantly higher risk of a diagnosis of GS ≥7 PCa.
(Sauvain et al., 2013)	PDUS	Sensitivity: 30% probability of having a significant cancer if PDS abnormal (However, 57% of all abnormal PDS had biopsy positive of all cancer grades including insignificant PCa); Specificity 96%
(Shoji et al., 2016)	TRUS Doppler	Multivariate analyses demonstrate significant predictors of progression as follows: increase (≥25 %) in major axis diameter of lesion (hazard ratio, 6.672; 95 % CI, 1.097–40.508; p = 0.022) upgrade of Doppler signature (hazard ratio, 4.091; 95 % CI, 1.673–24.878; p = 0.039)

Author and Year	Ultrasound mode utilised	Study outcomes &/or Sensitivity and Specificity of PCa detection
(Staerman, 2019)	High frequency B-Mode	Overall cancer sensitivity 84%
(Weiss et al., 2013)	Standard frequency B-Mode	Average prostate size measured with TRUS and eMRI correlated significantly with one another (R 0.801; P 0.0001), demonstrating a strong linear relationship (y0.891 x+2.622, R^2 0.642).

Of the 12 articles, reliable sensitivity and specificity data could be extracted in only six (Sauvain et al., 2013; Eltemamy et al., 2016; Eure et al., 2019; Perez, 2019; Press et al., 2019; Staerman, 2019; Maffei et al., 2020) with limited data available in the conference abstract published by Staerman (2019). High sensitivity of over 80%, indicating the imaging mode used identified biopsy proven clinically significant PCa, was reported in four studies using microUS (range 84% - 93.3%) (Eure et al., 2019; Perez, 2019; Staerman, 2019; Maffei et al., 2020) and one study using standard TRUS. This study by Press et al (2019) identified changes in ultrasound appearance of ROI's as an indicator of disease progression with sensitivity increasing to a maximum of 76% in lesions that were well demarcated and of a widely different echogenicity to the background prostate. Equivocal sensitivity was reported by Eltemamy et al (2016) with only 49% of biopsy proven progression being identified on TRUS imaging. A far poorer sensitivity was inferred in the article by Hruby et al (2001) with only 25% of the study cohort with biopsy proven progression demonstrating any changes on TRUS, although it must be acknowledged that this study was performed using now outdated technology; a repeat of this study, with up-to-date imaging, may yield improved results.

Specificity was only reported in three studies (Eure et al., 2019; Perez, 2019; Maffei et al., 2020) (range 27.5% - 45%) and all studies used microUS. Eltemamy et al (2016), demonstrated a reasonable agreement between the TRUS findings and the histopathology results post biopsy of 66% where there was no evidence of disease progression. No comparable sensitivity and sensitivity data could be extracted from the articles related to the assessment of prostate volume (Ko et al., 2011; Weiss et al., 2013) although both of these articles have demonstrated that ultrasound measurements are comparable with MRI and can be used to assess disease

progression. Hruby et al (2001), however, had extremely poor results when using prostate volume to assess progression with only 3.5% of the cohort demonstrating any significant change. Whilst appearances on imaging may change with updated technology, volume measurements are an inherent calculation in any machine and, therefore, a degree of caution is required when using prostate gland volume measurement alone to assess progression. Shoji et al (2016) demonstrated that a change in ROI size, rather than overall gland volume, as well as changes to the Doppler signature, could both be used as a predictor of disease progression. This supports the findings by Sauvain et al (2013) that indicated a normal power Doppler signature was a strong indicator of the absence of clinically significant prostate cancer. Combining changing ultrasound features of prostate appearance, ROI appearance, gland and ROI volumes and Doppler signature all lead to surmise that mpUS has a role in the diagnostic imaging of patients on an AS pathway.

2.6 Discussion:

2.6.1 TRUS

Despite the poor results of standard TRUS reported by Hruby et al (2001), the study by Eltemamy et al (2016) reported TRUS progression criteria in terms of lesion size and site. In those men with evidence of changes suggesting disease progression on TRUS, 47% had proven progression on biopsy compared to 53% with no upgrade. This contrasts with men with no evidence of TRUS progression, of whom 34% had biopsy proven progression compared to 66% with no upgrade ($p < 0.01$). The median time to progression was 14 months. The authors concluded that stable TRUS findings may allow for increased intervals between biopsy for men on AS. Press et al (2019) demonstrated an increasing sensitivity for disease detection when there were greater changes in appearance of an ROI compared to the background gland echogenicity. Prostates with hypoechoic regions visible on TRUS were reported to experience worse oncological outcomes than men without, suggesting a correlation of ultrasonography findings with disease aggressiveness (Press et al., 2019). The findings of both Eltemamy et al (2016) and Press et al (2019) demonstrate the potential use of TRUS to assist in risk stratification prior to biopsy among men with stable TRUS and / or low suspicion MRI findings. As reported by Press et al (2019), men with low or equivocal MRI suspicion could potentially avoid biopsy if no discernible ROI was present on

ultrasound imaging using TRUS. There are limitations to this study, however, in that US ROI's not seen on MRI were not included or scrutinised, but the purpose of this large cohort prospective study was to compare mpMRI lesions and the findings indicate a role for TRUS in this setting. Whilst this paper (ibid.) is not specifically related to the use of TRUS in AS it raises important points regarding the appearance and relevance of identifiable lesions seen on US without the need for microUS. Standard or microUS is operator dependent and thus, results can be skewed (Farina & Sparano, 2012). In the study by Eltemamy et al (2016), a single operator performed all examinations, and the intra-operator variability was not tested. In addition, only lesions with decreased density on US were considered for review despite previous papers (Harvey et al., 2012; Franiel et al., 2015) describing other US features indicating suspicious prostatic lesions in patients with known high-grade disease and correlated with radical prostatectomy (RP). Whilst hypoechoic lesions are clearly an important demarcation of disease, the range of differing US appearances will need to be considered in monitoring disease progression as the role of TRUS in AS is developed.

2.6.2 Micro-ultrasound

Despite the inherent limitations, ultrasound imaging, particularly microUS, can detect clinically significant prostate cancer (Bevilacqua et al., 2019; Lughezzani et al., 2020). The sensitivity for disease detection ranged from 84% - 93.3% in the studies included in this review using imaging frequency of 29MHz (Eure et al., 2019; Perez, 2019; Staerman, 2019; Maffei et al., 2020). Whilst there is limited methodology within the conference abstract available, Perez et al (2019) reported that microUS provided an improved sensitivity compared to mpMRI for both clinically significant prostate cancer and low-risk disease. Indeed, Maffei et al (2020) upgraded the Gleason Score to ≥ 7 cancer in 31 patients using microUS findings alone to indicate the site of confirmatory biopsy. The study by Staerman (2019) demonstrated a good concordance rate between mpMRI and microUS in the identification of suspicious lesions and benign findings in biopsy proven normal prostate. The findings of this review indicate that, whilst TRUS can identify suspicious ROI's, particularly as disease grading increases, microUS is an emerging technique comparable with MRI. However, this review also identified that there is only a small cohort of researchers publishing in this field and few full text papers available for analysis meaning potential difficulties with this new

technology cannot be readily assessed. Whilst this bias is to be considered, it is discussed and acknowledged by Eure et al (2019); further multi-centre trials of this emerging technology are indicated.

2.6.3 Lesion detection.

Being able to identify ROIs within a prostate is an important feature of any imaging mode, be that standard TRUS or microUS. The key consideration for the use of imaging in AS is the ability to demonstrate longitudinal change of quantitative image-related variables that can be confidently used as a clinical predictor for disease progression, such as diameter or volume of an ROI or the Doppler signature (Shoji et al., 2016). Shoji et al (Ibid.) describe a high specificity associated with Doppler signature when analysed over the duration of the patient's follow-up although they found two major limitations. The first was the limitation of visibility of very low-volume cancer rendering Doppler imaging difficult to assess. The second was the threshold volume of clinically significant cancer that could be identified was 0.5 mL and, therefore, small but clinically significant cancer may be missed or underestimated by imaging.

Volume calculations using TRUS, however, have been investigated and good correlation with gold standard MRI demonstrated. Murciano-Goroff et al (2014) identified the optimum parameters for prostate volume calculations as different methods produced disparate volumes. Ko et al (2011) found that in 95% of their cohort, variability in TRUS-guided prostate volume measurement did not affect PSAD calculations sufficiently to affect management. The study by Weiss et al (2013) demonstrated a high degree of correlation between TRUS- and MRI-based prostate volumes. The authors concluded that given the high degree of accuracy and reproducibility, in the hands of an experienced sonographer, a TRUS-based examination is a reasonable modality for estimating prostate size in all patients with disease of the prostate. In the study by Eltemamy et al (2016), 15% of patients with biopsy proven disease progression had changes to the ROI volume as the sole indicator on TRUS. Whilst the volume of the ROI is limited by visibility and a finite size, the evidence suggests that the use of this, as an ultrasound imaging parameter to monitor disease progression, is clearly beneficial on an AS pathway.

2.6.4 Perfusion characteristics

The size of the lesion is a limiting factor in the ability to identify perfusion as Shoji et al (2016) discussed. However, perfusion characteristics of the ROI are a good indicator of normality. Sauvain et al (2013) identified that a normal power Doppler signature (PDS) was associated with a 96% probability of not having a high-risk cancer. They concluded that a normal PDS may be used to delay biopsy in patients with low-risk disease. Doppler grading, assessed as a longitudinal variable, also had a positive bearing on assessment of disease progression in the study by Shoji et al (2016). A limitation of any Doppler technique is its reliance on operator performance. The accuracy of Doppler may be affected by technique and will need consideration in future studies.

Unfortunately, probe pressure may compress microvasculature within small peripheral lesions and thereby lead to misinterpretation of the Doppler signature. A further consideration is the qualitative assessment of the Doppler signature. Shoji et al (2016) used a subjective Doppler grade of blood flow signal within the lesion and classified from grade 0 to 3. Quantitative assessment of perfusion using solely Doppler demonstrated that the mean speed of coloured pixels and speed-weighted pixel density are good discriminators for prostate cancer in peri-urethral and the peripheral regions (Potdevin et al., 2001), although this technique has not been widely tested nor utilised in an AS pathway.

Perfusion can also be evaluated using contrast enhanced ultrasound (CEUS). A major limitation of CEUS is that the cycle of contrast inflow and outflow required for diagnosis is approximately two minutes and only one section can be recorded at a one time. Whilst good results have been demonstrated for CEUS of lesions 0.5 mL or larger, (sensitivity of 58–69 % and specificity of 93–95 %) (Postema et al., 2015), a study by Qi et al (2017) found that three-section CEUS was able to detect 92.3% of patients with cancer, whereas standard TRUS identified only 70.7%. The cohort for both studies, however, all had clinically significant cancer (Gleason ≥ 7) and had subsequent RP. There is an absence of evidence for the use of CEUS in an AS pathway and, given its limitations of scan duration and contrast agent cost (£92.00 per scan 2019/20 tariff) (NHS Improvement, 2019), it is unlikely to be considered as a viable imaging alternative to mpMRI for patients on AS. However, the strong evidence presented by

Sauvain et al (2013) and Shoji et al (2016) suggests that perfusion of the prostate and / or ROI should be considered as part of the mpUS assessment.

2.6.5 Elastography

An US imaging mode that has been trialled in the diagnosis of prostate cancer is both strain and shear wave elastography. Zhai et al (2012) performed a rigorous study of consecutive patients scanned prior to RP specifically looking at Acoustic Radiation Force Impulse (ARFI), (ARFI is brand specific and its general equivalent, shear wave elastography, is commonly available). Zhai et al (2012) noted that the bilateral stiffness asymmetry created by PCa in ARFI images may provide a convenient means to identify suspicious malignancy in the prostate by being able to differentiate between stiff abnormal tissue and stiffness caused by chronic benign prostatic calcifications that in strain (compression) elastography create false positive findings. A further study by Pelzer et al (2013) comparing strain elastography (SE) with endorectal MRI (eMRI) demonstrated that SE detected PCa in 46 of the 50 positive cancer cohort (92%) whilst eMRI detected PCa in 42 (84%). SE was found to be more sensitive in the apical and mid prostate; eMRI more sensitive in the base (peripheral zones) and transitional zone. In both studies, the patient cohorts all had known csPCa and had subsequent RP with direct comparison of elastography imaging and full mount slides made. The limitations of both studies, and with the technique, is the uncertainty as to how ARFI or SE can assist in AS when the elastography findings in a normal prostate or in presence of benign disease are unknown.

2.6.6 Limitations

This systematic review is the first specifically evaluating the role of all modes of ultrasound within an AS pathway. The eligibility of articles was rigorously reviewed by three independent reviewers, which resulted in 12 publications eligible for inclusion. Of these, only eight full text articles were available. Despite the rigour of the review there are limitations related to the reliance of abstract inclusion. Of the 3325 patients included within all publications, the data related to 14% of these were extracted from conference abstracts alone. The quality of the data extracted was limited by the reliance on conference abstracts as no assessment of methodology can be made. The paucity of full text articles was an indication of the limited current use of ultrasound within an AS pathway. However, there is confidence that a thorough review has been

completed given the number of patients that were included within all studies. Indeed, conference abstracts were included despite the limited information gleaned from such publications as they all provided information related to the clinical utility of US in AS and offered insights into both volume measurements and the use of microUS (Ko et al., 2011; Perez, 2019; Staerman, 2019; Maffei et al., 2020). The extracted data has demonstrated that microUS offers promise as an imaging tool comparable with mpMRI in AS with five of the 12 papers included related to studies assessing the utility of this imaging modality (Eure et al., 2019; Perez, 2019; Press et al., 2019; Staerman, 2019; Maffei et al., 2020). However, this review relied on data related to this emerging technique extracted from conference abstracts with only one full text paper eligible for inclusion. Bias was potentially introduced into the review findings although the authors acknowledge the lack of published trials. Literature searching for such relevant publications will continue.

A second limitation of this review is the variability of the modes of US imaging used within the included studies. A meta-analysis was not possible because of the wide heterogeneity across the studied, which reduced the comparative data that could be reviewed. It was difficult to combine the results of the varied studies to produce a generalisation for clinical practice. However, this review has indicated that ultrasound does potentially have a role in monitoring disease progression provided a multiparametric approach is utilised. MicroUS shows promise despite the limitations of the publications included in this review. Its use in the routine clinical setting remains uncertain and the technique, including the confidence of image interpretation, will require careful evaluation to fully understand its usefulness and acceptability. Multi-centred trials are essential if this technique is to be embedded into everyday clinical practice and ultrasound offered as a much needed, viable alternative to mpMRI for patients on AS.

2.7 Conclusion:

This review has demonstrated that there potentially is a role for multi-parametric ultrasound for patients with known prostate cancer within an active surveillance pathway. Given the capacity and demand issues that were discussed in Chapter 1, it was pertinent to review existing pathways and seek alternative imaging tests that are

safe for our patients, sustainable for future delivery and release capacity in the alternative high demand modalities, such as MRI. A multi-parametric ultrasound (mpUS) imaging protocol that combines prostate volume, lesion volume, lesion demarcation, lesion echogenicity, an assessment of the Doppler signature and microUS will provide a reasonable sensitivity and specificity.

Whilst the data demonstrates that standard TRUS is not comparable with mpMRI, it does indicate that, providing an mpUS approach is utilised, stable TRUS findings may allow for increased intervals between biopsy for men on AS. The advent of microUS, with its reported sensitivity in the range of 84% - 93.3%, offers more promise for a truly comparable imaging modality to relieve capacity issues within MRI. Further research is needed to optimise and evaluate mpUS and microUS for the monitoring of patients with low-risk PCa.

2.8 Addendum

Since the systematic review was performed, three further studies investigating the use of ultrasound in the active surveillance of prostate cancer have been identified using the original search criteria listed in Table 2.1 (Albers et al., 2022; Bhanji et al., 2022; Maffei et al., 2023). Enacting the same inclusion and exclusion criteria, one study was excluded from this addendum as it is a narrative review of previously published studies that have already been included in my systematic review (Bhanji et al., 2022). The two remaining original studies both investigate the role of microUS; no studies related to the use of standard or mpUS were identified.

A similar evaluation of each study was performed and detailed in Table 2.9 and Table 2.10 below.

Table 2.9 Secondary search - Study, patient, and inclusion characteristics

Author and Year	Study Design	Number of patients	Inclusion criteria	Study cohort inc. AS
Albers et al. 2022	Prospective	128	Any volume low-risk prostate cancer (ISUP Grade Group 1)	Yes
Maffei et al. 2023	Prospective	100	Men undergoing MRI-guided biopsy at 1 year following diagnosis of low-risk prostate cancer (ISUP Grade Group 1)	Yes

Table 2.10 Secondary search - Definition of disease, imaging modality and mode characteristics

Author and Year	Definition of disease on imaging (or progression if applicable)	Imaging modality & mode utilised
Albers et al. 2022	Detection of clinically significant prostate cancer (ISUP grade group ≥ 2)	MpMRI High frequency B-Mode (29MHz) - used for assessment and to guide targeted and systematic biopsy
Maffei et al. 2023	Detection of clinically significant PCa (defined as ISUP ≥2 cancer) at confirmatory biopsies	MpMRI High frequency B-Mode (29MHz) - used for assessment and to guide targeted and systematic biopsy

Both publications pertain to small cohort, prospective, single centre studies using mpMRI and microUS to assess the prostate in men undergoing imaging and biopsy as part of their AS pathway. The study outcomes are described in Table 2.11 below.

Table 2.11 Secondary search - Sensitivity & specificity of US modes utilised within each study.

Author and Year	Ultrasound mode utilised	Study outcomes &/or Sensitivity and Specificity of PCa detection
Albers et al. 2022	High frequency B-Mode with histology correlation	There was no significant difference in csPCa detection between the imaging modalities of mpMRI and microUS. Men with a PRI-MUS™ score ≥ 3 were more likely to be diagnosed with csPCa than men with a PRI-MUS™ score ≤ 2. Similarly, men with a PI-RADS score ≥ 3 were more likely to be upgraded to csPCa than men with a PI-RADS score ≤ 2. Histology analysed post biopsy (either confirmatory of a new target or systematic surveillance biopsy) demonstrated similar results. The sensitivity, specificity, and positive and negative predictive values for csPCa detection were 97%, 32%, 34%, and 97% with PRI-MUS™ ≥ 3, and 85%, 53%, 40%, and 91% with PI-RADS ≥ 3, respectively. Whilst all patients in this study diagnosed with csPCa had either a PRI-MUS™ score ≥ 3 or a PI-RADS score ≥3, 10% of these cases would have been missed if microUS were omitted.
Maffei et al. 2023	High frequency B-Mode with histology correlation	MicroUS and mpMRI showed a sensitivity of 94.1% and 100% and a NPV of 88.9% and 100% respectively in detecting ISUP≥2 patients. A microUS-mandated protocol would have avoided confirmatory biopsies in 18 patients with no PRI-MUS™ ≥3 lesions at the cost of missing 4 upgraded patients.

Both studies identified that microUS findings assigned to a PRI-MUS™ (Ghai et al., 2016) score correlated well with MRI and with histology. Albers et al, (2022) suggest that using microUS to guide the site of targeted biopsy could be used as an adjunct to detecting csPCa, and that this could prevent the need for MRI. Maffei et al, (2023) also identified that microUS was comparable to MRI in detecting high-risk areas of the prostate, and suggested that the use of microUS targeted biopsy, in addition to MRI targeted biopsy, could detect a higher number of patients with progressive disease. Both studies suggest that the use of real-time microUS during AS may reduce the need for biopsy in men with stable appearances, but that it also assists with targeting areas of potential progression during guided biopsy.

The study by Albers et al, (2022) was limited in that the authors were not blinded to the MRI findings prior to the microUS examination, and both studies are limited in cohort size. However, both studies conclude that a combination of MRI and microUS imaging results could potentially reduce the need for prostate biopsy in low-risk cases. Maffei et al, (2023) further suggest that microUS could offer an alternative imaging modality to mpMRI, particularly in men to whom MRI is unavailable or contraindicated.

In summary, both studies published after the completion of the original systematic review, have added to the evidence that the features of microUS may be able to identify disease progression in men with known PCa and managed on an AS pathway. This new evidence identifies that microUS offers promise and further investigation is warranted.

This chapter has evidenced that there are parameters of ultrasound imaging which potentially could be exploited to monitor men on an AS pathway. A gap in knowledge related to the use of mpUS, including microUS, within an AS regime has been identified and further research is indicated. Men's experience of AS is investigated in the next chapter to better understand the impact the addition of mpUS could have in this population.

Chapter 3 The active surveillance experience

In this chapter, a scoping review of literature related to men's experience of an active surveillance regime for prostate cancer is presented and the impact of a cancer diagnosis on men is discussed. The purpose of this chapter is to identify if there are any gaps in knowledge that could be explored during this research into the role of ultrasound in the prostate cancer pathway, and the impact the use of imaging may have.

This chapter was initially completed in January 2021 as the evidence gleaned was used to inform the research study design. Several older papers were included in the review which reflected men's perceptions at that time but may not reflect how men feel now. A secondary literature search was conducted in February 2024 and any relevant new publications have been included within an addendum to the original chapter.

3.1 Background

As has been discussed earlier in this thesis, prostate cancer is one of the most common cancers amongst men both in the UK and the developed world (Chapter 1.2). Despite its prevalence, recent studies have reported extremely low mortality rates of 1% after a median of 15-year follow-up, with no treatment-related reductions in mortality, in men with localised prostate cancer (Merriel et al., 2018; Hamdy et al., 2023). Up to a quarter of all men diagnosed with prostate cancer (PCa) have indolent disease requiring no immediate treatment. (Kasivisvanathan et al., 2018). This diagnosis of insignificant cancer, it is argued, may have more of a negative psychological impact for the patient than any benefit of early detection could infer (Kazer, 2012; Rittenmeyer et al., 2016).

3.1.1 The cancer diagnosis

It is important to minimise the psychological impact of any diagnosis and it is recognised that the word cancer is highly emotive and can cause distress (Ruane-McAteer et al., 2019). The slow growing nature of prostate disease, particularly those with ISUP grade group 1 and 2 classifications (Table 1.1), makes it amenable to delayed treatment than more aggressive tumours would be. However, this disease is still a cancer and the word, regardless of the context used, instils fear and substantial

uncertainty in diagnosed men (Ruane-Mcateer & Prue, 2021). As a study by Brooks et al (2018) determined

> "when people hear the word cancer, they freak out." P. 1721

However, for health care professionals, cancer is purely the diagnosis requiring a treatment plan, whether that entails immediate active treatment or deferred intervention, and does not necessarily carry the same emotional burden of that experienced by the patient. In view of this, clinicians and patients commonly have differing perceptions regarding insignificant or low-risk cancer (Fitch et al., 2020). This potential dissonance can lead to misunderstanding and a source of tension between clinician and patient (ibid.) The word cancer may negate patients accepting a less aggressive management strategy despite the fact that many clinicians see low-risk PCa as a chronic condition, similar to conditions such as diabetes or hypertension, which can be managed over time rather than a life limiting fatal condition (Brooks et al., 2018). As Ruane-McAteer et al discuss (2019), clinicians can assume that patients with a diagnosis of low-risk cancer do not experience distress which is inaccurate. It is this unanticipated distress that may lead to a patient choosing unnecessary active treatment as a coping mechanism. It is understandable how such a conflict originates. The common message to the public, often conveyed via public health broadcasting (Public Health England, 2018), is that early detection equates to a greater chance of cure. Indeed, this is the case for many aggressive but silent cancers which rapidly metastasise, such as lung, pancreas, or cervical disease (NCRAS, 2020). Early detection implies that there will be active treatment; as such, the prospect of watchful waiting (WW) or active surveillance (AS) completely contradicts this message leading to the potential conflict between clinician and patient (Pickles et al., 2007).

The overarching aim of any AS programme is to reduce intervention for cancers that are unlikely to become life threatening, but, which in itself, may have life changing side effects for the patient (Oliffe et al., 2009). Despite efforts being made to provide a standardised programme for AS of prostate cancer (NICE, 2021) the perception of some patients in a study undertaken by Ruane-Mcateer and Prue (2021) is that the process is vague and many of their cohort felt as though there was no action plan. A

feeling that AS is doing nothing pervades and has been described a potential barrier to this effective, and safe, management option (Kinsella et al., 2018).

3.1.2 Active surveillance and the clinician

For patients, the diagnosis of any cancer is described as a shell shock (Ruane-Mcateer & Prue, 2021) precluding men from processing any further information at the initial consultation once the "C" word has been used. A study by Waglan et al (2019) interviewed 97 men with stage I – III PCa to better understand the factors influencing decisions they made about their treatment. The study identified that men found the prospect of making cancer treatment decisions, in what was described as the most stressful stage of the journey, as being:

> "very, very difficult for an ordinary guy". P. 800 (ibid.)

The cancer diagnosis is met with anxiety, distress, and denial although, occasionally, a

> "bump in the road" p. 105 (Kronenwetter et al., 2005).

attitude prevails. Within the systematic review of prostate cancer and supportive care, King et al (2015), identified that patients commonly felt that prostate cancer diagnosis was an emotional entity. Participants in this study, identified that peer support was required to help confront and accept the disease (ibid.), but that the role of the physician remained crucial for diagnosis. However, evidence exists, within the study by Pickles et al (2007) evaluating the psychosocial barriers to AS, that highlights clinicians with differing clinical specialties have differing opinions about the best course of treatment or action, and this may further impact on the emotional distress experienced by patients. A further study by Kim et al (2019) presents the results of a national survey of radiation oncologists and urologists, which investigated the clinicians' perspective of treatment pathways. Whilst this survey (ibid.) demonstrated that AS is now more widely recommended to patients than in the initial study by Pickles et al (2007), it highlighted that the differing clinical groups identify patient anxiety at different levels. In the study by Kim et al (2019), the radiation oncologists interviewed felt that more of their patients had anxiety with AS compared to the opinion of urologists when asked about the patients they managed. A study by Ruane-McAteer et al (2019) demonstrated that men's experience of a diagnosis of PCa in non-

specialist AS centres appeared to be different in such units, in terms of communication and support, and the implications of this on patient management requires careful consideration in any future study design.

3.1.3 Benefits of AS

Avoiding active treatment is a primary benefit of AS with the potential side effects of urinary incontinence and loss of sexual function being avoided (Kazer, 2012; Bates et al., 2020). However, it is also noted that AS can be seen as a way of delaying decision making or putting off treatment in the hope and expectation that new technologies will evolve to improve outcomes (Seaman et al., 2019). This is germane to the diagnosis of low-risk PCa and changes to the pathway seen over the last 10 years. The PIVOT trial (Wilt & Ahmed, 2013) provided the evidence to support the management of low-risk cancer with observation rather than active treatment and changed the prostate pathway accordingly. The 15-year data from the ProtecT trial (Hamdy et al., 2023), has further strengthened the evidence in favour of AS. The PRECISION trial (Kasivisvanathan et al., 2018) data then found a better sensitivity in detecting clinically significant cancer by using a targeted approach compared to the conventional system of transrectal prostate biopsy. More recently, a review by Fiard et al (2020) supports the decision to avoid prostate biopsy altogether in men where there are no MRI visible lesions to target, thereby reducing the risks associated with these diagnostic procedures. The study by Fiard et al (ibid.) concluded non-suspicious mpMRI has a high negative predictive value in ruling out significant cancer without the need for confirmatory biopsy. Therefore, any changes to monitoring or diagnosis that can avoid life limiting active treatment, or complications following investigation, is clearly desired by, and will benefit, patients in the long term. Choosing AS affords patients, and science, time to investigate and develop new treatment options (Oliffe et al., 2009) and the evidence, to date, indicates these are regularly emerging.

3.1.4 The burden of AS

Despite the reported benefits of AS outlined above, it is reported that living with untreated cancer can be an emotional burden and some men have a perception that they are risking their lives by doing so (Hedestig et al., 2003; Kazer, 2012). Qualitative studies demonstrate heterogeneity in response from patients; some reporting a feeling of worry and uncertainty, with others reporting a feeling that the cancer is

under control (Hedestig et al., 2003; Pickles et al., 2007; Ruane-Mcateer et al., 2016). As acceptance of AS grows within the clinical community, a large and increasing cohort of men (and their partners or caregivers) are on a monitoring pathway and will, it is expected, live for many years albeit with the consequences of diagnosis and the potential for active, but life limiting, treatment. Men with prostate cancer consistently report a significantly worse patient experience than people with other common cancers (NCRAS, 2020). The importance of capturing the patients' experience of AS for prostate cancer is increasingly recognised as having the potential to affect care and management successes (McIntosh et al., 2019). Exploring and understanding the published literature related to the experience of patients on an AS pathway may identify gaps in knowledge and care that could be addressed by this research project and ultimately lead to service improvements in this ever-changing field.

3.2 Aims and objectives

The primary aim of this scoping review is to better understand the experience of patients with known low-grade prostate cancer who are managed under an active surveillance pathway.

The secondary objective is to better understand the impact that imaging related interventions, be they ultrasound procedures or MRI examinations, may have on the patients on an AS pathway.

The final objective is to identify any gaps in knowledge that could be answered by my research into the role of ultrasound in the active surveillance of prostate cancer.

3.3 Methodology

3.3.1 Scoping Review

A traditional systematic review to evaluate the published literature available is not being considered here. Largely, this is due to the broad topic being investigated and that many different study designs may be applicable to evaluate. This would negate my ability to effectively and fairly assess the quality of the studies as required by a systematic review (Arksey & O'Malley, 2005). Whilst the primary aim of this review is specific, a broad research question is being addressed and an understanding of the extent of the research available on this topic is required. Therefore, an appropriate

methodological approach is required, which facilitates my familiarity with the available literature whilst remaining reflexive and not too limited or restrictive when conducting searches for relevant publications (ibid.). As advocated by Kim et al (2018), a scoping review has been chosen as the methodological approach of choice. Whilst a scoping review is a rigorous exercise, it may not lead ultimately to a full systematic review. It will, however, inform me of any gaps in knowledge that may require further study (Arksey & O'Malley, 2005). The purpose of this scoping review was to map the key themes evident from the research into patients' experience of AS from the main sources and types of published evidence available (Levac et al., 2010). Given this broad review, the quality of included studies has not been assessed but a five-stage methodological framework, as described by Arksey and O'Malley (2005), was adopted.

The five stages included in this review were as follows:

- identifying the research question,
- searching for relevant studies,
- selecting studies,
- charting the data,
- collating, summarizing, and reporting the results.

3.3.1.1 The research question

During background reading related to the impact of the diagnosis and management of prostate cancer, several articles were identified measuring quality of life (Carter et al., 2015; Parker et al., 2016; Mazariego et al., 2020). These quantitative studies assess the physiological impact of a prostate cancer diagnosis and being on a monitoring pathway (ibid.) (Maggi et al., 2019; Matheson et al., 2019), but the voices of men and their experiences are not described. The proposed research project for this thesis is to evaluate the role of ultrasound (US) in the active surveillance of prostate cancer. There is a need to understand men's experience of AS to evaluate whether the use of US changes, influences, or impacts this experience in any way. Therefore, the research question for this review was developed to ensure data from published studies could be extracted to better inform the future project design. The agreed PEO research question for this scoping review was:

What is the experience of patients with known prostate cancer within an active surveillance pathway?

P - Population: Patients with known low-risk prostate cancer, which meet the criteria for inclusion on an active surveillance protocol or pathway.

E - Exposure: Patients being managed under an active surveillance protocol or pathway.

O - Outcomes: Identify the experience of patients in terms of satisfaction, understanding or perception of being on an active surveillance protocol or pathway.

3.3.1.2 Literature search

Prior to performing a systematic search of the literature, a search for previously published systematic review protocols was undertaken. A search of the PROSPERO database of the National Institute for Health Research was undertaken. No reviews of men's experience with a match to the research question were identified although a similar study was registered in 2015 by Rivas et al entitled:

> "Exploring the quality of life and wellbeing of men with prostate cancer and their partners or carers, and related care needs and gaps in service: protocol for qualitative meta-synthesis [CRD42015017836]". (National Institute of Health Research, 2020)

No subsequent publication from this registered review has been identified within the literature search either through author or title searching. The primary author was contacted for a publication update but has not responded to date.

The literature search for this scoping review was conducted between September and December 2020. Ten databases were systematically searched for eligible articles: AMED, BNI, CINAHL, EMBASE, EMCARE, HMIC, Medline, PsycINFO, Web of Science and Google Scholar. No date restrictions were placed on the search to ensure as wide a range of publications as possible were available as possible. Both forward and backward reference searching was undertaken.

PEO-based search terms were used with Medical Subject Headings (MeSH) to ensure keyword synonyms of these terms were acquired in each database search to increase the likelihood of identifying the location of relevant articles (Baumann, 2016).

Truncation (*) was used to include different forms of the word in the search (Volpato et al., 2014). The Boolean operator “OR” was used to include alternative keywords to broaden the search and the operator “AND” was used to combine search terms making the search more precise (McGowan et al., 2016). Table 3.1 summarises the search terms used with the PEO framework to form an accurate, systematic search strategy. (Boland et al., 2017). The results were filtered to include only English language abstracts to ensure that the articles obtained could be understood by the researcher.

Table 3.1 Scoping review search terms

Population	**AND**	Exposure	**AND**	Outcomes
Patients with prostate cancer		**Active Surveillance**		**Patient Experience**
1st term		2nd term		3rd term
prostate cancer **OR** cancer of the prostate **OR** prostate gland cancer **OR** prostate tumo* **OR** Prostat* neoplasm		active surveillance **OR** watchful waiting **OR** expectant management		patient experience **OR** psycholo* **OR** patient impact **OR** quality of life OR Patient satisfaction OR Patient belief* OR Lay belief* OR Patient attitude* OR Patient perception* OR Patient understanding* OR Illness cognition* OR Illness representation*

Given the range and depth of the PEO research question, only published studies were included in the literature search. One published study protocol was identified (Ruane-Mcateer et al., 2016) and the primary author contacted for subsequent publication information. A draft manuscript, which was pending publication at the time of the search, was shared and included within this scoping review (Ruane-McAteer, 2018).

3.3.1.3 Study Selection

The Preferred Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria (Moher et al., 2009) was used to aid in the selection of studies. A protocol for this review was not registered given its broad nature and limitations of reviewing published studies of mixed methods (Kim et al., 2018). After duplication removal, all titles were screened, and abstracts reviewed to exclude irrelevant publications using predetermine inclusion and exclusion criteria described in Table 3.2.

Table 3.2 Scoping review inclusion and exclusion criteria for study eligibility

Inclusion Criteria	**Exclusion Criteria**
Any article related to the active surveillance of prostate cancer. *and* Any article related to the investigation of men's experience of AS Qualitative studies evaluating the experience or impact of AS Observational studies of AS	Conference abstracts, editorials or grey literature which do not provide information suitable for extraction. Abstracts without subsequent full articles and / or articles containing duplication of data. Quantitative studies measuring quality of life of men on AS Studies pertaining to the medical or clinicians' perspectives of AS Untraceable or unrelated articles Commentaries, editorials, or opinion articles Studies in languages other than English

The exclusion criteria were required to avoid overlap between published studies and to ensure the qualitative data could be identified and extracted. Quality of life measures are useful to evaluate pathways but may not accurately reflect the men's journey through AS. The inclusion and exclusion criteria have been used to ensure the aim and objective of the scoping review can be met.

Once the studies had been selected, the eligible publications were reviewed to chart the study types and main emerging themes as per the fourth stage of a scoping review

(Arksey & O'Malley, 2005). The main themes were then summarised and discussed as per the fifth stage of the review.

3.4 Results

3.4.1 Study selection

The PRISMA diagram (Moher et al., 2009) was used to summarise the literature search, illustrated in Figure 3.1. The initial search identified 2824 titles. A further 11 papers were found by forward and backward reference searching of bibliographies during the preliminary search and one paper was identified following communication with the author of a published study protocol. Duplicates were identified and excluded using EndNote's (Clarivate Analytics) Author/Title/Year duplicate checker, followed by a manual verification by the reviewer. This yielded 1741 titles which were screened for relevance, and 1381 abstracts that were reviewed. Fifty-seven potentially eligible articles related to men's experience of an active surveillance pathway for prostate cancer were identified. Of these, 39 articles were excluded on secondary screening for the reasons listed in Figure 3.1 below. Despite carefully excluding quantitative studies on primary screening, eligibility assessment demonstrated 10 articles solely measuring quality of life (QoL) and 15 articles discussing the medical aspects of AS only; these were subsequently excluded. The remaining 18 articles were reviewed to chart the study types and main emerging themes, as per the fourth stage of a scoping review (Arksey & O'Malley, 2005).

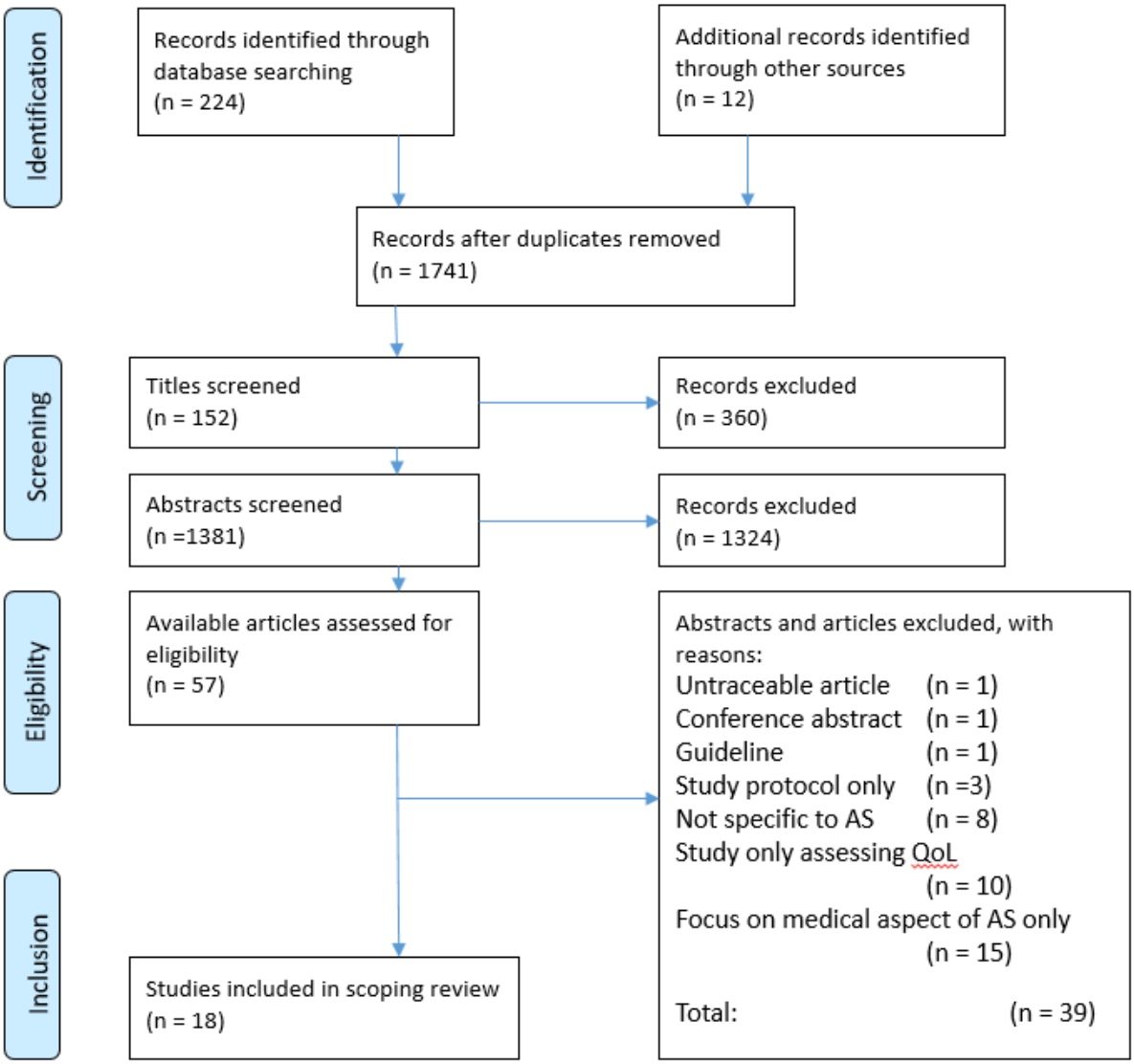

Figure 3.1 Scoping review PRISMA diagram (Moher et al. 2009)

3.4.2 Scoping review design

The study design and methodology of the included articles was assessed and tabulated to ensure the inclusion and exclusion criteria outlined in Table 3.2 had been met. The majority of included articles (n = 7) were qualitative studies, predominantly exploring the views and perceptions of patient (Hedestig et al., 2003; Kronenwetter et al., 2005; Oliffe et al., 2009; Kazer, 2012; Ruane-McAteer, 2018; Seaman et al., 2019; Shankar et al., 2019). Three mixed methods studies were included due to the relevance of the qualitative data produced (Hamoen et al., 2015; Wagland et al., 2019; Ruane-Mcateer & Prue, 2021) and one interesting review article provided further understanding of the subject under investigation and were deemed relevant for inclusion (Al-Dibouni, 2019).

The study aims and methods used for these individual studies are outlined in Table 3.3 below.

Seven systematic reviews were included in this scoping review although the study aims and methods are tabulated separately, (Table 3.4) (Pickles et al., 2007; King et al., 2015; Rittenmeyer et al., 2016; Ruane-McAteer et al., 2017; Kinsella et al., 2018; Spendelow et al., 2018; McIntosh et al., 2019). Relevant full text articles included within these systematic reviews were obtained and assessed for eligibility for inclusion within this current scoping review. Whilst this could lead to a possible duplication of data assessment, they were included if the aim of the original systematic review, as outlined in Table 3.4 was significantly different to the aim of this current scoping review and, therefore, different data could be extracted.

Table 3.3 Study aims, design and methodology of included original articles

Author and year	**Participants**	**Study aims**	**Study design and methods**
(Hamoen et al., 2015)	Men with low-risk prostate cancer	Not documented	A mixed method study as part of the MRI-based side study of the Prostate Cancer Research International Active Surveillance study (MR-PRIAS). The data from questionnaires of 111 men was reviewed to identify levels of perceived anxiety in those who were managed by AS with mpMRI. These were then compared with men that had to undergo treatment and with men that were managed with AS without mpMRI.
(Hedestig et al., 2003)	Patients with untreated localised prostate cancer	A study to improve the knowledge of the meaning of being a male patient living with untreated localised prostate cancer (u LPC) Men were interviewed with two main foci: • What was their experience when the disease was diagnosed? • Their experience of being a patient with prostate cancer	Qualitative study with seven patients with untreated localised prostate cancer. A phenomenological-hermeneutic approach was developed as a research tool to uncover the lived experiences of the men in the study. The intention of this was to understand the meaning of what was said by the patient during the interviews. Narrative discussion of outcomes.
(Kazer, 2012)	Men with PCa previously under AS who converted to active treatment	The purpose of this qualitative study was to examine the reasons why men convert from AS to active treatment.	A qualitative study using a purposive sample of six participants who were interviewed using defined questions by the researcher to examine reasons why participants converted from AS to active treatment. Outcomes of the interviews was provided in a narrative form.

Author and year	Participants	Study aims	Study design and methods
(Kronenwetter et al., 2005)	Men with early stage PCa	The aims of this study were to examine psychological, emotional, spiritual, and social reactions to (a) a diagnosis of early-stage prostate cancer and (b) participation in the prostate cancer lifestyle trial.	A Qualitative Analysis of Interviews of Men with Early-Stage Prostate Cancer: The Prostate Cancer Lifestyle Trial. Thematic analysis of responses from a cross-section of men who had elected AS and were participating in the longitudinal prostate cancer lifestyle trial.
(Oliffe et al., 2009)	AS with PCa	The aim of the study was to describe the range of behaviours used by men on AS as an interim step to suggesting specific psychosocial interventions with which men are likely to engage.	Qualitative study of 25 interviews with men on AS. Interpretive description to derive insights into men's AS-related practices and psychosocial issues.
(Ruane-Mcateer & Prue, 2021)	AS with PCa	The objective of this review paper was to discuss the psychological impact AS for PCa and the resulting implications of psychological wellbeing for treatment decision making and acceptance of AS protocols.	A review document that discusses outcomes of the longitudinal 9-month study by the same author. The paper discusses the areas of anxiety, depression, drawing from PCa literature as well other health conditions from which parallels are drawn.
(Ruane-McAteer, 2018)	AS with PCa	Report of patients' personal experiences of AS as a management option for PCa	Qualitative study using semi-structured interviews with nine participants. Thematic analysis undertaken of the outcomes of the interviews.

Author and year	Participants	Study aims	Study design and methods
(Seaman et al., 2019)	AS with PCa	To determine the clinical and psychological decisional factors associated with initial selection of and adherence to AS protocols.	Qualitative study using semi-structured interviews undertaken with 21 men representing a cross-section of patients either on AS or who had been on AS and were electing for treatment. An iterative, content-driven approach to analyse the interviews and to identify themes was used.
(Shankar et al., 2019)	AS with PCa	Study purpose was to assess the temporary health impact of mpMRI and / or TRUS Biopsy in AS PCa populations	Qualitative study of 122 men who either had MRI (n = 60) or prostate biopsy (n = 62). Men were interviewed using a multi component study questionnaire. Descriptive analysis performed
(Wagland et al., 2019)	Men with stage 1 – 3 prostate cancer	The aim of the qualitative study was to explore experiences of treatment decision-making (TDM) amongst men diagnosed with stage 1–3 prostate cancer.	Mixed-methods study incorporating UK-wide cross-sectional postal survey of men 18–42 months post-diagnosis and semi-structured interviews with a subsample (n = 97), including men who received both radical treatments and active surveillance. Interview data was analysed using a thematic framework approach.

Table 3.4 Study aims, design and methodology of included systematic reviews and review papers

Author and year	Participants	Study aims	Study design and methods
(Al-Dibouni, 2019)	All cancer survivors	To review and discuss fear of cancer recurrence and its association with scan-associated distress	Exploration of literature with a review of relevant papers by one author. Papers published with the last ten years, and which reported cancer distress and scan-associated distress were included

Author and year	Participants	Study aims	Study design and methods
(King et al., 2015)	Men with PCa	The aim of the review was to bring data from previously published qualitative studies of both men's experiences of prostate cancer and the less common topic of men's experiences of supportive care provision together to create an overview of men's experiences and needs.	A systematic review and qualitative synthesis. 20 journal articles were identified and critically appraised. A thematic synthesis was conducted in which descriptive themes were extracted out of the data. This was followed by the development of overarching analytic themes.
(Kinsella et al., 2018)	AS with PCa	To systematically review barriers and facilitators that patients perceive when selecting and adhering to AS for low-risk PCa	Mixed methods systematic review using PRISMA, PREFS and STROBE quality criteria undertaken. 47 studies identified and included. Key themes identified which influenced both choice and adherence to AS by patients.
(McIntosh et al., 2019)	AS with PCa	The review aimed to identify the specific unmet supportive care needs of men on active surveillance.	A systematic review following PRISMA guidelines was conducted. Qualitative and/or quantitative studies that reported unmet needs specific to men on active surveillance were included. Quality appraisals were conducted before results were narratively synthesised.
(Pickles et al., 2007)	AS with PCa	The aim of the review was to understand if long-lasting anxiety and psychological discomfort were provoked by AS if chosen as a treatment option.	Systematic review of 36 papers. Publications describing the psychosocial needs of men undergoing AS, and barriers to its uptake were reviewed. The findings are then integrated with the stress and coping model, and suggestions for strategies to enhance the uptake of AS through appropriate coping techniques are outlined.

Author and year	Participants	Study aims	Study design and methods
(Rittenmeyer et al., 2016)	AS - all cancer pathways using AS a treatment option	The phenomena of interest were accounts of the experiences of adult patients who choose watchful waiting or active surveillance as an approach to medical treatment.	Systematic review of qualitative study using the standardized critical appraisal instruments from the Joanna Briggs Institute Qualitative Assessment and Review Instrument (JBI-QARI). Sixteen studies were included, and 155 findings extracted. The extracted data were synthesised into ten categories and three findings.
(Ruane-McAteer et al., 2017)	AS with PCa	The aim of the review was to determine the psychological impact of AS to inform future study in this area and to provide recommendations for clinical practice	Systematic review of quantitative or qualitative non-interventional studies published in English that assessed the psychological impact of AS were included. The Mixed Methods Appraisal Tool was used to assess methodological quality. Twenty-three papers were included which were scored against four criteria and the main themes extracted were collated. A meta-synthesis was not possible due to the small number of studies included in this review.
(Spendelow et al., 2018)	Men with PCa	A review to identify self-initiated coping strategies reported by men diagnosed with PCa	Systematic review of the literature. A qualitative meta-summary was produced of the 18 studies included in the review.

3.4.3 Emerging themes

Six main themes emerged from the included eligible articles related to men's experience of AS, and which related to the aim and objectives of this scoping review.

- Uncertainty
- Security
- Anxiety
- Fear of progression / fear of cancer recurrence
- Interventions / repeat testing
- Coping

The emergent themes were charted, as per the fourth stage of a scoping review (Arksey & O'Malley, 2005), and are outlined in Table 3.5 below.

Table 3.5 Key emergent themes

Emergent themes						
Author and year	**Uncertainty**	**Security**	**Fear / anxiety**	**Fear of Progression**	**Repeat testing**	**Coping**
Al-Dibouni 2019	√			√		
Hamoen et al. 2015		√				
Hedestig et al. 2003	√	√		√		√
Kazer 2012	√					
King et al. 2015	√	√				√
Kinsella et al. 2018	√	√		√	√	
Kronenwetter et al. 2005						√

Author and year	Uncertainty	Security	Fear / anxiety	Fear of Progression	Repeat testing	Coping
McIntosh et al. 2019	√					
Oliffe et al. 2009	√		√	√	√	√
Pickles et al. 2007	√	√	√			
Rittenmeyer et al. 2016	√		√	√		√
Ruane-McAteer et al. 2017		√	√	√	√	
Ruane-McAteer 2018	√	√	√	√	√	√
Ruane-Mcateer and Prue 2021	√	√				
Seaman et al. 2019	√	√	√	√	√	
Shankar et al. 2019		√	√		√	
Spendelow et al. 2018						√
Wagland et al. 2019		√				

3.4.4 Collated results

As required by the fifth stage of a scoping review (Arksey & O'Malley, 2005) the emergent themes were then collated into a table and findings synthesised. From this, the key themes were identified. Each key theme is documented in the following six

tables (Table 3.6, Table 3.7, Table 3.8, Table 3.9, Table 3.10, and Table 3.11). A synthesis of findings related to each theme is provided after each table.

3.4.5 Synthesised findings – Theme 1: Uncertainty

Table 3.6 Key theme 1: uncertainty

Key theme: Uncertainty	
Author and year	**Findings**
(Al-Dibouni, 2019)	Medical imaging often associated with a sense of uncertainty amongst cancer survivors; their feelings are elevated due to the uncertainty of receiving results (p.6).
(Hedestig et al., 2003)	Patients describe living with untreated localised prostate cancer a constant threat; being uncertain about whether the disease will shorten one's life (p. 57).
(Kazer, 2012)	Men illustrate the emotional burden of AS by describing feelings of being uncertain, afraid, and worried and a perception of "risking one's life" whilst on AS. Participants commonly experienced a period of uncertainty or anxiety during AS which may be described as "dangerous waiting." However, little is known about the uncertainty that accompanies AS (p.83)
(King et al., 2015)	Uncertainty was associated with a perceived lack of information provision linked to treatment options and outcomes, about the extent and severity of treatment side effects, and likely prognosis (p. 628)
(Kinsella et al., 2018)	Concern expressed about the possibility of clinician bias at the time of the initial consultation discussing treatment. AS not offered as a treatment, or not recalled as choice being offered. Perception of AS as "doing nothing" (p. 270)
(McIntosh et al., 2019)	Lack of specificity regarding their prognosis resulted in confusion and left men wondering if they had cancer at all (p.2316)
(Oliffe et al., 2009)	Uncertainty related to three interconnected factors was determined. 1) most men were concerned about their mortality and the potential for the cancer to spread beyond the prostate gland, rendering them ineligible for curative treatments. 2) the potential imminent need for treatment created uncertainty about how men might cope with treatment-induced morbidities. 3) men's uncertainty was time sensitive and peaked leading up to the scheduled AS appointments and impending PSA and/or TRUS-Biopsy results. (p. 434 / 435)
(Pickles et al., 2007)	Difference in opinion for optimum treatment of low-risk cancer is identified between professional specialisms. The knowledge of this bias might add to patients' confusion and uncertainty about the most appropriate course of action, and subsequently increase distress and anxiety (p. 548)

	Patient's needs are unique and cannot always be predicted by physicians. As such, patients' information needs vary widely among individuals and patients should specifically be asked what information is required. Professional bias can lead to uncertainty (p. 548).
(Rittenmeyer et al., 2016)	Identified that decision making is difficult, complex, and fraught with uncertainty. Study participants live with a constant and nagging thought that they are in a situation of impending danger (p. 210).
(Ruane-McAteer, 2018)	Men struggle with feeling they had 'no plan' which was compounded by a lack of clarity surrounding the appointment schedule (p. 13 & 14). As described as a 'holding bay,' a grey, uncertain area in which they must wait until they are told what to do next by their clinician (p. 13) Not all participants were convinced of the sensitivity of the tests to detect disease progression, therefore participants were left further conflicted (p. 14) Uncertainty experienced about their diagnosis and disease characteristics decreased with time on AS (p.23) Feeling of constantly waiting contributes to uncertainty (p.26)
(Ruane-Mcateer & Prue, 2021)	Men had not internalised the low-risk nature of their disease, were unsure of monitoring and the ability of their clinicians and the clinical tools' ability to detect progression (p. 2).
(Seaman et al., 2019)	Men were found to be uncomfortable with AS because they view it as doing nothing (p. 9) Some men thought PSA values to be potentially unreliable leading them to question the validity of clinical measures alone whilst on AS (p. 9)

Uncertainty was the most common key theme recurring within the studies with this featuring in 12 of the publications and collated in Table 3.6 above, (Hedestig et al., 2003; Pickles et al., 2007; Oliffe et al., 2009; Kazer, 2012; King et al., 2015; Rittenmeyer et al., 2016; Kinsella et al., 2018; Ruane-McAteer, 2018; Al-Dibouni, 2019; McIntosh et al., 2019; Seaman et al., 2019; Ruane-Mcateer & Prue, 2021).

3.4.5.1 Summary

This theme identified the importance of providing all newly diagnosed men with comprehensive information about cancer prognosis and treatment options. Better informing men about the rationale and implementation of AS may help them appreciate that it is an active approach to PCa diagnosis. Unmet informational needs appeared to be the most reported requirement for men on AS, which has emerged under this theme. The feeling of uncertainty was also described as a feeling of doing nothing and, therefore, a perceived risk of, and uncertainty about, disease progression is evident. Differences in AS regimes was also a factor for men in this theme and was of

note as uncertainty peaked around the time of regular testing. Whilst regular testing may negate the feeling of having no plan, uncertainty about test accuracy also existed.

3.4.6 Synthesised findings – Theme 2: Security

Table 3.7 Key theme 2: security

Key theme: Security	
Author and year	**Findings**
(Hamoen et al., 2015)	Low-risk PCa patients on AS who had an mpMRI within the monitoring pathway tended to have a lower anxiety level compared to men who had no imaging performed during AS.
(Hedestig et al., 2003)	The experience of visiting the physician for check-ups described as both a feeling of uncertainty and security. The reassurance the check-up can bring adds to the feeling of security; that someone is taking care (p. 57)
(King et al., 2015)	A strong link between patients' need for information and individual levels of uncertainty. Information is required to ameliorate uncertainty (p. 629).
(Kinsella et al., 2018)	AS was seen to be more readily offered when there was availability of imaging facilities and expert clinicians (p. 271). Men who perceived that they received useful consistent information were more satisfied with AS and, therefore, more likely to continue on the pathway (p. 272)
(Pickles et al., 2007)	A study of interventions to modify lifestyle factors for men with prostate cancer managed with AS provided opportunities for informal support, socialization, connection to others, shared activities, and a sense of belonging. The result of this intervention was that a feeling of 'nothing is being done' was replaced with a feeling of control and meaning (p. 547). This study found that it was important to provide the patient with a sense of control and meaning. Patients reported empowerment when they were invited to become active participants in their management. An increased sense of control was seen to add to feelings of efficacy around problem-focused coping strategies that men could use (p. 548).
(Ruane-McAteer et al., 2017)	Stable or decreased disease characteristics at follow-up reduced uncertainty surrounding impending follow-up appointments and delays between monitoring appointments and receipt of results. Patients also discussed feeling more secure when they saw the same clinician at follow-up appointments. The role of clinicians was ambiguous. They were both sources of uncertainty in that they were potentially bearers of bad news that the cancer had progressed further, and of security in that they provided patients with the reassurance of regular check-ups (p. 15).
(Ruane-Mcateer & Prue, 2021)	AS related anxiety was identified to be particularly exacerbated by a desire for more regular monitoring appointments, and an awareness of the schedule and pattern of follow-up including the role of each clinician played in managing their care. The importance of the clinical relationship

	in navigating the experience of a PCa diagnosis and management with AS has been demonstrated (p. 2)
(Ruane-McAteer, 2018)	All men reported trusting the expertise of the consultant (p. 20) The most frequently discussed source of reassurance cited by participants was the MRI scan (p. 22). Participants described relief when the scan showed no signs of progression. While the prospect of the MRI remains daunting, the trustworthiness of the result and alleviation of concerns regarding possible progression led participants to have a generally favourable view of the experience (p. 22) Men felt that the uncertainty they experienced about their diagnosis and disease characteristics decreased with time on AS. Confidence in AS appeared to develop with hindsight, when participants realised that the inevitable death they feared did not happen, their cancer had not spread (p. 23).
(Seaman et al., 2019)	Participants in the study identified that a close relationship with their clinician built on trust, found comfort in regular monitoring. Patients were reassured by being monitored. These participants also trusted AS monitoring to detect potential PCa progression and that any progression would be detected in time to offer active treatment (p. 8). MRI results were considered more reassuring because other tests, particularly PSA values. Increasing the acceptance of AS may require incorporating additional modalities, such as MRI imaging, risk assessments (p. 9).
(Shankar et al., 2019)	Despite the pain of the probe insertion and the procedure itself being reported as the worst aspects of the transrectal biopsy, this procedure was also seen to be reassuring as the patients recognised that prostate was visualised on the ultrasound screen and that the test provided the ability to determine the histology and, therefore, any progression (p. 1390)
(Wagland et al., 2019)	Men were found to be disempowered when information was absent. The involvement or partners as information seekers and synthesisers was important. Patients forget between 40 – 80% of information given. The involvement of partners ensures patients receive the information to ensure they remain engaged with AS (p. 802)

Eleven studies described men's feelings of security on being on an AS pathway as collated in Table 3.7, (Hedestig et al., 2003; Pickles et al., 2007; Hamoen et al., 2015; King et al., 2015; Ruane-McAteer et al,. 2017; Ruane-McAteer, 2018; Kinsella et al., 2018; Seaman et al., 2019; Shankar et al., 2019; Wagland et al., 2019; Ruane-Mcateer and Prue, 2021).

Of these, seven studies found that men describe experiences of both uncertainty and security, which may indicate that the process of AS produces a mixture of widely differing emotion (Hedestig et al., 2003; Pickles et al., 2007; King et al., 2015; Kinsella

et al., 2018; Ruane-McAteer, 2018; Seaman et al., 2019; Ruane-Mcateer and Prue, 2021).

3.4.6.1 Summary

The use of imaging within an AS pathway appeared to provide additional security and confidence in the monitoring process. Men reported that regular monitoring and testing increased the sense of security regarding AS. Clinical review added to the reassurance that men experienced. The more relevant information patients received, the more their sense of security regarding AS increased. Having a plan engendered a feeling of being in control and, with it, increased security about the AS pathway.

3.4.7 Synthesised findings– Theme 3: Fear, anxiety and worry

Table 3.8 Key theme 3: anxiety

Key Theme: Fear, anxiety and worry	
Author and year	**Findings**
(Oliffe et al., 2009)	Anxiety, uncertainty, and lack of education about treatment options were barriers to the uptake of AS (p. 433)
(Pickles et al., 2007)	A source of anxiety reported was the monitoring of the disease (treated or untreated) with PSA testing, a condition that has been described as 'PSA-itis'. The authors found a variability in men's PSA test results in up to 25% of the cohort. They found this may lead to false progression or false reassurance and may result in anxiety leading to discontinuation from AS. Fear can also be caused by naturally occurring fluctuations in PSA levels, which might be interpreted as disease progression (p. 546). 8% of men with no evidence of cancer progression underwent active treatment because they had significant anxiety about living with cancer and the possibility of progression (p. 547).
(Rittenmeyer et al., 2016)	Pressure to make decisions about treatment was driven by patients own anxiety as well as anxiety of family members. Also participants experienced a constant and nagging worry. One fear described was loss of sexual function (p.210) following treatment and the effects this could have on marital relationships.
(Ruane-McAteer et al., 2017)	Reduced number of cores taken at follow-up prostate biopsy is associated with anxiety. This may be a result of the patients' perception, however inaccurate, that less of their cancer had been removed or that areas of cancer may have been missed.
(Ruane-McAteer, 2018)	Distress was consistently reported and described as a sense of doom (p.21) Participants report worry whilst waiting for results. AS described as time spent waiting for tests, waiting for results, or waiting for improved technology (p. 22).

	Participants “see-sawed” between seeing AS as favourable and profound fear of an inevitability of PCa-related death. A distrust in health care providers was reported (p. 24). An increase in AS patients' generalised anxiety symptoms over time was reported which may be a misperception of risk (p. 24). Participants discussed the need to feel that their AS involved a ‘plan’ to reduce anxiety and worry (p. 26).
(Seaman et al., 2019)	Anxiety was described in the days leading up to a follow-up appointment, but it was stated that the anxiety quickly dissipated after patients received their results (p. 8)
(Shankar et al., 2019)	The worst reported aspects of the AS care pathway were pain of the transrectal probe being inserted and pain during the biopsy procedure. This was closely followed by the fear or anxiety patients experienced prior to the test being performed. This experience of fear or anxiety had a health impact score of 1.4 for mpMRI but 2.1 for TRUS biopsy

Anxiety was a less common theme than may have been expected occurring in seven publications and collated in Table 3.8 (Pickles et al., 2007; Oliffe et al., 2009; Rittenmeyer et al., 2016; Ruane-McAteer et al., 2017; Ruane-McAteer, 2018; Shankar et al., 2019; Seaman et al., 2019). It is likely that overlap exists between descriptions and interpretations of uncertainty and anxiety. Indeed, anxiety in isolation, without associated uncertainty regarding AS, was reported in only two studies (Ruane-McAteer et al., 2017; Shankar et al.; 2019). However, anxiety in association with uncertainty was more commonly reported and featured in five of the studies featuring this key theme (Pickles et al., 2007; Oliffe et al., 2009; Rittenmeyer et al., 2016; Ruane-McAteer, 2018; Seaman et al., 2019).

3.4.7.1 Summary

Recurring findings within these studies highlighted the fear of the unknown. There was also anxiety about the effect of the diagnosis on sexual function. Distrust of health care practitioners added to the feelings of anxiety. Where closer relationships between patients and clinicians existed, lower anxiety levels were reported. Men appeared more content with their AS decision where there were high levels of information available and a high knowledge and understanding of PCa.

A simple strategy identified to address anxiety and worry was to provide a documented individual diagnosis and management plan. Studies in this theme also identified that patients with favourable-risk PCa deciding on treatment options may

require additional reassurance and information when considering AS, as well as throughout the pathway itself. Clinicians may need to adjust patient education and counselling in response to levels of anxiety.

There was evidence of fear and anxiety related to diagnostic tests during AS existing, with a greater health impact reported for transrectal imaging and biopsy than for mpMRI alone.

3.4.8 Synthesised findings – Theme 4: Fear of progression

Table 3.9 Key theme 4: fear of progression

Key theme: Fear of progression / Fear of recurrence	
Author and year	**Findings**
(Al-Dibouni, 2019)	Fear of progression (FoP) is acknowledged as a similar process as that of fear of cancer recurrence (FCR) but is more commonly used with patients with chronic conditions. The psychological impact of both FoP and FCR has been found to be the same (p. 9). Fear of recurrence literature suggests that most of the physiological impairment on quality of life for cancer patients is due to fear of cancer progression or recurrence. FoP was identified as an unpleasant weight to bear but there is no consistency as to what constitutes FoP. This burden can cause non-adherence to treatment strategies (p. 7). A lack of information contributes to a heightened FoP.
(Hedestig et al., 2003)	Having localised prostate cancer was described as living with a constant threat. Visiting the physician for a check-up was described as experiencing uncertainty and a feeling of security. The sense of uncertainty was related to worry and the fear of finding disease progression (p. 57). Living in the shadow of cancer results in experiencing uncertainty, worry and fear that the disease will progress (p.58)
(Kinsella et al., 2018)	Some studies identified within this systematic review suggested that FoP may be a limiting factor to choosing AS but no evidence to show that this contributed to a significant number of men opting out of AS without clinically documented progression. However, studies demonstrate that between 8 – 23% of men convert to active treatment for personal reasons alone (p. 272)
(Oliffe et al., 2009)	Men's uncertainty is seen to be time sensitive and peaked leading up to the scheduled AS appointments and impending PSA and/or TRUS-Biopsy results. A stable or decreased PSA score alleviated those concerns. As one participant on AS stated suggested that "every time [each appointment] it is like coming back from the dead" because when the results are in "I feel like I'm basically back to normal and life is fine." (p. 436)

(Rittenmeyer et al., 2016)	Despite reassurances of regular follow-ups and reassurances that the patients would die of something else before the prostate cancer affected them, the fear of spread was real and evident in the literature reviewed.
(Ruane-McAteer et al., 2017)	Fear of recurrence was a factor that appeared to be predictive of anxiety and FoP, a component of PCa-specific anxiety, was identified as a trigger for discontinuation of AS in favour of AT in this study (p. 12)
(Ruane-McAteer, 2018)	The wait for the next appointment regarding their AS was, for some, intolerable. Men feared that each PSA test, biopsy, or MRI, may trigger AT, therefore they were in a constant state of preparedness for what may or may not come (p. 13) There was a concern voiced by participants regarding the ability of AS and current monitoring tools (PSA tests, biopsy) to detect disease progression in time to receive the necessary curative treatment (p. 21)
(Seaman et al., 2019)	This qualitative study showed that most men switch to active treatment because there is evidence of disease progression, with fewer men switching due to anxiety – a meta-analysis suggests this is around 2% of men switched due to anxiety. Men reported anxiety around the time of surveillance testing (p. 10).
(Spendelow et al., 2018)	Men's responses in this survey identified that factors related to disease progression and treatment are an important contributor to their psychological wellbeing and coping strategies (p. 166)

3.4.8.1 Summary

Fear of disease progression / fear of cancer recurrence was identified in nine studies (Table 9). In eight of these, the description of fear of progression coexisted with either a feeling of uncertainty or anxiety (Hedestig et al., 2003; Oliffe et al., 2009; Rittenmeyer et al., 2016; Kinsella et al., 2018; Ruane-McAteer, 2018; Spendelow et al., 2018; Al-Dibouni, 2019; Seaman et al., 2019). In one systematic review, fear of progression was reported but without associated uncertainly or anxiety identified (Ruane-McAteer et al. 2017).

Synthesis of this theme identified that fear of progression (FoP) contributed to men's feelings of anxiety and worry. This fear was heightened around times of testing and waiting for results during the AS pathway. Concerns regarding test accuracy compounded the feeling of anxiety and fear that cancer may not have been detected gave false reassurance. Regular reassurance and information were required but the constant threat and FoP was real and appeared to be a factor in men's adherence to an AS pathway in the longer term. Men newly diagnosed with a low-risk prostate cancer should be provided with sufficient information about prognosis and treatment options, including AS protocols, to make informed decisions.

3.4.9 Synthesised findings - Theme 5: investigations and repeat testing

The studies included in the scoping review were undertaken when only transrectal biopsies (TRUS Biopsy) were undertaken for initial diagnosis and during AS. Transperineal prostate biopsies were only performed under general anaesthesia were not a common investigation at the time when studies included in this review were performed. As such, comments related to biopsy are specific to the TRUS biopsy technique.

Table 3.10 Key theme 5: investigations and repeat testing

Key theme: Repeat Testing	
Author and year	**Findings**
(Kinsella et al., 2018)	The physiological burden of AS, with respect to the associated repeat testing during AS, as well as the morbidity from repeat biopsies was found to be linked to reduce uptake of AS. However, evidence that men who were well informed about prostate biopsy were less likely to refuse repeat biopsy (p. 269).
(Oliffe et al., 2009)	Younger participants indicated that the physical discomfort of the TRUS biopsy procedure added to their anxiety about having regular AS check-ups. A participant on AS for 44 months was reticent to have his fifth TRUS biopsy because of the invasive nature of the procedure: *"I just felt really violated, I know it sounds funny, but you know I was sort of imagining well this must be what a woman feels like after she's been raped or something" (p. 436)*
(Ruane-McAteer et al., 2017)	The number of biopsy samples taken was also a factor that was predictive of anxiety. In particular, fewer cores taken at diagnostic biopsy led to a patient perception, however inaccurate, that more of their cancer had been removed (p. 12)
(Ruane-McAteer, 2018)	Participants characterised time on AS as time spent waiting, be it waiting for the next PSA test or biopsy, waiting for results, or waiting for advances in technology which would allow patients greater confidence in their results. *"You spend your time just waiting for the bloody postman" (p. 22).* However, the uncertainty around disease progression prevailed despite the initial sense of comfort provided by the medical test (p. 23) and overlap between the theme of uncertainty is identified here.
(Seaman et al., 2019)	Participants all had regular PSA testing and digital rectal exams, with frequency ranging from one to four times a year, though biopsies were performed less systematically. A few participants mentioned wanting to avoid biopsies, preferring the alternative of surveillance MRI tests. MRI guided TRUS biopsy results were perceived by some patients as being

	more reliable and reassuring than results from PSA tests or a standard TRUS biopsy (p. 7)
(Shankar et al., 2019)	Participants in the study reported the worst aspects of testing on AS. The worst aspect of the biopsy experience was the probe insertion followed by the pain of the procedure. The worst experiences of the MRI imaging were the noise of the scanner during the examination and the intravenous line insertion (p. 1398)

3.4.9.1 Summary

The studies included in this review identified that TRUS biopsies carried morbidity in terms of procedural pain, the invasive nature of the procedure, and uncertainty over accuracy. Tailored biopsy regimes may improve patients' experience but were dependent upon patient and clinician confidence in alternative testing and imaging. There was a desire to reduce the number of TRUS biopsy procedures required during AS and technological improvements may lead to reduced invasive testing. MRI imaging on AS provided reassurance and a hope that improved imaging techniques may reduce the biopsy burden.

Repeat testing was identified to be a source of anxiety with regards the waiting for results and the fear of progression until results were known. The repeat tests caused a continuous cycle of reassurance and uncertainty, plus a reluctance of invasive testing, which may lead to patients switching to active treatment. Active monitoring requires regular testing on any pathway. It is clear from the published studies that men understood the need for recurrent investigations and repeat testing whilst on an AS pathway as discussed in six articles (Table 3.10), (Oliffe et al., 2009; Ruane-McAteer et al., 2017; Kinsella et al., 2018; Ruane-McAteer, 2018; Seaman et al., 2019; Shankar et al., 2019). However, the required testing regime was met with mixed feelings. Heightened anxiety due to the uncertainty of the results was a likely cause of the association between repeat testing and the fear of progression described in four studies (Oliffe et al., 2009; Ruane-McAteer et al., 2017; Ruane-McAteer, 2018; Seaman et al., 2019). A dislike for painful, invasive repeat prostate biopsies was also a recorded concern related to repeat testing in four publications (Kinsella et al., 2018; Oliffe et al., 2009; Seaman et al., 2019; Shankar et al., 2019). The desire for new or improved monitoring techniques that may negate the need for invasive testing and was reported within this key theme with descriptions of the use and benefit of mpMRI emerged in two studies (Seaman et al., 2019; Ruane-McAteer, 2018).

It is recognised however, that the theme of security (theme 2) was also reported in conjunction with the theme of repeated testing. Five publications reported repeat testing and security as coexisting themes related to men's experience of AS (Ruane-McAteer et al., 2017; Kinsella et al., 2018; Ruane-McAteer, 2018; Seaman et al., 2019; Shankar et al., 2019). As described in Table 3.7, the regular check-ups and monitoring may indicate men felt more secure knowing that their cancer was being regularly assessed and investigated. Nonetheless, there was overlap in this theme with the themes of uncertainty, fear of progression and anxiety. The use of investigation and repeat testing is complex and multi-faceted for patients and needs to be carefully considered in any future research design.

3.4.10 Synthesised findings - Theme 6: coping

Table 3.11 Key theme 6: Coping

Key theme: Coping	
Author and year	**Findings**
(Hedestig et al., 2003)	Patients describe being alone with the disease; choosing to lead a solitary life with the aim of protecting and not worrying loved ones. Patients did not want to be pitied by others and chose to rarely talk about their disease with their families. Patients did describe the importance of talking to other patients with similar diagnose. This did not then involve the risk of being pitied (p. 59)
(King et al., 2015)	The value of peer support was evident at all stages of prostate cancer with diagnosis, treatment decision making and advanced disease being three critical times (p. 623). Support from a trusted other was beneficial for some patients but men recognised that family members have their own emotional reactions to cope with. For some men, the need to retain their 'normal' lifestyle despite their diagnosis was paramount (p. 624 – 625)
(Kronenwetter et al., 2005)	Reporting about the impact of a lifestyle intervention, men expressed positive attitudes towards participation believing it contributed to feelings of hope and a fighting spirit.
(Oliffe et al., 2009)	Living a normal life is seen to be an effective strategy to overcome uncertainty. Men stated that living a normal life was a protective mechanism to downplay and counter the uncertainty in monitoring, rather than treating, their prostate cancer, Men described stoicism to protect family members and ensure privacy in the wider community. This, however, led to tensions and contradictions. One spouse was surprised to hear that her husband had any uncertainty or anxiety about AS (p436 – 437).

	Some men were committed to self-help to prolong and compliment AS. Men investigate options and lifestyle changes that would improve their well-being. Doing something extra is a tangible way of contributing to AS (p. 438)
(Rittenmeyer et al., 2016)	Identified that men need to find ways of coping with the diagnosis. Some internalised and did not want to discuss with family or friends. Others adjusted their lifestyle and there was an unwillingness to medicalise their lives. Patients sought an empathetic, reassuring relationship with their healthcare practitioner and identify this as a way to ease the burden of AS (P. 211).
(Ruane-McAteer, 2018)	The need to protect, to appear in control and unaffected is consistent with the traditional male identity. Ironically, men feared that anyone they confided in would mirror their own fears of cancer-related death. The low-risk nature of their diagnosis was frequently cited as a reason to keep a level of secrecy about their health. Men implied that they were 'not sick enough' to be given the label of cancer patient (p. 11 – 12) Men felt a schedule naming and detailing the pattern of follow-up and relevant health care practitioner responsible for their care at each follow-up assessment point would provide a sense of comfort in terms of knowing what to expect at monitoring appointments throughout the course AS – making it feel more active. The author identified this a as a survivorship plan (p. 26)
(Spendelow et al., 2018)	Mutual support and camaraderie with other men diagnosed with PCa appeared to be a particularly important source of support to some (p. 162) This review summarised qualitative studies examining coping and adjustment of men diagnosed with PCa. A total of five meta-thematic categories were derived from this literature: avoidance, minimisation, and withdrawal: directing cognition and attention; reframing masculinity and seeking support; retain pre-illness identity and lifestyle; and symptom/side-effect management (p. 164)

Coping strategies and mechanisms were described within seven of the included articles and collated in Table 3.11, (Hedestig et al., 2003; Kronenwetter et al., 2005; Oliffe et al., 2009; King et al., 2015; Rittenmeyer et al., 2016; Ruane-McAteer, 2018; Spendelow et al., 2018). Of note, men's description or reference to coping with AS was only aligned with a feeling of security in the AS pathway in two of these publications (King et al., 2015; Ruane-McAteer, 2018) but was described in association with uncertainty in five publications (Hedestig et al., 2003; Oliffe et al., 2009; King et al., 2015; Rittenmeyer et al., 2016; Ruane-McAteer, 2018). This may indicate that coping strategies were adopted to better deal with the uncertainty of a monitoring pathway rather than an indication that they led to an improved sense of security for men. Indeed, coping strategies which support patients to minimise the impact of their

cancer diagnosis, have been shown to improve outcomes (Butow et al., 2000) in patients with other cancer diagnoses.

The benefit of sharing information with a family member or trusted other was discussed (King et al., 2015). Conversely, the need to internalize and avoid discussion with family or trusted others, for avoidance of pity or to reduce the burden on loved ones, was discussed in five studies (Hedestig et al., 2003; Oliffe et al., 2009; Rittenmeyer et al., 2016; Ruane-McAteer, 2018; Spendelow et al., 2018). Similar accounts from patients identified that creating a new-normal post diagnosis could assist with maintaining continuity of identity for patients, and that patients wishes for normality could produce differing responses to cancer in a patient cohort (Baker et al., 2016). Despite it being identified that avoidance was a coping strategy, of note, four studies (Kronenwetter et al., 2005; King et al., 2015; Ruane-McAteer, 2018; Spendelow et al., 2018) identified that men appeared to value the support of peers or clinicians to help them cope with the diagnosis and the AS pathway.

3.4.10.1 summary

Several coping strategies were discussed in the literature. Peer and clinician support was identified as a method men sought to assist when coping with AS. The desire not to medicalise AS or to burden loved ones with the diagnosis was described in these studies. Regular testing was identified as potentially impacting on men's ability to cope with AS.

3.5 Discussion

The six main themes identified by this scoping review demonstrate the complexity of men's experience of an AS pathway. Feelings of uncertainty were balanced against feelings of security that a monitoring process engenders; regular testing was shown to both cause anxiety and provoke a fear of progression, which could lead to patients questioning the validity of their decision for AS. There is evidence that men found coping strategies, but an overriding outcome from this review is the need to keep patients fully informed of their diagnosis, disease state and management plan. The primary aim of this review was to better understand the experience of patients with known low-grade prostate cancer who are managed under an active surveillance pathway. Following the scoping exercise, I have developed an in-depth appreciation of the mixed emotions that men experience, due to the burden of a cancer diagnosis and

then followed by the perceived lack of action. As succinctly put by Ruane-McAteer (2018), active surveillance is clearly a

> "cognitive emotional see-saw." (p. 1)

3.5.1 Key Themes

The six key themes that emerged from this review have a commonality that appear to be a factor in men's experience of AS. The need for additional, or bespoke, information during AS emerged within each key theme, but the lack of information, often perceived as inadequate and inconsistent, significantly contributed to the themes of uncertainty, anxiety, and fear of progression. Information was identified as an unmet need (McIntosh et al., 2019) and should be considered as an area in which patient care could be improved. The decision to select AS as a treatment strategy was reported to be difficult (Wagland et al., 2019). The recognition by clinicians of the importance to include trusted others in the decision-making process is testament to the anxiety that a cancer diagnosis causes (Brooks et al., 2018). However, evidence suggests that sometimes it is family members who press for more 'active' treatment, and it is, perhaps, the pressure exerted by loved ones that push men to internalise the diagnosis as a means to cope (Rittenmeyer et al. 2016, Ruane-McAteer 2021). Ensuring sufficient information is available at the time of diagnosis may reduce the attrition rate from AS later in the pathway. I have identified that adequate patient information will be required to ensure potential recruits to my research project are fully informed and able to make an informed choice to participate.

Fear of progression was also identified as a causative factor in patients choosing active treatment over AS (Pickles et al., 2007). The uncertainty of the accuracy of testing, in particular PSA testing, added to this fear (Ruane-McAteer, 2018). Regular reassurance and information are required to reduce this for patients. However, regular follow-up and testing was noted to provoke a cycle of uncertainty and anxiety, which may actually result in a barrier to the uptake of AS (Oliffe et al., 2009). Men appeared to cope with AS by either internalising the diagnosis (King et al., 2015; Brooks et al., 2018) or by finding coping strategies that helped them feel more in control (Kronenwetter et al., 2005; Oliffe et al., 2009). A monitoring plan, which includes regular testing and follow-up, aids men's ability to cope, and with that, an increased sense of security. The

impact of performing ultrasound examinations, as a research tool within the local AS pathway and part of my research design, requires careful consideration given this dichotomy of reassurance and anxiety testing that men experience.

Regular testing is a requirement for an AS pathway but this, in itself, created feelings of uncertainty and anxiety (Hedestig et al., 2003; Kinsella et al., 2018; Seaman et al., 2019). As this scoping review demonstrates, there was overlap between the negative aspects of monitoring and the feeling of security that comes with good results (Oliffe et al., 2009; Ruane-McAteer, 2018). The fear of disease progression was a concern to patients (Ruane-McAteer et al., 2017; Al-Dibouni, 2019) and created a feeling of living with a constant threat (Hedestig et al., 2003), which was exacerbated by the invasive nature of the prostate biopsies deemed essential on an AS pathway (Oliffe et al., 2009; Shankar et al., 2019). However, an identified benefit of AS is to delay active treatment to allow time for improved monitoring or improved treatments to catch up. Indeed, as discussed in Chapter 2 (2.7), developments in imaging (Eure et al., 2019) are suggesting an adapted biopsy regime can be implemented (Bates et al., 2020). Given that this scoping review has identified that patients were averse to repeat biopsies (Oliffe et al., 2009; Brooks et al., 2018; Shankar et al., 2019), and were looking to imaging to replace this invasive test, a role for alternative repeat testing may improve men's experience of an AS pathway. Research into the role of new imaging modalities in AS is clearly indicated.

3.5.2 The impact of imaging interventions on patients.

The secondary objective was to better understand the impact that imaging related interventions may have on the patients on an AS pathway. Whilst the theme of investigations and repeat testing did emerge within the scoping review, it was the least recurring. mpMRI featured in only two publications (Ruane-McAteer, 2021; Seaman et al., 2019) and ultrasound imaging, as a diagnostic tool, featured in none. Ultrasound guided investigative procedures did receive comment in terms of its use to guide the much-maligned transrectal prostate biopsy (Oliffe et al., 2009; Brooks et al., 2018; Kinsella et al., 2018; Seaman et al., 2019; Shankar et al., 2019). Indeed, the procedure itself, and pain of the probe insertion was noted to be the worst aspect of the biopsy experience closely followed by the pain of the procedure (Shankar et al., 2019). The outcome of this scoping review has identified that there is little known about men's

experience of imaging on an AS pathway. The impact of imaging, be that mpMRI or ultrasound for diagnostic purposes has not been explored and it remains uncertain as to whether it improves men's experiences in anyway. mpMRI has been identified as a reassurance for men (Ruane-McAteer, 2018) on AS and is perceived to be more reliable that PSA for example (Seaman et al., 2019) but little is known as to the impact or benefits of imaging. As discussed previously in Chapter 1 (1.12), access to mpMRI capacity for surveillance is limited but there is scope to develop monitoring using diagnostic ultrasound and a multi-parametric ultrasound approach as described in Chapter 2.7. With the advent of improved ultrasound imaging, and the availability of this imaging modality, there is opportunity to explore if the use of this technique adds value to the men's experience of AS.

3.5.3 Limitations

This scoping review is limited due to the paucity of published literature specifically exploring men's experience of imaging within an AS pathway. There have been many qualitative studies, included within this review, which have investigated various aspects of the AS pathway, but none have specifically assessed the role and impact of imaging. Whilst this has, therefore, identified a gap in the knowledge around AS, it has limited the value of this scoping review and its ability to meet its secondary objective. However, analysis of data extracted from this review identified six main themes, which can be extrapolated to the use of imaging, and, as such, men's experience of repeated scans inferred. Cognisance of these main themes will be essential in the design of the ERUP research trial.

A further limitation of this review is the selection of eligible publications. Only one reviewer assessed the validity of articles for inclusion although there had been input from three reviewers to agree on the inclusion and exclusion criteria used. This limitation subjects this review to selection bias. However, a wide range of publications have been included within the 18 studies reviewed, which provide a broad perspective on the subject under investigation. The inclusion of systematic reviews, as well as the primary research, may lead to duplication of data within the review itself and presents a third limitation. However, the research question of this scoping review has included the need to develop a broad understanding of men's experiences of AS and, as such, the primary publications were required to extract data which may have been omitted

from previous systematic reviews. Despite these limitations, the study aim and secondary objectives have been met.

3.6 Conclusion

In conclusion, this scoping review has identified that men's experience of AS is wide reaching and complex. The role of repeat testing can provide both a sense of security and a fear of progression. This review has identified that there is a desire to reduce the requirement for invasive and painful prostate biopsies during AS and that there may be a role for new imaging techniques in this pathway. Adequate patient information will be required to ensure study participants are fully informed of any research into imaging during their AS pathway to ensure that their feelings of security are maximised, and anxiety minimised.

The scoping review has answered the aim and secondary objective; a better understanding of the experience of patients with known localised prostate cancer has been achieved and the impact of repeat testing identified. However, data to better understand the role of new imaging technologies, and how they can be embedded within an AS pathway, remains unpublished and this remains an under investigated aspect of AS care.

3.7 Addendum

In April 2024, the original PEO MeSH terms were used to systematically search for any new, original publications. The same inclusion and exclusion criteria were used (Table 3.1) and two full text studies were identified (Al Hussein Al Awamlh et al., 2023; Sutherland et al., 2024). This are summarised in Table 3.12 below.

Table 3.12 Study aims, design and methodology of included publications from follow-up search (Feb 2024)

Author and year	Participants	Study aims	Study design and methods
Al Hussein Al Awamlh et al. 2023	Men with a 10-year survival of prostate cancer who had undergone AS, prostatectomy or radiotherapy. Participants were diverse regarding geographic location, education, and race/ethnicity	Aim to explore the early experience, long-term experience, and advice provided for others among long-term survivors of localized PCa	Semi-structured qualitative interviews of 66 men. A grounded theory approach was used to code and anlayse the data. The research team iteratively developed a codebook based on key domains reflected in the interview guide as well as themes emerging from a review of transcript
Sutherland et al. 2024	Men with localised low grade prostate cancer being monitored by MRI during AS A diverse racial and ethnic population was recruited	To understand men's perception of MRI during AS	Semi-structured interviews undertaken in a group of 20 men. Black and Latino men were purposely oversampled. Thematic content analysis performed

Both studies originate in the United States of America (USA), and in both of these studies, the authors purposively recruited and over-sampled men from diverse racial and ethnic backgrounds. This cohort of men are underrepresented in previous published studies to date, which may reflect the socio-demographic characteristics associated with health economics in the USA. Both studies elicited data correlating with the six emergent themes from the original scoping review. Al Hussein Al Awamlh et al, (2023) identified that anxiety was commonly reported by men on an AS pathway. They also identified that men required a coping strategy and that the strain of coping with an untreated cancer diagnosis on AS caused personal relationships to suffer. By contrast, Sutherland et al, (2024) found that men within their cohort experienced a high degree of security due to the value they placed on regular monitoring with MRI, and they identified that patients had an interest so that timings or omission of a repeat prostate biopsy could be considered. Both studies have identified that patients have a

need for information about the pathway and testing although detail is limited in the abstract alone.

In summary, both studies have contributed knowledge about the experience of men from a more diverse background. The studies have contributed to the knowledge gleaned by the original scoping review and have not contradicted the six key themes originally identified. The studies have gone some way to answering the gaps in understanding related to men's experience of MRI in AS, but the role of ultrasound imaging remains unanswered.

This chapter has identified that the experience of men on an AS pathway was explored in previous published studies, and that more recently published studies concur with the conclusion originally drawn by this scoping review. A gap in knowledge related to the role of imaging within an AS regime has been identified. The next chapter investigates how new technologies can be embedded into clinical practice and who is best placed to deliver them.

Chapter 4 Embedding new technologies in clinical practice

This chapter investigates the role of the sonographer and whether this professional group is best placed to introduce and embed new technologies into established clinical pathways. The rationale for role extension and the challenges that are associated with non-traditional roles undertaking advanced clinical practice are examined.

An abridged version of this chapter was published online in December 2022 and in print in May 2023:

Parker, P., Edwards, H., Twiddy, M., Whybrow, P. & Rigby, A. (2023) Embedding new technology into clinical ultrasound practice: Is role extension for sonographers the key to improving patient pathways? *Ultrasound*, 31(2), 84-90.

4.1 Context

The sparsity of published evidence I identified in Chapters 2 and 3, regarding the use of mpUS and microUS within active surveillance, indicates that this is a novel regime and will require knowledge and skill development, in the practitioners undertaking, interpreting and evaluating the outcomes of such imaging, if it is to be a useful tool. An acknowledged gap exists between developing new treatments and knowledge in a research setting and implementing these in daily practice (De Brún et al., 2016; May et al., 2016). This chapter of my thesis reviews what needs to be considered within a clinical radiology team to address the challenges of implementing new technology within the prostate cancer pathway. The historical workforce issues related to delivering new services in radiology, and the evidence to support skill mix and role extension, primarily within the scope of practice of ultrasound imaging are reviewed. The drivers for changes to roles, which include technological advances leading to improved diagnostic capabilities, and the barriers that exist that may limit how new technology can be embedded into clinical practice are discussed.

4.2 Implementing changes to clinical practice

Despite the publication of a defined framework for the development and evaluation of research (Finch et al., 2018), there remain substantial problems in the design and conduct of studies introducing complex interventions and their subsequent implementation in clinical practice. In part, these problems arise due to the assumption that practitioners within every day practice have the confidence,

knowledge, and skills to undertake the extended scope of practice that is required when implementing new techniques (Culpan et al., 2019). The understanding of an implementation process is key to ensuring that proposed changes to techniques, technologies or interventions are both implemented and sustained in practice. May et al (2018) identified that the desired outcomes of a 'successful' implementation do include the experiences of those providing the service and that the cultures of practice need to be understood before changes can be made. As Hancock et al (2012) discuss in relation to the use of enhanced diagnostic endoscopy techniques, new technology may provide good diagnostic results during its research phase, but when cumbersome and timely to undertake, such new technology is unlikely to be implemented into routine healthcare. Equally, complex or novel imaging or interventions undertaken by practitioners who lack the requisite confidence and skills are, at best, poorly delivered and, at worst, at risk of causing patient harm (Paulo, 2021). An understanding of the impact on practitioners that the new complex mpUS and microUS techniques may have in real-life clinical practice is required to ensure that the proposed benefits of these techniques can be realised within the patient pathway. Prior to initiating change, an appreciation of the historical practices within imaging is required to ensure there is an understanding of how past events influence current practice.

4.3 Historical Practice

In response to the 2000 NHS Plan, Price & Le Masurier (2007) surveyed radiology departments to identify what changes, if any, had been made to roles within their clinical teams, which would contribute to enhanced patient care. There is an argument within any established medical led service as to whom is best served to undertake specific roles and maintain safe patient care, not least within primary care as Nelson et al discuss (2018). Rycroft-Malone et al (2008) present strong evidence that nurse-led protocol-based care not only has a positive impact on the nurses' role but also leads to an improvement in care. Whilst this evidence exists, role extension, particularly in prostate cancer imaging has not always been prevalent within ultrasound practice. Traditionally, radiologists or urologists performed the diagnostic transrectal prostate biopsy procedures within the cancer pathway. Indeed, in Europe and North America, the idea of a non-medic performing ultrasound guided procedures remains something of an anathema (Seitz, 2017). Whilst there is a technical role for a non-medical

ultrasound technician, in many countries, ultrasound is seen as a natural extension to the clinical consultation of doctors and is performed by medical specialists

> "as frequently as they use their stethoscopes" (ibid.).

An emotive position statement by the German Ultrasound Society (DEGUM, 2018), in response to an earlier editorial by Edwards & Sidhu (2017), raised concerns about the reproducibility of ultrasound imaging by a technician as the felt this may preclude accurate retrospective interpretation by a third-party radiologist or medic. As such, they maintain the accountability for ultrasound examinations and reports should not be delegated beyond the medical profession. Indeed, the German position statement (DEGUM, 2018) goes so far as to state:

> "it would be inadvisable to jeopardize the quality of ultrasound by delegating examinations to medical support staff".

Despite the ongoing controversy and debate surrounding who the most appropriate person is to undertake medical imaging in Europe, it has been longstanding good practice within the United Kingdom (UK) for sonographers (non-medical practitioners) to independently perform and report medical ultrasound examinations (Edwards & Sidhu, 2017). The development of non-medical roles performing image acquisition and interpretation in the UK has been driven primarily by shortages within the medical radiologist workforce, which the Royal College of Radiologist (RCR) continue to report in their annual census statements (2022). In addition, as Hill discusses (2009), technological and interventional advances have resulted in radiologists extending their own skill set and roles into more complex procedures that have previously been undertaken by other medical specialities, resulting in a void, which has been filled by radiographers. As early as 1996, UK radiographers and sonographers were encouraged and supported by the RCR to undertake duties delegated by radiologists to ensure that service demands could be met (RCR, 1996). There is longstanding evidence, first presented by Bates et al (1994), and soon followed by Leslie et al (2000), that sonographers deliver safe and effective care and can fill the vacuum left by radiologists' own role extension. As such, sonographers would be the natural choice to consider developing knowledge and skills in the new ultrasound imaging techniques proposed to enhance the prostate cancer pathway.

4.4 Role of the sonographer

The role of a sonographer is defined by the UK professional bodies (BMUS & SCOR, 2023) as

> "A healthcare professional who undertakes and reports on diagnostic, screening or interventional ultrasound examinations."

The role is an almost uniquely UK based one; there are sonographer roles well established in Australasia, South Africa, the USA, and emerging in Europe but most have little in terms of reporting responsibility (McGregor et al., 2009; Miles et al., 2021). The UK education system for sonographers, endorsed by the Consortium for the Accreditation of Sonographic Education (CASE) (2019), reflects the responsibility and accountability encountered in the practitioner role and includes report writing skills. The closest comparative education model is the American Registered Diagnostic Medical Sonographer (American Registered Diagnostic Medical Sonographer, 2021) post graduate award, which does enable practice in the USA and the UK, despite sonographer reporting not being widely established in the USA clinical model. The most comprehensive survey of the sonography profession in the UK to date was undertaken by the Centre for Workforce Intelligence in 2017 (CfWI, 2017). This survey demonstrated that, whilst sonographers are from a diverse professional background, 70% are qualified radiographers who have undertaken additional post graduate training in medical ultrasound. Regardless of professional background, the vast majority of sonographers based in the UK will hold the minimum qualification of a post graduate certificate following a programme of study accredited by CASE (Harrison et al., 2021). As discussed by Parker and Harrison (2015) when they explored the career structure of sonographers, appropriate training in ultrasound is clearly the key to providing a safe and effective diagnostic and interventional ultrasound service regardless of whom is delivering that service. This can be no less essential when new and novel technologies are employed.

4.4.1 Sonographer role extension

For most sonographers, performing, interpreting, and providing an expert opinion on their findings now forms the fundamental aspects of their role. However, increasingly, sonographers are extending their roles to incorporate more complex procedures traditionally performed by radiologists, such as ultrasound-guided biopsies, fine needle

aspiration, and patient management (Kettlewell & Richards, 2021). The first instances of sonographer role development into the field of prostate biopsy were reported in 2005. In April of that year, Wright (2005) identified that four sonographers were trained to perform transrectal ultrasound guided prostate biopsies so that

> "spare equipment capacity could be utilised despite a lack of spare radiologist capacity."

Hunt (2005) reported the advent of sonographers leading a prostate clinic and performing prostate biopsies where required with eight sonographers being trained so that the service could be delivered. In both instances, these role extensions were introduced to meet the challenging targets set by the Department of Health with the aim to reduce 'referral to result' waiting times by streamlining patient pathways and optimising health care worker skills-mix (ibid). These early reports provide the scant evidence that the role of the sonographer was changing from an imaging technician to the advanced clinical practitioner of the modern service. A review of the evidence for role development published by Hart and Dixon (2008) highlights the limited peer reviewed evidence available to support practice. It is noted that, whilst the review contains reference to eight studies presented during professional study days, none were subsequently published. There is grey literature evidence of developing practice within the profession that does little to dissuade the potential inherent discordance between the professions of radiologist and radiographer. Despite the limited but compelling evidence that sonographers can safely and accurately interpret ultrasound imaging, there is little evidence from the medical professions to support the need for skill mix and role extension within the ultrasound profession.

4.5 Ultrasound skill development

Nicholls et al (2017) identified that, as in many other allied health profession roles and tasks undertaken by medics, ultrasound is commonly taught as a two-step, 'see one, do one' approach where the educator demonstrates the task to the learner. In the case of new technology, there is no practitioner, medical or otherwise, with the knowledge to be the educator. It is acknowledged that interpretation of diagnostic tests is subjective, and supervision and education of practitioner performance is important to establish and embed skills (Lin et al., 2018). As Harcus and Smith discuss (2019), learning new skills within a small cohort team encourages peer learning and

collaboration, which can enhance development. Strong performers within a team are known to assist others to improve their diagnostic capability and, as such, are an important factor in the diagnostic accuracy achieved by a test (Lin et al., 2018). Field and Snaith are leading authors in relation to the development of advanced practice skills. They identified the difficulties that some practitioners may encounter; pioneering individuals extending their own role can lead to a feeling of isolation and lack of support (Field & Snaith, 2013). As such, Culpan et al (2019) advocate the need for shared learning, with no differentiation between professions, as essential to successfully embedding new technologies into the prostate cancer pathway.

As identified, ultrasound imaging within the prostate pathway is niche with few practitioners performing transrectal ultrasound examinations and even fewer published studies (Hart & Dixon, 2008). There are considerations to be made with such a small cohort of practitioners developing new skills together. A leader of the team will be required to ensure that standard operating procedures can be developed, that boundaries of practice are agreed, and that standards for training are adhered to (Field & Snaith, 2013; Harcus & Snaith, 2019). Ideally, as Forsyth and Maehle (2010) discuss, a consultant sonographer should assume this role; their remit is to provide leadership, education, be a clinical expert in their field, and support research and audit within their service. However, this must be balanced alongside the professional protectionism barriers that may pervade in a multi-professional team if not carefully managed.

4.5.1 Image interpretation

A further consideration, as ultrasound skills are developed in this new technique, is an understanding of what constitutes an accurate interpretation of the microUS prostate imaging. There is published image interpretation guidance (Ghai et al., 2016; Eure et al., 2019) for the new microUS but no published standards for diagnostic accuracy; this is yet to be investigated. Even with established imaging modalities, there is no quality standard for image interpretation of ultrasound, so it is perhaps not surprising that none exist for novel techniques. The RCR suggest a benchmark accuracy of 80% against a known gold standard expert (Wright & Reeves, 2017), but with no expert in the team, skill development and role extension will require multi-professional collaboration and support to determine the appropriate level of agreement achievable.

4.5.2 Collaborative practice

The early publications by Bates et al (1994) and Leslie et al (2000) compared the standard of ultrasound reports generated by radiologists to that of non-medical sonographers. The audit by Bates et al (1994) determined that sonographers involved in non-obstetric ultrasound appropriately met locally agreed standards and concluded that they should be involved in service delivery as independent practitioners. Although this published audit, and a further study by Dongola (2003), provided positive evidence to support sonographer practice, questions of who the most appropriate practitioner to undertake abdominal ultrasound continued within both the radiology and radiography professions as demand for services outpaced the radiologist workforce in the UK in the early 2000's (SCOR & RCR, 2006). Hard copy images are routinely captured during ultrasound scans. These are representative of the findings observed by the ultrasound practitioner during the examination but are open to misinterpretation if the image has been captured incorrectly or potential pathology not observed so not captured. Despite the evidence that hard copy images captured are difficult to interpret (Dongola et al., 2003), at some centres radiologists routinely provided technical retrospective opinions on the images produced by sonographers. The rationale being that the request for imaging constituted a clinical referral and, as such, a reporting radiologist was required to provide the clinical opinion sought by the referrer (RCR, 1996) to meet the needs of the process rather than as an evidence-based need for medical expertise (Leslie et al., 2000). When accuracy of reporting and interpretation was tested, no statistically significant difference between sonographers and radiologists was detected (ibid). A further non-UK audit by Loh et al (2003) concurred with these findings and, gradually, sonographer practice has developed into the profession widely utilised in ultrasound imaging across the UK today. This largely comprises of the sonographer performing, interpreting and providing diagnostic opinion of ultrasound imaging as advocated by the UK professional bodies of the British Medical Ultrasound Society (BMUS) and the Society and College of Radiographers (SCOR) (2023).

4.6 Role extension

As Nightingale et al discuss (2021), enthusiasm in a role is the secret key ingredient often overlooked but essential for retention and role development. The first step to

ensuring new technology can be implemented into a clinical pathway is the identification of an individual(s) or a team(s) who will take on this new work with, at least, some degree of enthusiasm. Role extension is recognised as a mechanism to develop and promote a flexible, resourceful, and motivated workforce, as opposed to reducing cost frequently associated with skill mix. Commonly in healthcare, role extension refers to individuals attaining supplementary skills and responsibilities, which are an escalation of those obtained at the point of professional qualification and registration (Hardy & Snaith, 2006). Managers are encouraged to support role extension to avert crisis in either the availability of staff skills or resources. As Weobong (2021) discusses, allowing the workforce to extend their knowledge and skill base can positively enhance how practitioners consider their place in the team.

Role extension is not a new concept; Murphy (1970) authored one of the first publications to debate whether the role extension of nurses would result in a loss of the primary functions of a nurse and a consequent detriment in patient care. Indeed, this theme has continued as role extension continues to be debated. Roles naturally develop in response to innovations in healthcare, but as skills of healthcare providers, be that doctors, nurses or radiographers, expand a void is created and concerns, as discussed by Pearcey (2008), over the abdication of a role as opposed to the delegation of roles are raised. There is documented reluctance to empower junior staff (Bowler & Mallik, 1998) and, clearly, promoting role extension whilst maintaining safe and effective practice is a fine balance that needs to be considered prior to implementation. Nelson et al (2018) identified the wider consequences that skill mix may bring in a primary care setting; role extension for one group may not lessen the workload burden for others, particularly for those responsible for the delegation and oversight of tasks.

Radiology departments have seen significant changes to technology, particularly as the digital age has embedded in healthcare. The advent of computerised radiography and digitally assisted image capture (Hill, 2009) resulted in swifter turnaround times from image capture to outcome report being expected and this has outstripped the traditional workforce capacity (RCR 2022). As services change, and new technology becomes available, it is inevitable that the role of practitioners has to develop beyond the skills learnt during initial training. For some, this will take the form of advancement

beyond learning new technical skills, and will involve the attainment of higher professional knowledge, commonly for sonographers, by undertaking master's level programmes of additional study (Hardy & Snaith, 2006). However, not all development may require formal academic support; indeed, within radiography and sonography, role development has occurred through the adoption of new radiological tasks leading to role extension (Field & Snaith, 2013). As Henderson et al (2016) acknowledge, with this extension of skills comes the mixed feelings of improved job satisfaction balanced against the increased responsibility and accountability that can prove challenging in complex patient care pathways.

Role extension for practitioners will, inevitably, provide options and viable solutions for developing new imaging technologies and techniques. Indeed, role extension is seen to provide a more resourceful and dynamic workforce with transferable skills and attributes (Field & Snaith, 2013) that can add resilience to a team. Without the development of practitioners to support their medical colleagues, there is evidence that some radiological services would be undeliverable (Henderson et al., 2016) and the high correlation between radiologist and radiographer performance provides reassurance that safe practice can be delivered when specific tasks are delegated (Gaarder et al., 2015).

4.6.1 Sonographer role extension

Sonographers aptly lend themselves to role extension. As Forsyth and Maehle identified, (2010) sonographers are commonly the first point of contact for patients, particularly for patients attending for surveillance imaging where scans are performed prior to consultation. The intimate nature of prostate imaging requires an innate professionalism and an understanding of the needs of the patients under investigation for suspected cancer. Advanced practice role extension in this field could only be entered into by practitioners with these skills given the sensitivities involved. However, despite role extension being well developed within imaging, Field and Snaith (2013) noted that this is not replicated across disciplines and sonographers working in the field of both radiology and urology will be required to cross professional boundaries as they take on roles commonly performed by urologists rather than radiologists (Grummet et al., 2020). Role extension is known to broaden the outlook of practitioners beyond the narrow scope of imaging. As Henderson et al (2016) discuss,

role extension is identified as a mechanism to improve recognition and standing within a hospital setting thereby easing the path for multidisciplinary service development across those profession boundaries. This will be essential if sonographers are to extend skills in prostate imaging that traditionally sit within the urologists' scope of practice.

4.7 Scope of practice

Role extension, leading to advanced practice for individuals, is well established in some UK NHS trusts but, as Culpan et al (2019) have also identified, the scope of practice for sonographers and radiographers varies widely. A recent review of a small cohort of sonographers, undertaken by Kettlewell and Richards (2021), identified that only 34.8% (n = 32 / 98) felt they had extended their role beyond that of initial training; of these only 9% (n = 3 / 32) performed ultrasound guided prostate biopsies. A more recent, larger cohort study of 300 sonographers undertaken by BMUS (2021) identified that 81% of respondents were practising at an advanced level in terms of clinical practice but, on further analysis of the data, it emerged that only 25% of sonographers truly fulfil the Health Education England criteria for advanced clinical practice (HEE, 2017). Within this BMUS survey, only 2.7% (n = 8/300) stated that they routinely perform prostate ultrasound examinations and, most commonly, this was done to guide biopsy sampling and not diagnosis (BMUS, 2021). Neither survey is an extensive cohort sample from the sonographer population, although the exact number of sonographers working in the UK is poorly understood; in part due to the diverse entry route into the profession and in part due to the fact sonographer is not a protected title and not identifiable on the NHS staff returns (CfWI, 2017). Neither survey, therefore, may be truly representative, but both do indicate that prostate imaging, by sonographers, is niche.

The reasons for so little role extension in prostate imaging is not explored in either study. It may be that the demand for such skill development is limited; equally, it could be that the desire to extend skills in this area is lacking. This may lead to limitations in the development and implementation of new technology given the scarceness of peer support. Whilst there is evidence in studies by Culpan et al (2019), and the BMUS survey (2021), that role extension can bring positive benefits to working lives, practice in some institutions develops in response to local service demand rather than due to the enthusiasm and desire of practitioners (Henderson et al., 2016).

4.8 Drivers for change

There are many drivers for role extension. As Edwards and Sidhu (2017) discuss, although a shortage of radiologists in the UK has historically driven the change in practice, this has allowed the development of the sonographer role beyond that originally performed by medics in the 1990's. Role extension within the UK is certainly required if the demands for health care continue to rise as predicted. Demand for diagnostic ultrasound imaging continues to rise at approximately 5% per annum (RCR 2022), although this could increase as the effects of the COVID-19 (NHSE&I, 2022) pandemic and subsequent increasing demand for cross-sectional CT and MRI are fully realised. The 2021 RCR workforce census, identified that the NHS radiologist workforce is currently short-staffed by 33% and this short fall is predicted to grow to 44% by 2025 (RCR 2022). This significant shortage, coupled with the aging population presenting with increased incidence of cancer (Field & Snaith, 2013) may result in unmet demand and increased waiting lists unless other means of providing essential diagnostic imaging can be met (Henderson et al., 2016).

These drivers for change encourage role extension which is augmented by the technological improvements in image quality, ease of use of diagnostic machinery, and recognition that a multi-professional service supporting skill mix allows for significant pathway redesign and improvements in referral to diagnosis waiting times (Culpan et al., 2019). These drivers provide a sound argument for role extension that will also lead to service improvements. Faster and more effective diagnostic outcomes were identified in a study by Woznitza et al (2018), when chest X-Rays were reported by radiographers, leading to improved life years following lung cancer diagnosis. There is, however, little published evidence to support the notion that radiologists' capacity is released by radiographer role extension. Indeed, whilst guidance and standards have been published to underpin skill mix (RCR, 1996; SCOR & RCR, 2006), Loughran (2015) describes the strength of opposition encountered by a minority when radiographer reporting was first proposed. The anecdotal evidence Loughran reports (ibid.) suggests that the introduction of role extension is a contentious issue, however beneficial to improved activity or patient care that may be. In support of role extension for radiographers, Forsyth and Robertson (2007) identified that a large proportion of the radiologists they surveyed (82%) were in favour; despite this, a greater understanding

of the benefits and risks, particularly in areas of practice using new and developing technologies, is required.

4.9 Benefits of role extension

Role extension not only benefits patients and provides support to radiologists and imaging services, but it is also identified to be of benefit to the practitioners themselves. Respondents to Henderson et al's (2016) questionnaire described a feeling of increased job satisfaction and morale within the team due to their input into improving patient care pathways. At a time of workforce supply issues (CfWI, 2017; Nightingale et al., 2021), anything that can enhance the wellbeing of staff within teams has to be valued and encouraged. Inter-professional learning and development can help strengthen team bonds by increasing mutual respect and breaking down barriers that can occur (Harrison et al., 2021), particularly as new services emerge or there is role extension across professional boundaries. The professional recognition within teams develops over time and with increased confidence and experience, further enhancing the feeling of personal achievement, self-reward, and job satisfaction (Field & Snaith, 2013; Culpan et al., 2019). For service providers, this increased motivation is more likely to lead to staff retention and promote career development for junior staff (Mitchell et al., 2019) providing yet a further cost saving benefit. However, role extension leading to embedding new interventions and techniques in practice, improvements to services, improved patient care, and provide benefits to practitioners can only be realised with support from multi-professional teams working together with a common goal (SCOR & RCR, 2006; Culpan et al., 2019).

4.9.1 Maximising benefits: minimising risk

The benefits of delegation must be balanced against the risk to both the role extended practitioner and the delegating clinician or employing organisation. Adverse events that, hopefully rarely, occur require accountable practitioners. Keenan et al (2001) discuss how risks of role extension can be minimised within a validated system of delegation providing there are clear guidelines on medico-legal implications, valid consent and accountability available. Skill development can be supported safely within an environment that offers appropriate training and assessment of competence, provides suitable departmental protocols, and clearly identifies the allocation and delegation of responsibility (Keenan et al., 2001). However, even with this in place,

delegation of duties carries a medico-legal risk that cannot be underestimated and remains a factor in the reluctance of some to support role extension (Calafiore, 2019) for non-medical practitioners.

4.10 Risks of role extension

Any changes in practice must also be considered in terms of risks to both patients and practitioners. The perception that radiographers do not receive appropriate and relevant education to ensure safe practice is the perspective from Royal Australian and New Zealand College of Radiologists (RANZCR) that Calafiore (2019) describes. RANZCR suggest a lack of medical education in the sonographer curriculum limits the knowledge and understanding within clinical practice (ibid.). Closer to home, a survey of 132 Scottish radiologists, undertaken by Forsyth and Roberston (2007), identified a further five key risks that radiologists expressed when the issue of radiographer role extension was explored. The risks identified were:

- Impact on specialist registrar training.
- Dilution of radiologist's own skills.
- Radiographer's recognition of own limitations.
- Lack of clear medico-legal responsibilities.
- Clinical governance issues.

I have collated concerns into four main themes to explore further.

4.10.1 Impact on training and dilution of skills

The two risks of impact on training and dilution of radiologists' skills are not supported by published evidence. These perceptions may be related to professional protectionism, particularly as new roles traditionally performed by one staff group, are undertaken by a less qualified practitioner. However, the reality is that recruiting radiologists is difficult due to the workforce shortages that the RCR describe (2022). As Willson (2006) identified, role extension was essential within breast imaging given the recruitment of radiologists was unsuccessful. Willson (ibid.) identified that appropriately trained radiographers could successfully take on roles traditionally performed by radiologists, including supporting the training of specialist registrars and, as such, the impact on training was minimised.

Professional protectionism is the risk and barrier to role development most frequently discussed in published literature (Culpan et al., 2019). Field and Snaith (2013) describe the entrenched hierarchy within medicine, which sets up an inherent, and potentially inherited, resistance to non-medical role development. The issue of professional protectionism appears to have a greater impact within radiology than in other multi-professional groups. This maybe, in part, related to the technical aspect of the sonographer role within radiology (Henderson et al., 2016), although most recent reports of resistance to role development are related to radiographer reporting X-Rays (Culpan et al., 2019). The clinical application of ultrasound has expanded beyond the scope of radiology and now forms part of many clinical examinations although greatest users of ultrasound remain sonographers (Nicholls et al., 2017). Published evidence supports the safe and effective development of the sonographer role (Bates et al., 1994; Gaarder et al., 2015) with little evidence of inconsistency between professions. Despite the reported perception that sonographers performing traditional radiologist roles may impact on medical registrar training (Forsyth & Robertson, 2007), sonographer role development is now widely established and supported within the UK.

4.10.2 Limitations to practice

Identifying limitations to practice is key to the delivery of safe and effective patient care, whomever is undertaking the procedure. Indeed, this is such an important factor that it is documented as a key component of professional ultrasound practice by both BMUS and SCOR (2023), as well as featuring as a mandatory component of any clinical assessment during CASE accredited ultrasound training programmes (CASE, 2019). Underpinning education is essential to ensure that practitioners who extend their role have the knowledge and skills to deliver safe patient care. The perceived lack of education of radiographers, by radiologists, was identified by Loughran (2015) as he explored the extended role of radiographers within his own clinical setting. However, he later identified that radiographers undertaking post-graduate training were assessed to a far larger degree than their radiologist colleagues within the narrow scope of practice in which they were being trained (ibid.). Such is the emphasis on delivering underpinning knowledge and skills that recent policy and practice guidance for radiographers reporting has been published with the aim of establishing and maintaining standards across imaging networks in England (Woznitza et al., 2021) and reducing the risk of misdiagnosis.

4.10.3 Error and discrepancy

Misinterpretation of imaging is a known risk within radiology. Errors or discrepancies in imaging reports are estimated to occur in between 3 – 5% of cases (Brady, 2017). Errors can occur due to human factors or be related to system malfunction or software inaccuracies (ibid.). Whilst RCR (2018) guidance is published to minimise error and to standardise practice, it is acknowledged that misdiagnosis can have a significant impact on patient care (Brady, 2017). Radiographer role extension is a duty delegated by a consultant radiologist; the radiologist retains the responsibility for any image interpretation undertaken and this is clearly described by the SCOR and RCR joint publication (2006) and by the RCR standards for reporting (2018). However, the SCOR and BMUS professional guidance (2023) indicates that the practitioner performing the ultrasound examination is both accountable and responsible for writing and issuing the diagnostic imaging report. Whilst this remains a delegated duty, there is, perhaps, some ambiguity surrounding the medico-legal responsibilities and, as such, this remains a real risk to extended role practitioners and delegating radiologists. A risk, however, that can be mitigated by the development of clear standard operating procedures and protocols.

4.10.4 Clinical governance procedures

Clinical governance procedures are essential if providers are to assure a quality service can be delivered. As Hardy and Persaud (2001) attain, measurable standards of practice are required to support the development and role extension of radiographers. An understanding of the quality of practice within a clinical setting is crucial if practitioners are to improve and deliver an optimal standard of patient care. Chandy et al (2000) describe the role of clinical governance in radiology, primarily from a radiologist's perspective. They describe how audit and peer review can be established to review standards and reduce the discrepancy rate of image interpretation pertinent to a wide range of radiologists' functions. Parker and Byass (2015) published evidence of a peer review tool that could be used to provide a transparent and tangible account of sonographer performance and, thereby, improve service delivery. Clinical governance procedures are now well established within radiology practice, with the process of learning from discrepancy meetings now an advocated standard published by the RCR (2020). Peer review processes, and identifying learning from errors, is a documented requirement for professional practice as described by SCOR and BMUS

(2023). Whilst clinical governance issues may present a risk to patient care if role extension is supported, the tools and guidance now in place for all practitioners mitigate the risks and allow the benefits of role extension to be appreciated safely in a clinical setting.

4.11 Barriers to changing practice

As evidenced, well-established skill mix teams, with supported and encouraged role extension, are a reality in many UK centres (Forsyth & Maehle, 2010; Field & Snaith, 2013; Henderson et al., 2016). Nonetheless, there is recent evidence to indicate that, where role extension is not advocated or supported, there is attrition from the profession at a time when there is a pressing need for increased volume of diagnosis imaging activity (Nightingale et al., 2021). Ultrasound imaging is operator dependent and requires interpretation of moving images. As Hill (2009) describes, the ultrasound technology requires the machine operator to interpret the acquired images in real time if the scan is to be of diagnostic value. As technology improved, sonographers were amongst the early implementers of role extension as they began to report ultrasound images, they produced independent of radiologists providing a second review (Bates et al., 1994). The emerging technological developments of multi-parametric (mpUS) and micro ultrasound (microUS) lend themselves ideally to role extension for sonographers within the current prostate cancer care pathway, particularly as there is a drive to meet the faster diagnostic pathways that are dictated by NHS England (NHSE, 2022). For such developments to be meaningful there has to be cross professional support as well as support from medical colleagues within the radiology field.

Role extension for sonographers into external professions, such as urology, is a rare occurrence and comes with its own challenges of the lack of an understanding of professional roles that is otherwise inherent within radiology departments (Field & Snaith, 2013). However, the inherent understanding of the roles of radiographers and radiologists within a radiology team does not preclude challenges nor, indeed, significant barriers to role extension that need to be overcome if implementing change and new practice is to be a success (Culpan et al., 2019). Understanding roles does not necessarily mitigate against professional protectionism as a barrier to change,

although, more pressing fiscal, or workforce supply issues are real challenges to be overcome.

4.11.1 Resource challenges

Within the UK, concerns regarding patient welfare are rarely expressed in relation to reports of role extension; these patient welfare concerns remain within healthcare systems, such as Germany and Australasia (DEGUM, 2018; Calafiore, 2019) that are funded in entirely differing ways to the "free at the point of delivery" NHS (Delamothe, 2008) and, as such, cannot be considered as barriers to UK based role development. However, despite the NHS funding model, or perhaps because of it, fiscal issues certainly are a concern of health care providers, with managers having to find funds to ensure staff are appropriately rewarded for increased responsibility and accountability. Disparity in pay for equivalent roles is a factor in attrition from radiology (Nightingale et al., 2021). The NHS Agenda for Change pay structure (National Health Service (NHS), 2021) was implemented in 2004 to bring parity of pay for roles undertaken across employers; the reality is that a wide variation between employers exists, primarily due to the range of advanced practice and range of job titles that now occur (Wood et al., 2020). As such, there is reluctance by some practitioners to take on further responsibility if this is not recognised with financial reward (Forsyth & Maehle, 2010) although, this is infrequently reported and far outweighed by the reported desire to progress and extend practice for the satisfaction this brings (Henderson et al., 2016).

4.11.2 Workforce barriers

Fiscal barriers are also an issue when additional training is required. Despite support for role extension from professional bodies and higher education institutes (HEI's), post graduate training comes at a cost. This cost must be met by the service provider in the majority of cases and, commonly, training budgets are the first to be assimilated when cost savings are to be made. Whilst this direct cost may well provide an attractive source of savings in the short term, the budget of the NHS does not readily allow for long term planning, nor for a spend-now-save-later ethos to exist (Delamothe, 2008). Of course, there are times where the funding for additional training is available, but the limiting factor is the availability of practitioners to train. Workforce constraints in terms of both number of available staff, or appropriately

qualified staff, can impact on training and role development. Practitioners learning new knowledge and skills require time to develop and mature these before fully embedding into practice (Culpan et al., 2019) but that can be constrained by staff shortages compromising time for capability development (Mitchell et al., 2019). Within ultrasound, the skills required are related to the use of technology and the interpretation of images produced; this has an intrinsic, but varied, learning curve that needs time to embed within clinical practice (Harcus & Snaith, 2019). Time for such a learning curve will need to be accounted for if new microUS technology is to be embedded successfully within the prostate cancer pathway.

4.12 Role extension in the prostate cancer pathway

The argument to support sonographer role extension in the imaging of the prostate during active surveillance has been made; there is evidence of improvements to patient pathways that can be realised when a multi-professional approach is utilised (Woznitza et al., 2018; Culpan et al., 2019). The evidence presented suggests that the role of sonographers could be extended to safely develop knowledge and skills in the use and interpretation of mpUS and microUS. However, the published evidence relates to delegated tasks that were previously undertaken by radiologists; there are no known studies reviewing the implementation of new, untested, technologies in imaging by non-medics (sonographers) or by a multi-professional group. This knowledge gap will be investigated by my research project.

4.13 Summary

The evidence reviewed identifies that role extension of non-medical practitioners, in particular sonographers, adds value to patient care. Role development of sonographers should be supported to ensure that new technology can be embedded in the prostate cancer pathway. However, multi-disciplinary support is essential if services are to be delivered in a safe and sustainable manner, which subsequently benefits patients. Changes to imaging within the prostate cancer pathway will require multi-professional team working to support knowledge and skill development of all involved. However, barriers to non-medical role extension need to be recognised and mitigated for with excellent communication and shared learning to avoid failure.

It is recognised that the proposed new technology has no benchmark standard for performance to be measured again; this study is designed to determine if such a standard can be identified as expertise within the multi-professional team develops. However, careful assessment and evaluation of the process of embedding technology in practice is required to ensure this is robust and accepted by the multi-professional team delivering patient care on the prostate cancer pathway.

This chapter has evidenced that sonographers are well placed to extend their role within the prostate cancer pathway. In the next chapter, the methodological options available to evaluate the performance of ultrasound, and how well the new technology of microUS is normalised into clinical practice, are discussed.

Chapter 5 Research plan and methodologies

This chapter provides a summary of the thesis thus far and outlines the two main themes under investigation. The methodological options considered in the study design are discussed. The study aims and objectives, the imaging parameters to be used, ethical considerations, the considerations for evaluating the implementation of new ultrasound technology are presented alongside the options for processing and analysing the data obtained.

5.1 Thesis summary

In Chapter 1, I discussed the current state of active surveillance (AS) of men diagnosed with low grade prostate cancer (PCa). Capacity constraints for reference standard magnetic resonance imaging (MRI) for this cohort of men led to the consideration of alternative imaging modalities to evaluate the prostate during an AS pathway. Evidence collated during the systematic review of Chapter 2 drew the conclusion that there may be a role for multi-parametric ultrasound (mpUS) and that the emerging technology of micro-ultrasound (microUS) may provide reasonable sensitivity and specificity, and more comparable to MRI than standard ultrasound. Further research into this new technology is indicated. However, to gain a wider understanding of patients' experiences and perception of AS, including the role that imaging plays for them in such a pathway, I undertook a scoping review of current literature, presented in Chapter 3.

The scoping review identified that many studies and systematic reviews are published in this field and concluded that there were few remaining gaps in knowledge or understanding of men's experience of AS. It also identified including imaging within an AS could provide reassurance to men on such a pathway, although this was largely evidenced by a single author, Ruane-McAteer (2018). Despite the limited data available related to the use of transrectal ultrasound imaging as an investigation, given the volume of evidence related to men's experiences of AS it is reasonable to deduce that the six themes I identified are mirrored by men when having surveillance ultrasound scans. There was limited gain to be had by investigating this further. Nonetheless, a knowledge gap emerged related to the understanding of how new technologies are successfully embedded into AS pathways that are reliant on

diagnostic imaging. Chapter 4 of this thesis, therefore, considered whether it was appropriate to extend the scope of practice of sonographers within a multi-professional team to assess the feasibility of using mpUS and / or microUS in this setting.

5.2 Research study themes

Following completion of the four previous chapters, I identified the role of the sonographer was well placed to test the concept of using ultrasound in this pathway. I also identified that there was a lack of published research into the use of new ultrasound technologies in AS. Where published evidence existed, how such technology was embedded into real-world clinical practice had not been explored. In essence, two main themes emerged which required investigation:

- Is there a role of emerging ultrasound technologies in the assessment and monitoring of localised prostate cancer in men on an active surveillance programme?
- How can new ultrasound technology and techniques be implemented and embedded into clinical practice within the multi-professional team?

With these identified themes, my research was designed to identify if ultrasound could have a role in the AS pathway.

5.3 Prostate anatomy

Before I explore the imaging parameters that could be utilised in the evaluation of the prostate, it is important to understand the anatomy of the gland and where prostate cancer is likely to be sited. The prostate gland is situated between the rectum and bladder with both the urethra and ejaculatory ducts running centrally, Figure 5.1. Optimum ultrasound imaging is via the rectum using a specifically designed endocavity transducer. *[All the following graphics are reproduced with kind permission of Radiology Assistant (Loenhout et al. 2024)].*

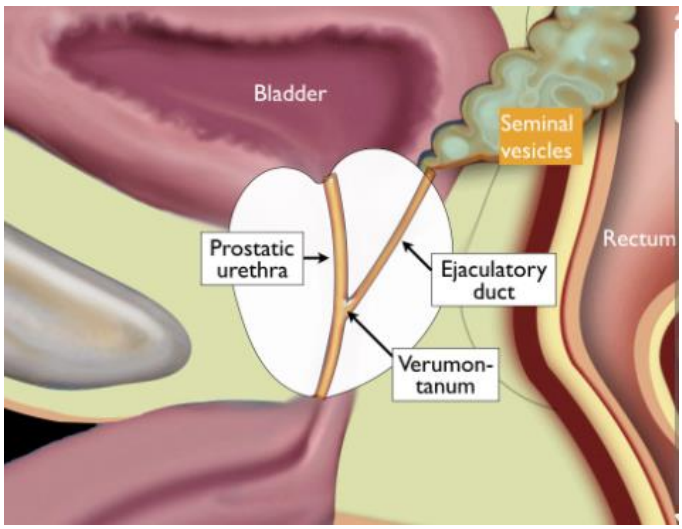

Figure 5.1 Anatomical position of the prostate (Loenhout et al. 2024)

The gland is comprised of zones with the tissue structure of the transitional (Figure 5.2) and peripheral (Figure 5.5) zones having marginally different acoustic impedance and, therefore, have a subtle identifiable pattern on B-mode ultrasound (US) imaging (Mitterberger et al., 2010).

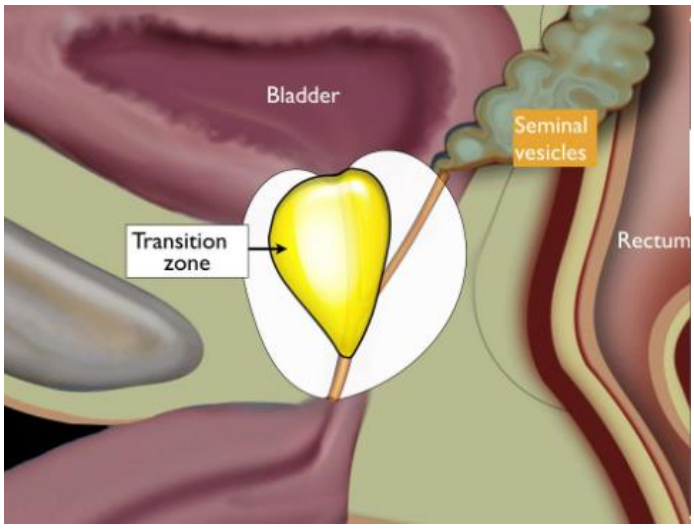

Figure 5.2 Depiction of the site of the transition zone (TZ) (Loenhout et al. 2024)

The transition zone (TZ) (Figure 5.2) surrounds the prostatic urethra and enlarges in aging men resulting in benign prostatic hyperplasia, commonly noted as rounded areas within the mid gland on US. Approximately, 25% of cancers develop in this zone.

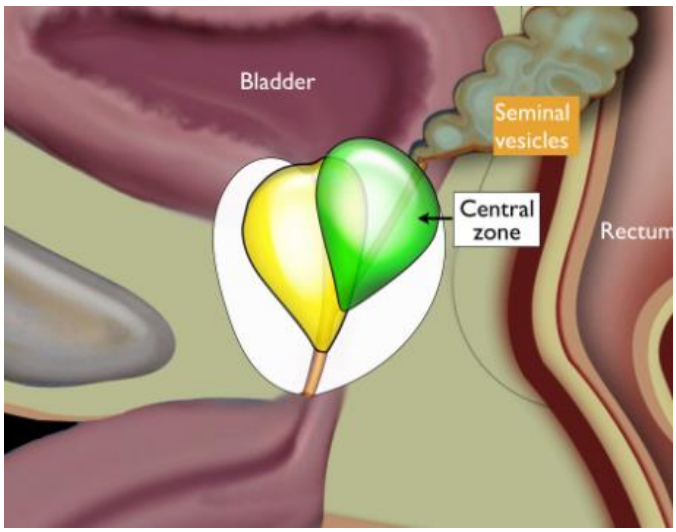

Figure 5.3 Depiction of the site of the central zone (CZ) (Loenhout et al. 2024)

The central zone (CZ) (Figure 5.3) lies in the base of the prostate behind the transition zone and surrounds the left and the right ejaculatory duct. This area, and the anterior fibromuscular stroma (AFS) (Figure 5.4), a small area of tissue that is situated on the anterior side of the prostate, are rarely a site for malignancy. Neither the CZ nor AFS have sufficiently different acoustic impedance to be clearly identifiable on US imaging.

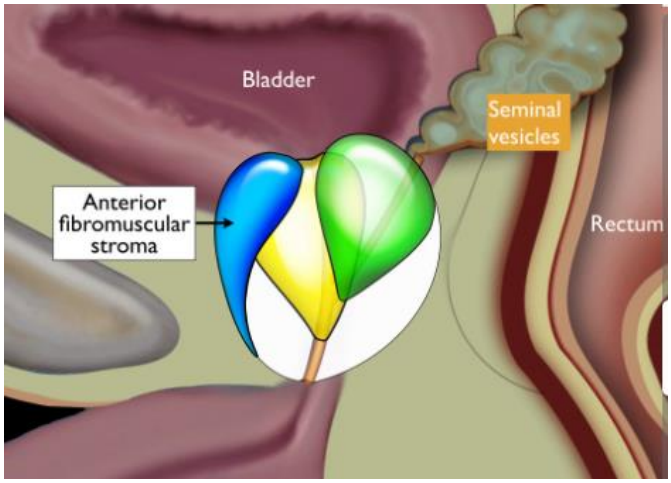

Figure 5.4 Depiction of the site anterior fibromuscular stroma (AFS) (Loenhout et al. 2024)

The peripheral zone (PZ) (Figure 5.5) is situated on the posterior and lateral side of the prostate and envelops the TZ and CZ on the posterior and inferior aspects of the prostate. The PZ accounts for the site of between 70-75% of all prostate cancers. It can be delineated on B-mode imaging and is usually marginally brighter (hyper-echoic) compared to the TZ on standard US.

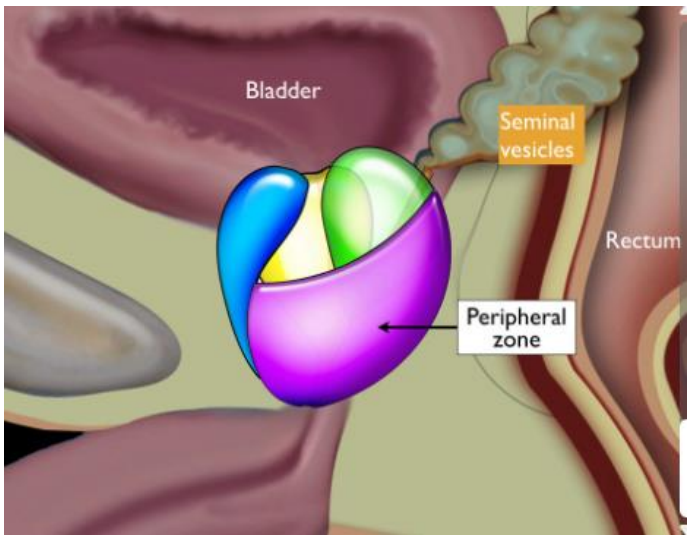

Figure 5.5 Depiction of the site peripheral zone (PZ) (Loenhout et al. 2024)

Radiologically, and histologically, the prostate is subdivided into sectors, which include right and left zones, and anterior (a), posterior (p) to the centrally sited verumontanum (Figure 5.1). Due to the importance of the PZ with regards likelihood of malignant change, radiological reporting of the prostate using the Prostate Imaging–Reporting and Data System (PI-RADS v 2) (Vargas et al., 2016), further subdivides this zone into right and left medial sectors. Sector anatomy is represented in Figure 5.6, again reproduced with kind permission from Radiology Assistant (Loenhout et al., 2024).

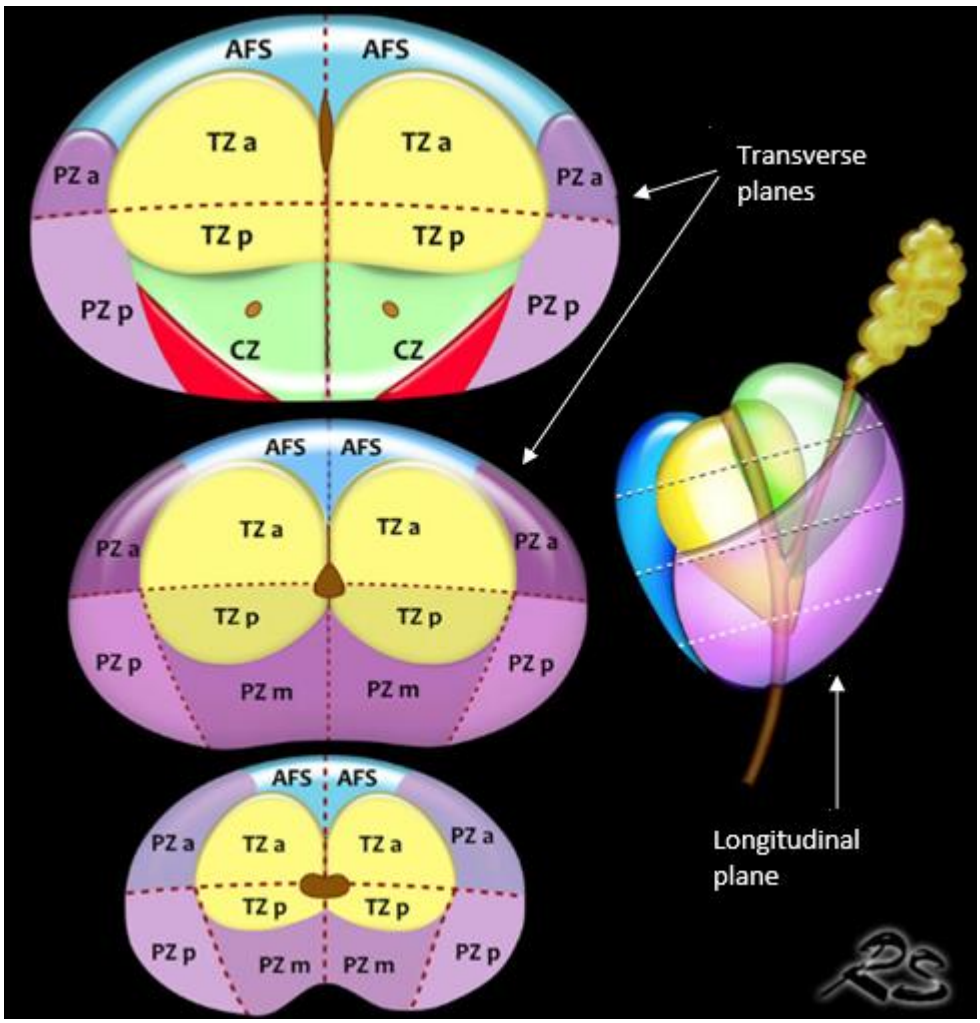

Figure 5.6 Sector anatomy of the prostate gland using PI-RADS v2 regions (Loenhout et al. 2024)

With this anatomical knowledge, an imaging protocol, which concentrated on the high-risk areas of the prostate gland, was planned, and factored into the study aims and design.

5.4 Study aims and objectives

The primary aim of this proof-of-concept study was to evaluate if emerging ultrasound technologies could provide reproducible imaging that could be used to assess the prostate gland in men with known localised prostate cancer and who were being managed with active surveillance.

The secondary aim as to investigate the impact of new technology, and additional role extension, on health care practitioners within diagnostic imaging, in the field of prostate cancer assessment and monitoring. The practicality of implementing changes to the imaging pathways in AS was evaluated with the clinical team delivering the current and future service.

5.4.1 Measurable Objectives

Measurable objectives to address these aims were:

1. To evaluate the diagnostic parameters of diagnostic ultrasound that could be utilised to assess disease within the prostate gland.
2. To evaluate the diagnostic parameters of diagnostic ultrasound that could be utilised to assess disease progression within the prostate gland.
3. To evaluate if the intra and inter operator variability in the assessment of ultrasound imaging parameters of the prostate gland could be investigated.
4. To determine if a suitable standardised imaging protocol and reporting tool or model could be utilised in the reporting of transrectal ultrasound imaging of the prostate.
5. To gain a better understanding of how new ultrasound technology and techniques could be implemented and embedded into clinical practice.

5.5 Imaging techniques

Ultrasound imaging was clearly the cornerstone to this research project. There are several parameters of ultrasound which could have been exploited to maximise the effectiveness of this imaging modality. These were identified in Chapter 2 of my thesis and were carefully deliberated during the planning of my study design. In this next section, I describe the functionality of ultrasound that I considered to investigate my primary aim. Alternate parameters that were contemplated as they may have provided different methods of assessing the prostate gland are discussed.

5.5.1 Ultrasound imaging explained

B-mode imaging is the most widely accessible and base line ultrasound function available; it is the real time imaging that provides both still frame grab or cine loop files that can be stored and reviewed retrospectively (Jensen, 2007). A frame grab is the capture of an individual still frame from an analogue video or digital video signal, which is stored as a digital version of that image. A cine loop file is a sequence of digital images that are capture together and viewed as a moving loop. They can be viewed as moving stream or each individual frame within the loop can be scrutinised independently. On retrospective review, cine loops are more comparable with real-time ultrasound scanning than a single frame grab, but they are both reliant on the operator storing appropriate representative images or loops corresponding to what they interpret during the live scan.

Early studies of the ultrasound appearances of the prostate, such as that undertaken by Flanigan et al (1994), indicated that dark (hypoechoic) areas on ultrasound within the prostate may correspond to the presence of malignancy. However, a comparison with histology post biopsy of suspicious areas, which Loch undertook (2004), yielded a low positive predictive value of between 18 – 42%. One explanation for this low yield was identified by Callejas, (2022); on standard frequency B-mode US of 6 to 9 MHz, malignant and non-malignant prostate tissue, regardless of the zone of situ, can have a similar acoustic impedance and, therefore appearance, which consequently limits the diagnostic capability of this modality. As such, standard US has been seen to be a poor predictor of disease (Ghai et al., 2022). Whilst Dias et al (2022) describe typical features of prostate cancer as being hypoechoic on standard US, they identify that a few become bright (hyperechoic) due to cellular dysmorphic change, and up to 35% are isoechoic to the surrounding tissue and invisible using solely B-mode imaging. Harvey et al (2012) identified alternative features on B-mode such as asymmetry, breaches to the prostate capsule, and increased vascularity, which could be used to improve identification of significant malignant abnormalities, as opposed to benign chronic hypertrophy in older men. However, the prevalence of multifocal disease is a hindrance to being able to confidently identify focal cancer as Fütterer et al (2009) acknowledge.

5.5.2 Probe technology

Ultrasound probe technology influences imaging output. Ching (2009) identified that the construction of the probe affects cancer detection rates, but it was suggested that this was due to the biopsy sampling technique, which the difference conferred, rather than lesion identification. No further studies have identified issues and probes specifically designed to guide transperineal prostate biopsies have a side fire lens and, commonly, a co-existing axial lens to ensure the prostate can be imaged in both the longitudinal and transverse planes, as depicted in Figure 5.6 above. Typical construction of an endocavity (transrectal) transducer is depicted in Figure 5.7 below.

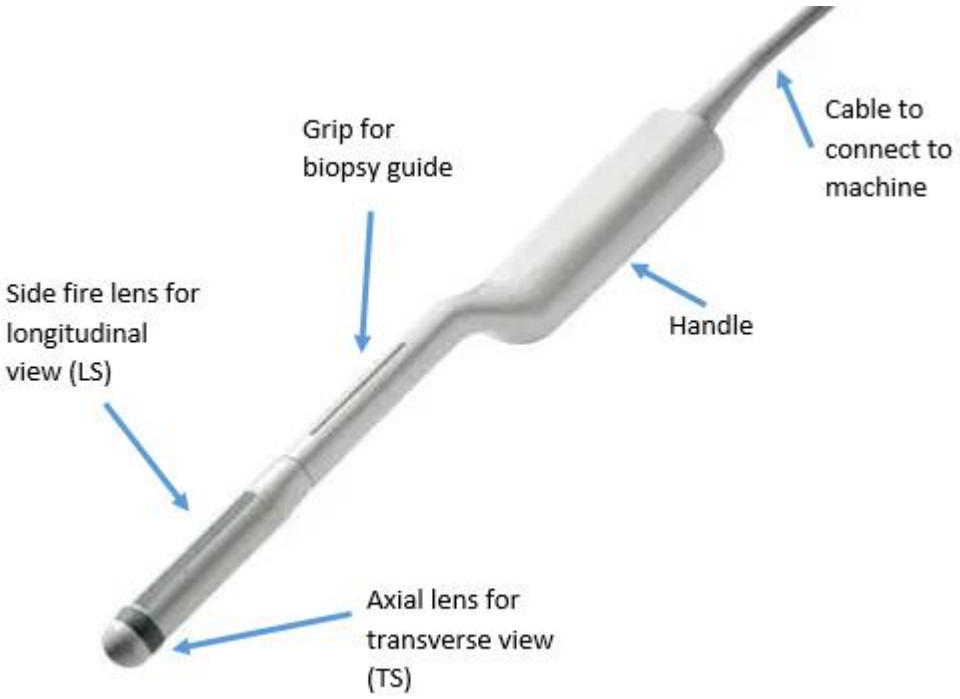

Figure 5.7 Typical construction of a bi-planar endocavity probe, specifically designed for prostate imaging and biopsy guidance (Canon Medical Systems, Crawley UK)

5.5.2.1 Signal to noise

Regardless of probe design, ultrasound technology presents unique difficulties due to the inherent signal to noise ratio, which is a compromise between the penetration of the ultrasound bean against the resolution, attenuation and scatter of the soundwave (Brattain et al., 2018; Liu et al., 2019). These inherent factors can be compensated for by manipulating the image processing within the machine but is wholly operator dependent. As Liu (ibid.) identifies there is wide intra and inter-operator variability both across differing ultrasound manufacturers and across differing clinical settings. A consideration in the study design was to develop a reproducible imaging setting, commonly known as a pre-set, that required little operator interference, but which could be optimised for each participant under review.

Despite the challenges of identifying abnormalities on B-mode US, there are changes within the prostate that could be identified and documented on retrospective review. However, due to the wide range of sensitivity reported by Ghai (2012), Lui (2019), and Correas (2021), image evaluation of the prostate in my project only assessed the

presence of the predominate descriptors of focal lesions, heterogenous texture and obvious benign hypertrophy.

5.6 Ultrasound parameters

Given the challenges that B-mode US imaging presents in the evaluation of the prostate, there were functions of ultrasound considered, in terms of Doppler, elastography, and contrast enhanced imaging, which may have enhanced cancer detection. None of these parameters have a significant published evidence base, although a recent paper by Dias et al (2022) identified improved visualisation of perfusion within lesions when using contrast enhanced imaging and new low flow Doppler techniques, and the term multiparametric ultrasound (mpUS) for the prostate entered the arena (Correas et al., 2021; Dias et al., 2022). In terms of the ERUP trial, I considered what imaging functionality was available, without the need for additional financial resource, and which could be reproduced in future studies, to develop a multiparametric approach. I took a pragmatic approach to develop an applicable study design that was translatable to a wider real-world clinical setting outside of this research site.

5.6.1 Multiparametric ultrasound - Doppler

Standard ultrasound systems have colour flow Doppler as standard and can be utilised to evaluate perfusion within the prostate and any identified lesions. Doppler is limited as it reported to have low sensitivity for the presence of prostate cancer (Futterer et al., 2009), although systems have improved since the publication of this paper. Indeed, Doppler technology was identified by Harvey et al (2012) and Dias et al (2022) as demonstrating increased vascularity in focal abnormalities. Recent technological Doppler signal developments have improved the detection of low flow even further; both Brattain et al (2018) and Correas (2021) identified that there is encouraging positive correlation between flow and pathology despite the limited availability of published evidence. However, as with all ultrasound techniques, the use of Doppler is largely operator dependent and, for a translatable study, the new technologies will need to be widely available. In 2020/21, at the study design and planning phase of this project, colour Doppler was readily available and commonly utilised by operators, but low velocity imaging was not present on the endocavity probe. As such, in my project, the prostate was assessed using colour Doppler, with images stored and

retrospectively analysed for the presence or absence of a recorded colour Doppler signal only.

5.6.2 Multiparametric ultrasound - Contrast

To complement Doppler imaging, perfusion within the prostate and suspected lesions can be interrogated with the use of contrast enhanced ultrasound (CEUS) (Sidhu et al., 2018). This requires the injection of microbubbles into the venous blood stream. Limited published literature exists regarding the efficacy of CEUS in the assessment of prostate cancer. Nonetheless, Correas et al (2021) identified in their review paper that CEUS of the prostate demonstrates early and increased enhancement in areas of malignancy. These are features that are well published as being associated with liver malignancy but, whilst the prostate remains to be of clinical interest (Brattain et al., 2018), CEUS of this organ is not presently advocated as a diagnostic tool and remains a focus for future research (Sidhu et al., 2018). The use of CEUS was considered within my project but was not without significant challenges. Primarily, the use of the contrast agent in the prostate is off-licence and, as such, cannot be administered under a patient group directive (PGD) (Aronson & Ferner, 2017). Sonographers are unable to prescribe medicines, of which contrast agent are classified, and must work under a PGD. In this sonographer led research project, CEUS is therefore not feasible. The second major limitation is that CEUS is optimised at scanning frequencies much lower than those used for transrectal imaging. CEUS imaging is therefore sub-optimal using the required endocavity probe and provides limited information (Correas et al., 2021). Given these limitations, CEUS has been discounted was an imaging parameter in this project.

5.6.3 Multiparametric ultrasound - Elastography

Elastography is identified as a feature of mpUS (Mitterberger et al., 2010). Elastography is an application commonly used in breast imaging to assess tissues stiffness. Tissue stiffness is interrogated by compression of the tissue under investigation, either manually or mechanically. Manually, the technique requires the endocavity probe to be gently agitated within the rectum by the operator. This can led to variability in technique and inter-operator inconsistencies (Dias et al., 2022) although is reported to be easy to use (Correas et al., 2021). However, the invasive nature of transrectal imaging does not lend itself to agitation of the transducer in a

real-life setting. Indeed, as reported by Appleton et al (2015), men do find transrectal investigations intrusive, and some considered it to be a breach of body boundaries. Ethically, I was sensitive to this and balanced the benefits of using this technology against the intimate nature of obtaining data. Mechanical elastography is less intrusive for the participants as the ultrasound beam is agitated electronically and cannot be felt by the participant. However, the technique is again operator dependent and requires no compression of the rectum during the examination if false results are to be avoided (Correas et al., 2021; Dias et al., 2022); a near impossible task if contact with the prostate is to be maintained to optimise imaging within the cavity that commonly contains gas. Guidelines published from the European Federation for Ultrasound in Medicine and Biology (EFSUMB) (Cosgrove et al., 2013) identify that there are limitations in prostate elastography as not all cancers are known to be stiff and not all stiff lesions are cancers. Within this guidance, prostate elastography is recommended only for targeting lesions for biopsy and not for diagnostic purposes. Brattain et al (2018) also identified that elastography is invasive and offers only a poor predictor of disease due to the operator dependent technique, although Correas (2021) identified that in the hands of an expert, elastography exhibits high reproducibility. Ultimately though, the use of elastography was discounted from this research protocol as the invasive nature of obtaining data outweighed any limited clinical value.

5.6.4 Multiparametric ultrasound - Microultrasound

As identified in the Chapter 2 systematic review, micro-ultrasound (microUS) is emerging as a useful technology in the assessment of the prostate and presence of disease (Basso Dias & Ghai, 2023). This technology is bespoken to a particular manufacturer (ExactVu™, Markham, ON, L3R 2N2, Canada) and utilises high frequency ultrasound to increase the resolution of the prostate. The technical make-up of the transducer results in a detailed image of high resolution (Dias et al., 2022). This high spatial resolution is reported to provide visualisation to approximately 70 microns (Ghai et al., 2022), the size of the prostatic ducts, and changes indicating malignancy, at an almost cellular level, purport to be seen (ibid.).

MicroUS is a novel technique and few practitioners have built up sufficient knowledge and experience to confidently differentiate between normal appearances of a benign prostate and the findings associated with suspicious lesions (Callejas et al., 2022).

Although, in early trials of this technology, Ghai et al (2022) identified that microUS improves sensitivity of disease detection. MicroUS has been identified by Fusco et al (2022) as having benefits for patients with suspected prostate cancer in whom MRI is contraindicated, but that further, randomised control trials are required to better evaluate its efficacy. A systematic review by Dariane et al (2022) identified that microUS may provide a 30% improvement in spatial resolution of the prostate and, thereby, improve lesion detection. However, microUS as a technology that remains in its infancy; it is not widely embedded in practice and with no clear recommendations for use (Fusco et al., 2022).

Despite the lack of recommendations for use, there is a growing body of evidence in favour of microUS with several systematic or comprehensive reviews being published, including the peer reviewed publication of Chapter 2 of this thesis (Parker et al., 2021; Sountoulides et al., 2021; Calace et al., 2022; Dariane et al., 2022; Dias et al., 2022). This technology was seriously considered as an imaging modality for my research project and was fortunately available in the local hospital trust having been purchased in the financial year of 2019/20. This research project provided the perfect opportunity to test this technology prior to wider implementation in clinical practice.

5.7 Computer assisted imaging

Ultrasound is accepted as a safe and effective form of imaging (Ashdown et al., 2018), however, a fundamental aspect of this diagnostic modality is the assessment of the findings and quality of images produced (Cantin & Knapp, 2013). Ultrasound requires the operator to be able to assess internal anatomy and understand the 3-dimensional structures, as provided in the anatomical figures above, as they are displayed on a 2-dimensional monitor. Ultrasound is, therefore, highly dependent upon the operator (Liu et al., 2019) and, unfortunately, inherent interpretation error rates are known to exist (Currie et al., 2019). Advances in computer processing, technology, and software have led to significant innovations, which aim to reduce these known error rates and improve disease identification (ibid.). Progress in computer assisted imaging (CAI) has resulted in artificial intelligence (AI) with capabilities to detect and classify lesions, automatically segment anatomical borders, extract radionomic features within the image, and reconstruct 3-D anatomy (Currie et al., 2019; Liu et al., 2019).

There is an increasing volume of published research offering promise that CAI, in various formats, will provide clinical applications in medical imaging. As Thrall et al (2018) discuss, AI may offer increased diagnostic certainty and this may be of benefit to patients, particularly with follow-up of known disease.

5.7.1 Aspects of CAI

Within imaging, the common theme of CAI is the process of extracting useful features within radiological imaging, the process known as radionomics, and linking these to outcomes. The benefit of using any of the CAI techniques is that it prevents observer fatigue and, therefore, human error can be reduced (Thrall et al., 2018). Indeed, Currie et al (2019) identified that there is a hypothetical increase in sensitivity by as much as 5% when compared to a human operator, but the question exists as to whether this increased sensitivity actually translates to improved outcomes or swifter diagnosis for the patient.

5.7.2 CAI in prostate imaging

Current published literature identifies three main tasks of CAI in ultrasound: classification, detection and segmentation (Liu et al., 2019). Liu et al (ibid.) identified that a CAI system used to classify thyroid nodules resulted in an improved accuracy of 14%. Within the prostate, Liu et al (ibid.) identified a similar CAI system used to achieve segmentation of anatomical features, which could aid targeting biopsy, particularly of importance in this cancer pathway. In a study evaluating serial MRI scans of the prostate, CAI was used by Roest et al (2023) who identified that this technique detected diagnostically relevant changes. Operator dependence could, therefore, be avoided. CAI algorithms are being developed by Chiu et al (2022) in a bid to enhance prostate cancer diagnosis and they identified that their system could lead to a reduced need for biopsy. However, none of the CAI techniques published to date are beyond a research stage and are not widely available within real-world clinical practice.

5.7.3 Challenges of CAI

Despite CAI techniques demonstrating positive outcomes, they require significant amounts of training data sets (Thrall et al., 2018; Soffer et al., 2019). The study by Roest et al (2023) utilised datasets from 1434 patients, whist the study undertaken by Chiu et al (2022) utilised 3881 datasets. Both studies identified that additional data

was required to improve CAI technology deployment. Both Liu et al (2019) and Choi et al (2020) acknowledge that there is a current limitation as training data sets are unavailable and are creating a bottleneck in technology development. The datasets require human interaction. They need collecting from patients and collating. Additionally, the datasets require annotation to provide information from which the systems can learn, and that annotation relies on experts in the field to undertake this (Brattain et al., 2018; Edwards et al., 2022). Such requirement on human interaction leaves the data open to error and subsequent noise in the input quality as Choi et al (2020) identified. Additional challenges relate to the quality of the datasets used for CAI training. They tend to be sub-optimal for clinical practice as are obtained from a homogenous population rather that the heterogeneous population seen in real-world clinical practice (Liu et al., 2019). Prostate image acquisition can result in compression, deformation and distortion of anatomical features that are subject specific and solely due to the technique employed to acquire the dataset (ibid.), and this distortion can be understood as variance by a human but not necessarily by algorithm-based CAI.

5.7.3.1 The human operator

Whilst CAI offers promise in terms of improved accuracy, sensitivity, and consistency as I have evidenced above, ultrasound imaging needs practitioners and subjective assessment. CAI techniques are currently unable to replicate the skills of perception and analysis underpinned by underlying knowledge that is inherent in an expert human operator (Cantin & Knapp, 2013). Humans benefit from heuristics that CAI is unable to achieve; fundamentally, the tacit knowledge that comes with learnt experience. Although heuristics is open to bias dependent upon experience, it enables human operators to make decisions in response to heterogeneous or unusual findings (ibid). It is this skill that is required in the interpretation of ultrasound images within the context of individual patient presentations.

5.7.3.2 CAI summary

Given the lack of readily available CAI in the field of prostate ultrasound, alongside the challenges presented here, and with benefits of human operators in mind, I excluded the use of any CAI systems within my study design. However, concurrent technological developments make CAI an exciting development for future patient care, which is discussed in the final chapter of my thesis.

5.8 Multiparametric ultrasound summary

Within my study design, I considered a range of ultrasound parameters but selected a pragmatic and translatable approach to the study design. Parameters were chosen that maximised disease detection but required human experts, over CAI, to assess and interpret the acquired images. On balance of patient considerations over technique, elastography was discounted. CEUS was not feasible due to its required contrast agent being off-label and not practical for sonographers use. Low velocity Doppler imaging was unavailable, but colour Doppler was and commonly used. The availability of microUS technology provided the novel imaging parameter to facilitate a study, which met the identified gaps in knowledge.

5.9 Consent and ethical considerations

Written consent from all participants was required for this study and appropriate information was provided to patient participants as well as the professional team, (Appendix 1 and 2, pages I and IV). Given the nature of how prostate ultrasound imaging is performed, by using a trans-rectal approach, awareness of and sensitivity to participants' feelings was required as well as an appreciation that this study may not be acceptable to all patients. Clearly, respect for patients' autonomy and dignity must be maintained (Kelly, 2019) throughout and, as such, the ethical issues related to prostate imaging and data collection were considered in my methodology. What could be considered to be a rational choice as a researcher may be difficult for patients to accept and therefore, patients have to feel empowered to decline without issue or impact on their ongoing health care (Varkey, 2021). As Kelly (2019) discusses, patients required time to consider the proposed research, time for discussion of the risks and benefits and the option to withdraw at any point.

5.9.1 Ethical considerations

Four key ethical issues were considered as the study was designed. These are listed below with the steps taken to mitigate the impact for participants.

1 The additional transrectal ultrasound imaging undertaken for research only.

a. Despite transrectal ultrasound being routinely used for assessment of the prostate, and, as Descotes (2019) discuss, the current reference standard method for guiding biopsy, the procedure is not without

discomfort. The examination required clear explanation within a patient information leaflet (PIL) and time taken to discuss prior to consent being obtained (HRA, 2023a). The impact of this procedure in terms of comfort and patient dignity was balanced against the potential positive impact on making an earlier diagnosis of disease progression in the long term. Considerations regarding the research environment and communication to participants was made in a bid to improve comprehension of the method of data collection for potential recruits. Appleton et al (2015) report that men identified transrectal probes as a threat to their masculinity and an invasion of their body profile. Callejas et al (2022) identified that new biopsy techniques involve placing patients in a lithotomy position but that is standard practice despite it being unusual for men. The participants within the study by Appleton et al (2015) identified gender specific communication and gender sensitive settings reduced this perceived threat. This was included in my study literature and design to better support inclusion in the study.

b. The research plan incorporated steps to follow should incidental abnormal or suspicious findings become evident to ensure that possible early diagnosis or treatment was not delayed (HRA, 2023b).

2 Participants may have been investigated for suspected cancer or have been given a cancer diagnosis with which they are living.

a. As advocated by Leathard (2007), informed consent was clear that the aim of the study was to inform future research and that this study would not change the participants management or prognosis.

b. The ERUP trial was designed as a longitudinal study and, as such, participants' experiences over the study period may affect their attitude towards ongoing participation. As such, the PIL made it clear that, at the time of the research commencing, there was no optimum follow-up or treatment for current patients but that this research may benefit men in the future. Their participation was altruistic but of value to future patients.

3 My role as the lead sonographer within the ultrasound may influence and impact on other team members' attitude towards using new imaging techniques to evaluate the prostate.

a. The phenomenon known as the Hawthorne effect (McCambridge et al., 2014) was considered as I asked my team to work with me to interpret new ultrasound imaging technology. The Hawthorne effect acknowledges that participants may perform better if they believe or know they are being observed (ibid.) Again, non-ambiguous informed consent was required, with the option for non-participation or withdrawal at any time being clearly understood by both me as the researcher and by my colleagues who were asked to participate.

4 Commercial bias may impact on the integrity of the study.

a. The final consideration relates to the diagnostic data set which may originate from new technology as this was new to the UK and there may be a desire for positive outcomes from the commercial manufactures. However, the research was performed independent of any manufacturer, and they had no influence on the outcomes. This potential commercial conflict of interests was managed throughout the project.

5.10 Study design

5.10.1 Rater and sample size considerations

To achieve the measurable objectives of this study, images collected during the ultrasound examinations of participants required reviewing. Fundamentally, the number of observers reviewing the images, and the number of subjects can affect the sample size (Rigby, 2000). However, as Rigby (ibid.) acknowledges, it is the number of observers that has the greatest influence. As Sim & Wright (2005) discuss, a balance between number of raters and the number of subjects is required. They (ibid.) identify it can be more practical to increase the number of raters rather than participants as a potential sample size to provide sufficient power could be prohibitively large (Donner, 1998). However, this can increase inaccuracies and the kappa test assumes no variance between rates (Sim & Wright, 2005). With this in mind, an appropriate balance

between the number of participants and the number of practitioners reviewing the images had to be considered (Sim & Wright, 2005). Indeed, as Wilson et al (2022) discuss, too large a sample size may delay results or have resource implications, such as funding or scan capacity, whilst a small sample size may provide insufficient results for meaningful analysis.

The study undertaken by Chiu et al (2022), which evaluated identification of prostate disease from ultrasound images, had a sample size of 3881 datasets of images. This large volume was required to input the computer programmes of a CAI system. As such, a large sample size would be required and is impractical in a real-world clinical setting. Time and resource constraints do not allow for a study as large as the one conducted by Chiu et al (ibid.). However, a more comparable study would be that of Cantin and Knapp (2013) who examined how ultrasound images could be measured and used observers' evaluations as outcome measures. This trial used 114 individual image datasets reviewed by nine observers. This appears a pragmatic and comparable method for assessment and, as such, was considered in my study design.

5.10.1.1 Power

To estimate sample size, the power of the test is an important indicator of the probability that it will find an effect, or rater agreement, assuming that this exists in the population (Field, 2013). In real-life clinical settings, it is assumed that agreement between raters will be better than expected by chance and therefore, the value of the null hypothesis for kappa is set higher than 0.0. As Sim & Wright discuss, it is reasonable to assume that a kappa value of greater than 0.40 can be considered for the null hypothesis, as anything less than this would be clinically unacceptable. In my study, it was assumed, given the published evidence collated in the systematic review of Chapter 2, that there would be common outcomes from the image evaluation that were found by the majority of reviewers in normal and abnormal prostates, and a kappa of 0.40 or above would, therefore, indicate moderate agreement. Flack et al (1988), Donner (1998) and Sim & Wright (2005) all provide tables, which indicate the sample size required to provide a reasonably powerful comparison of observers, assuming a kappa of 0.4 is the null hypothesis and the power of the test, that is the probability that the test will detect if there is agreement present, is 80%.

5.10.1.2 Sample size estimation

The annual population under investigation for prostate cancer by the Hull University Teaching Hospitals Trust is on average 550 patients. The table provided by Donner (1998) indicates that a sample size of 97 participants is required to be able to test the statistical significance of difference between observers, whereas that of Flack et al, (1988) suggests a sample size of 99 and Sim & Wright (2005) suggest between 39 - 50. Attrition from the study has to be taken into account (PASS, 2024) and, therefore, a sample of approximately 100 participants would provide an adequate sample to perform a reliable kappa test. This sample size represents approximately 20% of the available population and importantly, is a comparable with the previously published similar study by Cantin and Knapp (2013).

Practicalities of recruiting 100 patients for initial assessment were unlikely to be problematic given the volume of referrals for prostate biopsy and assessment. However, numbers of participants that could potentially be recruited into the follow-up assessment of their prostate was a challenge as it was reliant on numbers of patients who are managed on an AS regime. Given time and resource constraints, this study was designed as a proof-of-concept trial with potential to expand to a full trial once initial data has been analysed. This would then enable a greater number of patients potentially eligible for follow-up during their AS.

5.10.2 Image collection

Ultrasound images are displayed as near real-time frames. Visually, during the scan process, the frame rate is such that individual frames are not discernible. To capture an image, the scan is frozen and that, or a particular recent frame, is stored. The machine converts the image to a Digital Imaging and Communications in Medicine (DICOM) format. This DICOM format includes the image alongside metadata that the hospital picture archiving and communication system (PACS) needs to be able to identify and store images (Varma, 2012). PACS will also store cine series or cine loops. In whichever way the images are collected, they still require human resource to capture and, as Brattain et al (2018) identifies, having that expertise available to capture data without variation is challenging for ultrasound.

Cantin and Knapp (2013) recognised a limitation of studies involving review of ultrasound image is that static frames provide only a representation of the dynamic

scan. Captured frames are subject to bias by the practitioner who collects them. Brattain et al (2018) discuss that cine loops provide the spatial-temporal data, which is evident in live scanning and may improve results of retrospective interpretation. Nevertheless, as both Salomon et al (2008), and Parker & Byass (2015) acknowledge, the process of image review is time consuming and potentially expensive; a use of expert resource that is needed for clinical activity.

A benefit of cine loop storage is that all data is captured and can be reviewed retrospectively with little difference to the real time imaging. Optimally, a study design requiring retrospective review of ultrasound would involve the storage of cine loops, but sufficient bandwidth is required to transfer DICOM images from ultrasound machine to PACS. Unfortunately, this was a limiting factor in my study design; as I discuss further in the next chapter (6.4.2), the hospital network could not support reliable transfer of data files containing cine loops from the microUS machine. Whilst cine loop acquisition provides a more comparable option for review, and several studies, such as that by Callejas et al (2022), used cine loop format, there are other limitations with this that also require careful consideration. Callejas et al (ibid.) identified that cine loop reviews suffer from the same inadequacy as a review of still images, that of retrospective analysis distant to the patient and without the ability to manipulate the image in real time. Moriarity et al (2016) identified that significant improvements in information technology (IT) are required before effective image data transfer of large files can be achieved. Without this, large datasets of cine loop images can be difficult to transfer to PACS. Brattain et al (2018) identified that limitations in image processing prevented robust retrieval of cine loops. Indeed, Currie et al (2019) identified the need for large bandwidth to transfer the volume of data within cine loops and such large data transfer is complex. They question the validity of large data transfer at such a time where investment is needed in both IT and human expertise (ibid).

The ability to transfer large data sets was a limiting factor in my study as not only did it prevent cine loop storage, but it also precluded practitioners external to the local trust being invited to be involved in the image review. The image datasets, even when stripped of patient identification metadata, were too large to transfer beyond the local network.

Single frames could, however, be stored as still images; they remain large files but were more readily transferred and stored within the current the network system and PACS. Several studies have successfully stored and reviewed still images and achieved significant measurable outcomes; two early studies contributed to changes to obstetric image review (Herman et al., 1998; McLennan et al., 2009). A more recent study by Gilany et al (2022) is applicable to prostate imaging. They saved single frames for an image of each biopsy core obtained from the prostate and retrospectively reviewed. The lack of cine loop information was not noted to be a limitation in this study (ibid.) and, as such, comparable image collection for my trial protocol was favoured.

A further consideration with respect to image collection was that different machines, as proposed in my study, are open to differing echo brightness as Metcalfe and Evans (1992) discuss. These authors identified the need for consistent machine settings and the use of a pre-set collection of parameters in a bid to prevent variability in image acquisition. Wolstenhulme et al (2015) also identified that performing scans in differing ambient lighting may affect the interpretation of the image. However, they concluded that this caused limited difference between operators but the conditions under which images are retrospectively reviewed in my study needed to mimic scan room conditions to reduce variance.

5.10.3 Image assessment and scoring

Images collected for retrospective review need some manner to document a subjective opinion or provide an objective score. Cantin and Knapp (2013), whose study most closely aligns with my proposed study, trialled multiple methods of image scoring despite acknowledging that inherent difficulties exist in retrospective analysis. Initially, the authors used a nine-point questionnaire but failed to use questions one to six in their data analysis and they proposed that a simplified image scoring system could be used (ibid.).

Roest et al (2023) identified that, whilst recommendations exist for the reporting of prostate MRI, there is no guidance on how to document likelihood scores. Where reporting guidance does exist there remains no agreement as to which to utilise. For MRI there is both the Prostate Imaging Reporting & Data System version 2 (PI-RADS v2) (Vargas et al., 2016) and the Likert scoring system (Renard-Penna et al., 2015). Both

provide a five-point scoring system although PI-RADS v2 is seen to provide a more site-specific stratification, which is useful for biopsy planning. However, PI-RADS v2 is known to have limitations in identifying equivocal lesions. Aussavavirojekul et al (2022) have suggested that a machine learning model with binary output would aid diagnosis. With two MRI scoring systems in use, it is of little surprise that confusion exists within the UK. This confusion is exacerbated further by recommendations from the National Institute for Health and Care Excellence (NICE, 2021), which advocates the use of the Likert scoring system for reporting MRI, whilst the United States of America and Europe have adopted PI-RADS v2 as it is believed to improve standardisation of reporting (Latifoltojar et al., 2019). Locally, PI-RADS v2 is the MRI reporting tool of choice due to this reason.

The advent of microUS has led to early adopters searching for a similar standardised reporting system. Ghai et al (2016) published the microUS protocol for prostate risk identification and created the five-point Prostate Risk Identification Using MicroUS (PRI-MUS™) system. In part, the five-point scale was created to align with the five-point MRI reporting systems but is hindered by the subjective interpretation challenges inherent in ultrasound. Ghai et al (2022) has since attempted to validate PRI-MUS™ by comparing microUS scores using this system with the histological outcomes post biopsy. The authors' most recent published study (ibid.) identifies similar rates of cancer detection between MRI and microUS, with Gilany et al (2022) adding further to this validation when using a similar methodology. MicroUS lesion detection and interpretation within the anterior aspect of the prostate gland has been further validated in a study by Shaer et al (2023) who compared PRI-MUS™ scores of the anterior aspect of the prostate with histological outcomes following prostatectomy and conclude that the entire gland can be assessed for prostate cancer using microUS. However, issues remain with subjectivity of microUS and characterisation of equivocal lesions, which became apparent in my research study outcomes.

Comparable challenges present throughout ultrasound imaging and were identified as a particular problem with regards ovarian assessment. In 2013, a strategy for improving the diagnosis of ovarian cancer was published (Kaijser et al., 2013). This strategy is known as the International Ovarian Tumor Analysis (IOTA) (Timmerman et al., 2016) and uses simple descriptors and simple rules to characterise a three-point

risk of pathology. By utilising this strategy, ovarian masses are characterised as benign, malignant, or indeterminate/equivocal (ibid.). Whilst not directly comparable to the prostate, the IOTA use of simple descriptors of ultrasound findings, and a three-point characterisation, reduces subjectively and aids decision making. No such rules exist for the interpretation of standard US, but the adoption of a modified simple descriptor and the use of a five-point scale, comparable with PI-RADS v2 and PRI-MUS^{TM}, for initial evaluation of the images was indicated in this study. A three-point risk stratification, more aligned with IOTA, was postulated as a feasible option for categorising outcomes following the image review component of the ERUP trial.

5.10.4 Image evaluation and peer review

Having identified an optimum method for assessing the prostate with ultrasound, an estimated sample size, and a mechanism for retrospective image review, it was important to consider who was best placed to review and score the images. In any form of operator agreement, there needs to be as much standardisation as possible. Despite the limitations of single frame store, providing there is little variation in imaging parameters and machines, Salomon (2008) identified that experienced ultrasound operators could perform an objective score of images. Parker & Byass (2015) identified sonographers felt that performing image review contributed to their own learning and professional development. Indeed, Itri et al (2018) identified that peer review of images led to reduced diagnostic errors and increased satisfaction of stakeholders involved with the process. Peer review strives to standardise practice and, as Smith (2022) discusses, where there is no benchmark, such as here with regards interpreting ultrasound findings in the AS of csPCa, peer review can ensure consistency of practice.

Various methods to ensure consistency and standards of practice in radiology are explored by Moriarity et al (2016), specifically related to radiologists' practice. This paper (ibid.) recognises that there is no evidence base to determine the most meaningful method for peer review. It further identifies that it is time consuming to perform and advocates for limiting the number of reviews undertaken. However, to test inter-rater reliability, each study 1, phase 1 participant will have their image datasets reviewed twice, which may result in approximately 200 standard ultrasound and 200 microUS images datasets to be reviewed. Thrall et al (2018) identified the risk

of observer fatigue if a high volume of reviews is undertaken and, as such, the number of reviewers compared with the sample size for this study has to be optimised. To reduce burden on individuals, recruitment for reviewers was sought from within the multi-disciplinary clinical team involved with imaging prostate cancer within the Hull Teaching Hospitals NHS trust. An optimal number of reviewers would be ten with a minimum of five. This enabled images from a sample size of approximately 100 patients to be shared equally resulting in a maximum of 80 and minimum of 40 datasets per reviewer. Reviewers were asked to review these over a period of six weeks and advised to review a maximum of five in any one sitting, particularly as experience was gained.

5.10.4.1 Reviewers' experience

There is no evidence to suggest that either a sonographer or radiologist is better placed to perform image reviews. Indeed, a study by Lewis et al (2015) found no significant difference in abnormality detection between dedicated ultrasound sonographers and radiologists and point-of-care medics using US to aid clinical assessment. However, what is recommended is the need for a degree of experience. Cantin and Knapp (2013) identified that image review without prescriptive rules can reduce confidence in the process; experience and an individual's heuristics tendencies may overcome this limitation. Ultrasound experts, regardless of professional background, were required to be able to review the images and provide a subjective interpretation of normality or otherwise, and simultaneously provide an objective score related to the quality (good/fair/poor for example) of the scan within the limitations of a retrospective review. Underpinning knowledge of the prostate anatomy and ultrasound appearances are essential if valid reviews are to be performed. Inexperience of microUS was not a limiting factor as the imaging characteristics are supported by the validated PRI-MUS™ (Ghai et al., 2016) reporting system. Interestingly, Ashdown et al (2018) identified that inexperienced observers could distinguish 'better', 'good' or 'poor' image quality. Whilst they did not match experts, inexperienced observers could comment, and they concluded limited experience is not a limiting factor in reviewing images. This was of particular importance given that the use of microUS was novel for the whole team.

5.10.4.2 Bias and blinding

There are limitations of peer review however, particularly if there is a lack of standardised image capture. As McLennan (2009) identify, there is significant variation in observer rating if images are not consistent leading to poor quantitative analysis of outcomes. The art of sonography is a subjective assessment of images with inherent intra- and inter-operator variability, which Herman et al (1998) identified in their study. Assumptions must be made when retrospectively reviewing US images. The key assumption that Lucas et al (2019) suggest is that techniques used to obtain the images are unaffected by whomever acquired the dataset. This assumption has to be made to avoid framing bias. As Itri (2018) discusses, framing bias will exist as observers tend to be influenced by the clinical presentation. This can be avoided in general peer review, but in a study specifically evaluating prostates, the observers will all be aware that participants are under investigation of prostate cancer. This was a limitation of image review in this study but could not be mitigated for. To reduce the risk of bias, reviewers were blinded to the findings of MRI and histopathology by only being given access to anonymised images, stripped of all patient identifiable data. In addition, it was vitally important that reviewers were blinded to each other's scores to, again, prevent bias and maintain integrity of the study. This was achieved by storing all images into individual Microsoft PowerPoint® presentations, each with a unique number before being allocated to each reviewer. Even though each case was reviewed twice, to prevent unintentional bias, each presentation was duplicated, and each version given a different unique number.

5.11 Data Analysis

5.11.1 Measurable objective assessment

The use of an objective scoring system lends itself to an objective analysis of the data. My measurable objectives required an understanding of whether individual practitioners could identify pathology on ultrasound imaging. I was also investigating the rate of agreement between practitioners. Following the initial image collections, all study 1, phase 1 participants progressed to have biopsy of the prostate. This provided a definitive histopathological diagnosis of the presence or absence of prostate disease. Histopathology is deemed to be the reference (gold) standard technique used for diagnosis (Tseng et al., 2023). Biopsies were directed by findings of the MRI, which remained blinded until the ultrasound image acquisition for the ERUP trial had been

completed and stored. The primary study compared ultrasound appearances with histology; a subsidiary study, as yet unanswered would be to compare ultrasound findings with MRI.

5.11.2 Options for statistical tests

Previous studies, which have reviewed inter-operator agreement, used various statistical tests to understand agreement and variance. McLennan (2009) looked at the proportion of suboptimal or non-diagnostic images and used a Huber–White sandwich estimator. Their method is useful for evaluating image quality, but this is not something I test in this ERUP trial. More comparably, Herman (1998) used an X^2 test to analyse the distribution of reviewers and undertook an analysis of variance. This test looks at variance between observers as opposed to agreement, and it is the assessment of agreement which was more suitable for my study. Evaluating agreement between reviewers of diagnostic tests is important as it can provide valuable insight into how the reliability of the test may be improved (Nelson & Edwards, 2010). Cantin and Knapp (2013) investigated the systematic differences between reviewers and used a paired t-test. Levels of agreement were reported using Bland Altman analysis (1986). As Giavarina (2015) discussed, Bland Altman analysis is useful to assess the mean differences between observers, although it is limited when two separate imaging methods are being assessed. It could be used when comparing standard ultrasound against microUS but to compare observers against the known reference standard of histopathology, a two-sample comparison was required, as Donner discusses (1998).

To assess the agreement between reviewers, a kappa statistical test is the most appropriate method of analysis (Rowntree, 1981). As Rigby (2000) discusses, kappa can determine the reliability of the ultrasound test when compared to histopathology, and its use was to provide answers to the first four measurable objectives of this study.

5.12 Practitioners experience of using mpUS

The fifth measurable objective was to investigate how new technology is embedded in practice. In this next section, I identify implementation strategies considered to capture practitioners' views, experiences, and how new technology is implemented in practice. Options for data collection are explored and discussed.

5.13 Practitioner considerations

As Edwards (2022) discusses, ultrasound practitioners are directly coupled with technology and, whilst their own knowledge and skills develop with experience and time, a consideration of implementing new technology is whether it improves inter-operator consistency within this expert group. Ashdown et al (2018) identified that a novice can rate images, but they are unlikely to appreciate the reason such images were acquired. In my study, practitioners will fully understand the rationale for acquiring images, but may not appreciate or be confident with how they are acquired when new technology is introduced. Dependent upon their own perspective of the new technology, as Ashdown et al (2018) elude, either a positive or negative bias may be introduced into the image interpretation. A recent systematic review, published by Darianne et al (2022), identified that the learning curve for practitioners already experienced in prostate ultrasound is limited to understanding the techniques and the PRI-MUS^{TM} systems. As such, assumptions could be made that the learning curve for microUS will have little impact on practitioner performance in this study and this was explored further within the local team.

5.13.1.1 Practitioner satisfaction

Itri (2018) identified that peer review can lead to improved job satisfaction, and this supports the earlier evidence presented by Parker & Byass (2015). However, if new technologies or techniques are not introduced and embedded well into practice, there may be a detrimental effect on practitioner satisfaction, and microUS will need to be framed in context to ease adoption (Nilsen, 2020). Edwards (2022) identified that sonographers are the conduit between patients and technology and are key to optimising imaging. However, if practitioners are not engaged with introducing new technologies into practice, there is a risk of failure (Rycroft-Malone et al., 2013).

The fifth measurable objective of my study was to better understand how new ultrasound technology and techniques could be implemented and embedded into clinical practice. This is reliant on practitioners adopting and adapting to these changes. To explore this, tools were used to help identify whether implementation barriers existed, where they were, and, therefore, what solutions might be applicable for facilitating normalisation of this new technology in practice.

5.14 Embedding technology in practice

5.14.1 Multi-professional team considerations

As Bauer et al (2015) report, the reality is that some evidence-based practice can take up to 17 years to become embedded into routine clinical practice. Within a real-life clinical setting, this will have a significant impact not only on patient outcomes, but also on effective use of resources and, within imaging, changing technology. However, rapidly introducing new interventions, based on clinical urgency rather than based on evidence, could lead to implementation failure and potential unsafe patient care (Auerbach et al., 2007). As discussed by Greenhalgh (2017), there is a need to understand not only what works within a clinical context, but within ***this*** clinical context i.e. this team of practitioners, and with the capacity constraints facing the local department.

New interventions challenge the norm; it can be difficult to change opinions, particularly of those practitioners not heavily invested in the need to change (Campbell et al., 2007). Understanding the context in which this intervention will be implemented is important, as often the results are context-specific (Jacobs et al., 2014; May et al., 2016).

5.14.2 Challenges to implementation

There were four recognised challenges that presented themselves in the implementation of microUS into an AS pathway:

- Acceptance of novel intervention within the AS pathway, particularly by practitioners not invested in developing imaging modalities.
- Professional boundaries between the traditional urology practitioners and radiologists, and the non-medical practitioners who undertook the microUS examinations.
- Confidence of the non-medical practitioners of their own knowledge and skills of microUS.
- Time to implement novel intervention within the AS pathway.

The use of an implementation theory was crucial in order for other challenges, as yet unknown, to be identified, and it would provide data to inform how strong some of the identified challenges were. Facilitating communication between the multi-professional

team should aid implementation and reduce the challenge of professional boundaries, but the crucial understanding and explanation of the implementation could be missing if individuals are not supported to appreciate how their own actions influence the team's outcomes (May, 2013). The use of an implementation process was essential to identify any individual influences on normalisation.

5.14.3 Identifying Implementations theories and processes

Multiple processes, theories, and frameworks have developed over time to aid implementation. Nilsen (2020) describes five theoretical categories that can be adopted to aid implementation. These are listed as:

- Process models
- Determinant frameworks
- Classic theories
- Evaluation frameworks
- Implementation theories

A process model provides guidance for the planning and practicality of implementing new practices. Whilst guidance is useful, it does not explore how the implementation affects or impacts on the team. It was therefore not applicable in my study. The main aim of a determinant framework is to understand the influences that effect implementation outcomes and explain these. Commonly this is retrospective and may not assist in understanding how practitioners normalise new technology on a prospective basis. The Promoting Action on Research Implementation in Health Services (PARIHS) framework (Rycroft-Malone et al., 2013) looks to explain and explore the interactions between three core components of evidence, context and facilitation but lacks the ability to develop an understanding of how new technologies can be normalised in practice.

As Nilsen (2020) describes, the category of classical theories relates to those that originate from human sciences external to implementation science such as psychology or sociology. They can be applied to aspects of implementation in a bid to provide understanding of the process but, again, do not necessarily explore how new technologies can be embedded. This could be achieved by using an evaluation

framework, specifically scrutinising an explicit aspect of the implementation process, such as practitioner satisfaction, but is unlikely to capture the process and impact of change. Implementation theories have been developed to provide such an understanding of the process of embedding change. Normalisation process theory provides a well-defined framework that analyses incremental knowledge gains over the process of the change (De Brún et al., 2016) and provides an opportunity for early identification of gaps in understanding or familiarity of new technology and techniques.

5.14.4 Normalisation Process Theory

Normalisation Process Theory (NPT) provides a reliable and effective way of identifying in what manner the new technology impacts on how people work. Effective implementation in my study requires practitioners to engage with, and support changes to, the AS pathway. Learning new ultrasound skills for the non-medical practitioners is unlikely to be a barrier as professional skill development is inherent within imaging clinical practice roles at an advanced level (Kettlewell & Richards, 2021). However, it cannot be assumed that new knowledge will be easily assimilated, and the assumption that only the short learning curve described by Dariane (2022) needs to be tested. A benefit of NPT is that it provides a well-defined framework for analysis and provides an opportunity for assumed incremental knowledge gains to be explored throughout the implementation process (De Brún et al., 2016).

5.14.4.1 Accepting new technology

The context in which this new technology is to be embedded is complex due to the multi-professional roles within the AS pathway; potentially there will be a difference in acceptance between sonographers who will be using and interpreting microUS and radiologists or urologists who will be interpreting and acting upon microUS findings. Whilst microUS is a practical clinical intervention, the complex context in which it is to be implemented is a social process with multi-professional involvement; NPT focusses on how the actions of practitioners, individually and collectively, affect the implementation of changing practice (May et al., 2014). As May et al (2011) describe, to understand how practice is embedded and becomes normalised, it is important to evaluate what practitioners do, and how they feel they work, individually and collectively. NPT focusses on just that; at what people (individually and collectively) do

(May et al., 2018). NPT was an appropriate tool to use within this AS context as it provided evidence about how change happened and provided insight into the interaction between the introduction of microUS and the impact on the multi-professional team (Murray et al., 2010). Murray et al (ibid.) further explain that NPT is used to identify factors that impact, both positively and negatively, on the normalisation of new interventions into routine clinical practice. This normalisation is assessed by subdividing the implementation process into four constructs; each essential for success (May et al., 2009). Critical understanding and ongoing appraisal of these constructs, in the real-life clinical setting, is crucial.

5.14.5 NPT tools

Rapley et al (2018) developed an on-line tool for assessing implementation using NPT known as the **No**rmalisation **M**e**A**sure **D**evelopment (NoMAD) tool. Finch et al (2018) identified the tool provided a valid and consistent method for assessing staff perceptions related to embedding new interventions that changed real-life practice. This tool has been used in many other studies (Holtrop et al., 2016; Gillespie et al., 2018; Huddlestone et al., 2020; Hindi et al., 2023; Shaw et al., 2023) but there is no evidence to suggest it has been used before to evaluate the normalisation of imaging procedures within clinical pathways. Processes are evaluated under four constructs of coherence, cognitive participation, collective action, and reflexive monitoring. The following Table 5.1 outlines the definitions, and questions for evaluation of each construct, as provided by the Normalisation Process Theory website (May et al., 2015).

Table 5.1 Definitions of the four constructs of NPT (Murray et al., 2010; May et al., 2015)

Construct	**Definition**	**Questions considered within the framework**
Coherence	Sense-making work that people do individually and collectively when they are faced with the problem of operationalizing some set of practices.	Is the intervention easy to describe? What benefits will the intervention bring and to whom? Are these benefits likely to be valued by potential participants?
Cognitive participation	The relational work that people do to build and sustain a community of practice around a new technology or complex intervention.	Are target user groups likely to think it is a good idea? Will they be prepared to invest time, energy, and work in it?
Collective Action	The operational work that people do to enact a set of practices, whether these represent a new technology or complex healthcare intervention. (*The associated components of this construct reflect the qualities of technologies or complex interventions, rather than the character of the work that these involve).*	How will the intervention affect the work of user groups? How compatible is it with existing work practices? What impact will it have on division of labour, resources, power, and responsibility between different professional groups?
Reflexive Monitoring	The appraisal work that people do to assess and understand the ways that a new set of practices affect them and others around them.	How are users likely to perceive the intervention once it has been in use for a while? Is it likely to be perceived as advantageous for patients or staff? Will it be clear what effects the intervention has had?

To facilitate investigation of the process of implementation using NPT, each construct is sub-divided into a further four sub-constructs. These sub-constructs assist in the understanding of the processes involved with embedding the new intervention into the prostate pathway (Murray et al., 2010). In the context of the implementation of microUS into the prostate cancer pathway, the NPT constructs and sub-constructs are described as follow (Finch et al., 2012; Hindi et al., 2023; Shaw et al., 2023):

Coherence: describes the implementation of new ways of working required so that people can make sense of it and its associated practices (coherence). This involves individual and collective work to understand how microUS differs from previous practices (**differentiation**), what this new technology means for team working (**communal specification**), what microUS means for individual roles (**individual specification**), and its value in clinical practice (**internalisation**).

Cognitive participation: while coherence is important, successful implementation also depends on relational work to develop and sustain practices around new ways of working. This needs key people to drive the new technology forward (**initiation**), motivate and organise others to be active participants (**enrolment**), instil a shared belief that it is right for practitioners to be involved with microUS (**legitimation**), and identify a determination to keep microUS going in practice (**activation).**

Collective action: the operational work that practitioners do, individually and collectively, to enact new ways of working. It involves working with others and the new ultrasound technology to perform microUS in practice (**interactional workability**), building accountability and confidence in the team and microUS (**relational integration**), distributing of the microUS appropriately within the team (**skillset workability**), and an appreciation of how resources of training and technology used is shared and allocated (**contextual integration**).

Reflexive monitoring: the appraisal work that people engage in to understand if the new technology of microUS is worthwhile. This involves obtaining information to evaluate microUS (**systemisation**), working together to assess its impact (**communal appraisal**), personal assessments about how microUS will affect their work and working context (**individual appraisal**) and work to modify practices to embed this new technology successfully (**reconfiguration**).

These four constructs, and associated sub-constructs, required investigation in the context of practice change within AS and were appropriate to be evaluated using this tool.

5.14.6 NPT Limitations

NPT will provide a good insight of how the new technology has been embedded into the AS pathway. However, it is not without its limitations. Firstly, there is no one agreed way of analysing the data collected using the NoMAD tool (Finch, 2018). This tool is used to collect data from the perspective of professionals directly involved with the implementation, which, with a large sample size, some authors have attempted quantitative statistical analysis (Gillespie et al., 2018). However, in this instance data will only be available from a small sample and, as such, descriptive analysis of responses was appropriate.

The second limitation is the absence of an explicit facilitator that can be evaluated; this is a benefit of the PARIHS framework (Rycroft-Malone et al., 2013). This facilitator leads the change, and outcomes can be measured using the PARIHS model. NPT evaluates both individual and collective perceptions and responses, which may conflict with each other, particularly in the absence of a facilitator to act as the benchmark measure. However, in the context of my team and clinical setting, where advanced practitioners work with individual autonomy and are accountable for their own actions, NPT maps more to the real-life setting than other theories, frameworks or processes do. As such, NPT was the strategy of choice for evaluating implementation of microUS within the AS pathway.

5.15 Conclusion

In this chapter I have explored the methodology that could be used to achieve the aims and objectives of my thesis. I have identified that a modified multi-parametric ultrasound imaging protocol, which includes B-mode, colour Doppler and microUS offered a pragmatic and practical approach to assessing the prostate. Limitations of IT bandwidth and data transfer resulted in the decision that still images of the prostate for each patient and each imaging parameter would be captured, as opposed to large volume cine loops. I identified that peer review of images is an acceptable and evidence-based method of evaluating imaging outcomes, and these reviews could be scored using an objective scale, loosely based on current prostate reporting systems but consistent with validated ovarian tumour analysis risk scores. I identified the

appropriate statistical test of kappa could be employed to evaluate inter-reviewer agreement rates to answer one to four of the measurable objectives of the ERUP trial.

To avoid observer fatigue, and to explore how the team adapted to new technology, all practitioners involved in the interpretation of prostate imaging were invited to participate in the image review and implementation study. The impact of implementing new technology within an experience team needed to be explored and I identified that NPT provided the most reliable tool to measure longitudinal assessment of implementation. This theory was employed to answer the fifth measurable objective.

In this chapter, the methodological options, which could have been utilised to address the two main research themes have been discussed. The methods offering the most pragmatic, practical, and appropriate method to collect data to answer the measurable objectives of this study have been identified. In the next chapter, the study design and protocol employed, the ethics approval obtained, and the method used for study 1, phase 1 of the ERUP trial are presented.

Chapter 6 ERUP trial – Study design and study 1, phase 1 method.

The thesis so far provides the background evidence required to design a study to investigate the role of ultrasound in the active surveillance (AS) of prostate cancer. The aims and measurable objectives were presented in the previous chapter. The purpose of this chapter is to describe the study design, explain the research phases employed, and to outline the ethics approval and updates that were required once the trial commenced. This chapter also includes the study method for phase 1, with the results and analysis presented in Chapter 7.

6.1 The ERUP trial – study considerations

This PhD research project was undertaken within a radiology department of an NHS care setting. The project was designed to use the technology and staffing resources available within a real-life clinical setting and, as such, had to consider the standard care pathway of patients that were potential recruits for the trial. I considered the impact on patients, staff, and activity of undertaking a clinical research project within a secondary care diagnostic imaging department. This was prudent as the department was experiencing pressures related to increasing clinical demand, the obligatory social distancing measures in place at the time of data collection, and a potentially "at risk" patient population - all factors related to the coronavirus (COVID-19) pandemic, which commenced in March 2020 (Office for National Statistics, 2023) as the study design was being prepared.

The ultrasound parameters and technologies available to assist with this study were B-mode standard ultrasound, colour Doppler imaging, and microUS. These formed the multiparametric ultrasound (mpUS) scan protocol utilised for image capture, which I discuss in section 6.7 below. No resources were available to increase the range of ultrasound parameters, such as elastography or contrast that could otherwise have been employed. However, these had been discounted due to reasons discussed in Chapter 5.6.2 & 5.6.3. All scans were performed to the strict study protocol outlined in later in this chapter (6.7) and in compliance with the British Medical Ultrasound Society Safety Guidelines (ter Haar, 2010) and the Trust infection control policy (HUTH, 2023a).

6.2 Study Design

To capture the data that was relevant for this proof of concept study and provide answers to the measurable objectives outlined in Chapter 5.4.1, this research was originally planned to be undertaken in three distinct studies, with two phases to study 1. Figure 6.1 below provides a pictorial demonstration of the study flow and questions under investigation during each phase. A multiphase approach was required to understand the diagnostic capabilities of the mpUS parameters and their subsequent use in surveillance. The purpose of study 1, phases 1 and 2 was to explore if any ultrasound parameters and technologies, as evidenced within published literature and discussed in Chapter 2 of this thesis, possess the pragmatic and practical potential to identify disease within the prostate. Study 2 (Chapter 9.1) was to provide evidence to answer the question of whether the technology could be embedded as the mpUS techniques became more regularly used in clinical practice.

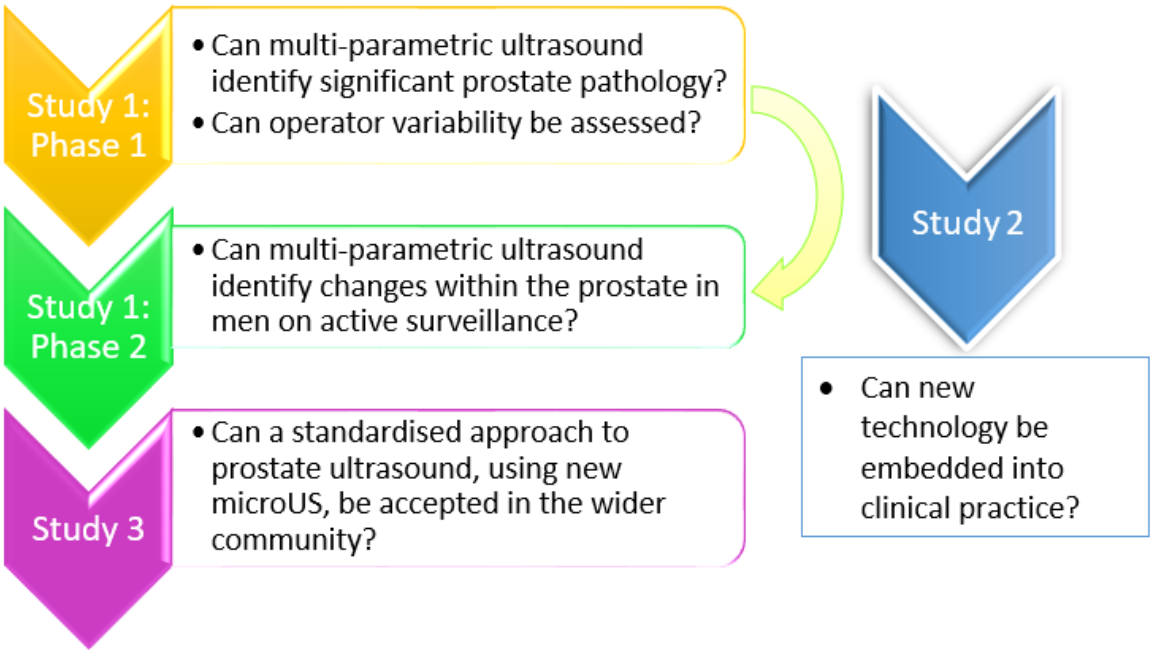

Figure 6.1 ERUP trial and phase flow diagram

6.2.1 Study Phases

Study 1, Phase 1: Question - Could the use of multi-parametric ultrasound identify significant prostate pathology?

Measurable objectives under investigation:

1. *To evaluate the diagnostic parameters of diagnostic ultrasound that could be utilised to assess disease within the prostate gland.*
3. *To evaluate if the intra and inter operator variability in the assessment of ultrasound imaging parameters of the prostate gland could be investigated.*
4. *To determine if a suitable standardised imaging protocol and reporting tool or model could be utilised in the reporting of transrectal ultrasound imaging of the prostate.*

Participants were recruited from men attending for prostate biopsy who had had recent previous MRI imaging of their prostate, associated with their current referral. Baseline mpUS of the prostate was undertaken and images captured for retrospective review by the team of practitioners. Reviewers were blinded to the MRI, histopathology, and previous ultrasound results to prevent bias. Images scores were evaluated using histopathology as the reference standard. Inter-operator agreement and variance were measured. The study method used for this phase is provided in section 6.6 below, with results presented and discussed in Chapter 7.

Study 1, Phase 2: Question - were there features of multi-parametric ultrasound that could be used to identify changes within the prostate in men on active surveillance?

Measurable objectives under investigation:

2. *To evaluate the diagnostic parameters of diagnostic ultrasound that could be utilised to assess disease progression within the prostate gland.*
3. *To evaluate if the intra and inter operator variability in the assessment of ultrasound imaging parameters of the prostate gland could be investigated.*
4. *To determine if a suitable standardised imaging protocol and reporting tool or model could be utilised in the reporting of transrectal ultrasound imaging of the prostate.*

Phase 2 was planned as a longitudinal study following initial histological outcomes of the phase 1 participants. Participants were recruited from men in phase 1 who had

clinically insignificant cancer or no disease identified at histopathology following the initial biopsy, and who were being managed under an AS regime. The mpUS image protocol of the prostate was repeated using the same pre-set parameters as the initial baseline scan. Images were captured and stored on PACS, and then retrospectively reviewed by two of the team of practitioners. The original study design anticipated that reviewers were blinded to the MRI, histopathology, and previous ultrasound results to prevent bias. However, to better represent real-life clinical scenarios, reviewers had access to all previous imaging. A retrospective review of stored images was undertaken to evaluate any change in appearance. Image scores were evaluated using histopathology as the reference standard and against scores obtained from the previous phase 1 review. Inter-operator agreement and any potential variance were measured. Study 1, phase 2 methods, results and analysis are discussed in Chapter 8.

Study 2: Question – How successfully could new technology be embedded into real-life clinical practice?

Measurable objective under investigation:

5. *To gain a better understanding of how new ultrasound technology and techniques could be implemented and embedded into clinical practice.*

This second study explored the views of the health care practitioners regarding the use and implementation of the proposed new technologies. The participants were recruited from differing professionals involved with the AS prostate cancer pathway within the Hull University Teaching Hospitals NHS Trust and who either used and interpreted, or only interpreted standard ultrasound and microUS in this setting. Skill mix between these professional groups was required for successful long-term practice (Wood, 2021) and the study was designed to capture views of both radiology and urology practitioners.

The purpose of this phase was to understand how, and if, the new, complex, multi-parametric ultrasound techniques could be implemented within the organisational setting of everyday routine practice. Participants in phase 3 were provided with training using specific mpUS techniques, including the use of microUS and were already regularly interpreting prostate US examinations to varying levels of expertise.

Participants' confidence in their knowledge and skills, related to prostate cancer evaluation using mpUS, and how they felt about implementation of this into regular patient care was assessed at the start of the research project and at 12-months' post implementation. A questionnaire was utilised to collect participants' opinions using the normalisation process theory (NPT) tool (May et al., 2015). This theory was discussed in Chapter 5.14.4 and its relevance as a tool in the ERUP trial is presented, along with the results of study 2, in Chapter 9.6 of this thesis.

Study 3: Question – Is new technology, related to prostate imaging, widely accepted within the ultrasound community?

Measurable objective under investigation:

5. *To gain a better understanding of how new ultrasound technology and techniques could be implemented and embedded into clinical practice*.

Given the novel nature of this technology, and the unique position of having access to microUS, it was anticipated that the results from this thesis would be shared amongst the wider uro-radiology community to help form aims and measurable objectives of future studies into this new technology. However, upon completion of phase 1, it became apparent that there was insufficient confidence in the results, nor sufficient data available from phase 2, to ask the imaging and urology community to take time out to come together to discuss microUS. A decision was made to postpone any discussion specifically related to microUS until this technology was more widely utilised within the UK. Results of the remaining study phases will be published in order for my findings to be distributed within the prostate community and to add to the knowledge of this new technique.

6.3 Ethical Approval

The study was approved by the Oxford NHS Research Ethics Committee (reference 21/SC/0326) on 23 November 2021 (Appendix 3, page V). NHS permission to undertake the study in my local institute was obtained via the Confirmation of Capacity and Capability at Hull University Teaching Hospitals NHS Trust (HUTH) process on 06 December 2021 (Trial number R2706). Faculty of Health Sciences ethics committee,

University of Hull was granted using Chair's approval on 07 December 2021. The study was sponsored by the HUTH Research and Development department.

To ensure transparency, and to ensure there is open access for fellow researchers and the general public, clinical trial registration is considered both a scientific and ethical responsibility (Viergever et al., 2014). To that end, the trial protocol was registered with clinicaltrials.gov (2021) (NCT05326282).

6.4 Protocol changes

The ERUP trial was initially designed, and sponsorship agreed by HUTH, in late 2019 and early 2020, prior to the start of the COVID-19 pandemic. The study protocol was refined during the first year of the pandemic and considerations related to the effects caused by global travel restrictions and social distancing measures implemented by the UK government had to be made. Whilst it was anticipated that sufficient considerations had been included within the final study protocol, it became apparent that, given the unprecedented circumstances, changes to the approved design were required once recruitment and data collection commenced. As recruitment was initiated, and image capture attempted, unforeseen issues arose in the real-life clinical setting, which lead to a variation from the planned study design. Whilst the issues affected participant inclusion, image storage and image scoring, none of the following changes were deemed sufficiently significant by the study sponsor to require ethics amendment. The fundamental trial aims and objectives were not affected by these protocol changes, but they are discussed here to ensure transparency of practice during this research project.

6.4.1 Study 1, Phase 1 inclusion criteria changes

Whilst the eligibility criteria included men equal to 75 years or less, there were five men over the age of 76 who otherwise met the criteria and requested participation as they had been given the relevant PIL at their initial urology consultation.

Eligibility criteria for the study included PSA of equal or less than 20. There were three men with PSA over 20 who, again, requested inclusion as they too were aware of the trial. These men outside of the age and PSA criteria were included in the study following discussion with my clinical supervisor as they were deemed fit for surgery if needed, and all had had a pre-biopsy MRI completed. There were no participants over

75 and with a PSA over 20 included. Men who did not have pre biopsy MRI were excluded.

Compliance with the eligibility criteria is documented in Table 6.1.

Table 6.1 Compliance with eligibility criteria

Status of participant	Frequency
≤ 75 years AND PSA ≤ 20	94
≥76 years OR PSA ≥ 20	8
≥76 years	5 (PSA range 5.6 – 15)
PSA ≥ 20	3 (Age range 63 – 74)
≥76 years AND PSA ≥ 20	0

6.4.2 Study 1, Phase 1 and 2 image acquisition and storage changes

The approved study protocol anticipated that cine loops acquired during the ultrasound scan would be stored for both the standard ultrasound and microUS examinations. Cine loop review better replicates real time live scanning than a review of still images. However, cine loops create a large amount of data that needs to be transferred to PACS. At the time of study protocol approval, very few cine loops had been acquired by the microUS system as only still images had been required clinically up to the time of the ERUP trial commencing. Once data for the ERUP trial started to be collected, it became apparent that the size of the cine loops of one gigabyte (GB) per patient exceed the bandwidth available on the ultrasound department IT network. The network was upgraded in June 2022. Nevertheless, the data files were still too large to transfer in their entirety. Following discussions with both clinical and academic supervisors, it was agreed to take the pragmatic approach of still image storage for each case but to ensure a standardised image protocol was followed. At the time of data collection, the impact of saving still images rather than cine loops was not envisaged to be significant. It is common practice to store and retrospectively review still images and is standard practice for the department's quality assurance programme (HUTH, 2023c).

6.4.3 Study 1, Phase 1 baseline microUS scoring changes

Whilst the study protocol was finalised in mid-2021, and the microUS machine was delivered to Hull University Teaching Hospitals in April 2021, the machine was not functional until September 2021. It required installation by the manufacturer specific

engineer who, unfortunately, was not UK based. Travel restrictions in place due to the COVID-19 pandemic constrained the time when both the engineers and application specialists could visit the UK. The machine was initially installed in September 2021 but, due to the ongoing image storage issues, required further visits from the manufacturer specific application specialist, again non-UK based, which had to be delayed until December 2021 and January 2022. The team were unable to gain experience in using and interpreting microUS until the latter visit, and there were increasing time pressures to collect data within this PhD timeframe. In a bid to ameliorate the situation, it was agreed that, once the trial images had been obtained and stored, the two sonographers undertaking the scans conferred and agreed a microUS score prior to proceeding to complete the biopsy procedure. The purpose of this process was for the team to gain experience and confidence in the new technique whilst acquiring data for this feasibility study. The approved study protocol stated that a baseline result would not be recorded but, as the study commenced, I felt that this baseline score, acquired during the real-time scan, could provide useful, and potentially more accurate, data for comparison with histology than that obtained from the retrospective review of still images alone. As such, the baseline score was recorded as part of the dataset of phase 1. The baseline result of the microUS was recorded independent of the patient's standard care and was not used to plan the biopsy. The standard ultrasound, and transperineal procedure protocol, was used to guide the biopsy and target tissue sample collection from any lesions identified on MRI.

Given that images acquired during the live examination were stored to PACS and retrieved later, and that all images presented for retrospective review were completely anonymised, the risk of interpretation bias between the original scan team agreeing the baseline score and the subsequent review were negligible.

6.4.4 Study 2 data collection change

To collect data related to the four constructs of NPT, the Normalistion MeAsure Development questionnaire (NoMAD) (Finch et al., 2015) was adapted to relate specifically to microUS. The original study protocol stated that this questionnaire would be circulated to consenting practitioners as the ERUP trial commenced and then at a period of 12 months, or when the phase 1 data had been collected. During the progress of phase 1, the steep learning curve being experienced by all practitioners

involved with microUS became apparent. Following discussion with the research supervisors, it was agreed that a shortened version of the ERUP NoMAD questionnaire circulated at the mid-point of phase 1 would be useful to capture practitioners' feelings about the technology and make adaptations to the study design if required. The mid-point questionnaire was enhanced by team engagement discussions covering three main topics.

- How was the practitioner finding the use of the microUS machine?
- How did the practitioner feel about their ability to identify areas of change in the prostate?
- Was there any support that they felt they needed to help their skill development, including undertaking any online training or having access to publication?

I led all the informal discussions with each of my colleagues within the prostate imaging team with their verbal consent, and I obtained verbal consent to make contemporaneous handwritten notes of their responses to be used to help inform the findings of the ERUP NoMAD survey. The informal discussions were not originally planned as the difficulties experienced with the use and interpretation of microUS were not fully anticipated. I felt it necessary to arrange discussions to facilitate practitioners being able to voice their opinion about what was being asked of them, not just for this research project, but in clinical practice. Whilst outside of the original study design and ethics submission the peer debriefing was helpful and is a recognised criterion for credibility in qualitative research (Sousa, 2014).

6.5 Study reporting

This proof-of-concept study was designed to evaluate if there were any aspects of the role of ultrasound that could be further explored and investigated as to its usefulness in clinical practice. Study 1, phases 1 and 2 are diagnostic accuracy studies and are reported in accordance with the Standards for Reporting Diagnostic Accuracy (STARD) (Cohen et al., 2016). The STARD guidelines and checklist (ibid.) aims to improve the quality of reporting diagnostic accuracy studies and promote transparency and are available at https://www.equator-network.org/reporting-guidelines/stard/ (Equator, 2015). This alignment ensures that all necessary information is included so that readers

are aware of limitations, exclusions and any factors that may impact on the estimated sensitivity and specificity of the tests under investigation in this trial.

6.6 Study 1, phase 1: method

To date in this chapter, I have described the study design and updates that were required due to factors faced as the trial was implemented. In this next section, I detail the study population and recruitment of participants, and the methods employed to collect appropriate data to answer the study 1, phase 1 question. The results are presented and discussed in the following Chapter 7.1.

6.6.1 Study population

NICE (2021) advocates that pre biopsy MRI is performed in men with suspected prostate cancer as this can identify areas of high-risk of disease and, as Kasivisvanathan et al (2018) identified in the PRECISION trial, it can be used to target biopsies in a bid to improve diagnostic yield of significant disease. However, to confirm or exclude disease a histological diagnosis is required, and this was deemed to be the reference standard comparator in this study, as it is in other studies comparing imaging to disease (Sonni et al., 2022). Therefore, participants to the ERUP trial were invited from men who had had a pre-biopsy MRI and in whom a histological diagnosis was obtained following transperineal ultrasound guided prostate biopsy (TP Biopsy).

In my institution, capacity for MRI is limited as demand for timely diagnostics outstrips the capacity available as is evidenced in the NHS diagnostic datasets (NHS England & NHS Improvement, 2020). To maximise the usefulness of the available capacity, clinical agreement between radiology and urology has led to MRI being available to men who present at age 75 or under, with a PSA level of 20 or under and / or with a life expectancy of 10 years or more. The majority of eligible men on this pathway are ≤75 but occasionally extremely fit-for-age men of 76 or over may be offered investigations on this pathway if they are deemed fit enough to cope with, and recover from, radical treatment.

6.6.2 Inclusion criteria for phase 1

To align with the MRI clinical pathway, the inclusion criteria used for this study were as follows:

Men referred to urology within Hull University Teaching Hospitals NHS Trust with suspected, but undiagnosed, prostate cancer and:

- Are aged equal to 75 or less
- PSA equal to 20 or less
- Have had a clinical assessment and deemed to have a life expectancy of 10 years or more
- Able to tolerate a rectal ultrasound examination
- Able to provide informed consent to the study
- Had a multi-parametric MRI performed as part of the routine care pathway
- Consent to the addition ultrasound imaging required for this study
- Able to tolerate and have a TP biopsy of their prostate
- Images complying with the study protocol could be obtained and saved for retrospective review.

6.6.3 Exclusion criteria

The exclusion criteria used for this study are as follows:

- Patients accessing care in HUTH but who are not suspected of having prostate cancer
- Men referred to urology but who do not meet the eligible criteria for MRI as part of the routine care pathway. This includes men who are over 75, and / or have a PSA over 20, and / or have a life expectancy of less than 10 years
- Men who meet eligibility criteria but in whom MRI has not been completed (due to lack of compliance, artefact, contraindications etc.)
- Men who are eligible for inclusion but who cannot tolerate rectal ultrasound examinations.
- Men who are unable to consent to the study
- Men who do not consent to the additional ultrasound examination
- Men who do not have a histological diagnosis following prostate biopsy
- Incomplete datasets of images recorded and saved

6.6.4 Recruitment

Recruitment for the study commenced in March 2022 and continued until October 2022. Participants for phase 1 of the study were invited from the cohort of patients referred into HUTH with suspected prostate cancer and who met the criteria above. Men attending an initial assessment clinic were provided with a patient information leaflet (PIL) about the ERUP trial and inviting them to participate (Appendix 1, page I). The leaflets were distributed by the Urologists and Cancer Nurse Specialists who met the patients at their initial consultation. Participants were given a minimum of five days to consider participation and I then contacted the patients, prior to their planned prostate biopsy procedure, to gain consent for participation. The imaging for this study

was performed immediately prior to the biopsy procedure. This was for the benefit of the participants as it avoided the need for an additional attendance at the hospital.

6.6.5 Sample size

As this is a proof-of-concept study testing the technology of ultrasound, and with no previous comparable data, little is known about the standard deviation and distribution of ultrasound scores. This made determining a sample size based on means and variances difficult as I discuss in Chapter 5.10.1. Therefore, the sample size estimation was based on the statistical theory of inter-operator agreement analysis outlined by Donner (1998) and based on a representative proportion of the annual referral rate into this service. Donner (ibid.) identified that power of the test of agreement increased with the number of observers, which supported inviting all users of ultrasound in the prostate pathway to become reviewers. Conversely, it is noted that increasing reviewers is at the expense of the sample size and a balance had to be achieved. Whilst there are good arguments provided by authors such as Sim & Wright (2005) and Wilson (2022) for estimating an optimum sample size, a formal power calculation was rejected due to the likely imprecise estimation of standard deviation that could occur in this feasibility study (Whitehead et al., 2015)

6.6.6 Ultrasound appointments and consent

An appointment for the prostate biopsy was made and agreed with the participant. Upon arrival, the participant had a face-to-face consultation with me, as the lead researcher, and time was taken to discuss the ERUP trial and obtain written consent (Appendix 2, page IV). At this stage, I was blinded to the results of the MRI or previous imaging investigations to minimise undue coercion into the study. I always maintained my professional integrity; I was open and honest with potential recruits, and I ensured I did not review any of the patients relevant previous imaging prior to consultation with the patient. A clinical colleague was always in attendance for the scans and biopsy as the procedures require two sonographers to perform; one using an aseptic technique scanning and acquiring images and the biopsy samples, the other to manipulate the ultrasound machine, store images, and complete relevant documentation. The colleague was introduced and consented the patient for biopsy, separate to the ERUP trial consent.

6.7 Study 1, phase 1 and 2 scan protocol

Once written consent was obtained, the patient was escorted into the scan room for the procedure to be undertaken. A chaperone was present, with consent of the patient, as per standard clinical practice. Imaging for the ERUP trial was undertaken immediately prior to the biopsy procedure and blinded to the results of the MRI examination, which may have indicated areas of abnormality within the prostate.

The patient was positioned in a lithotomy position on the examination couch. Once comfortable, an ultrasound probe from the standard ultrasound machine, with a scan frequency of 7.5MHz, was gently placed into the rectum and the prostate identified. During the ultrasound scan, the prostate gland was scanned in a transverse plane from the apex to base, including seminal vesicles, and right and left lateral borders were included in the scan plane. Longitudinal images could not be obtained as, due to the probe design, the transducer could not be sited in the rectum far enough to be able to capture images from apex to base. A standard imaging pre-set was used with no changes to the scan frequency, or pre-processing software made. The overall gain settings, and time-gain compensation (TCG) were manipulated to optimise imaging. B-mode images were captured. The scan was repeated in the transverse plane using colour flow Doppler assessment. Colour flow Doppler imaging was applied to evaluate the presence of any perfusion within the gland. Again, an optimised colour-Doppler pre-set was employed and only colour gain manipulated to optimise the image. The following systematic static images of the prostate, in both B-mode and colour Doppler imaging were obtained and saved onto the picture archive and reporting system (PACS). Figure 6.2 depicts a typical image of a normal prostate on standard US imaging.

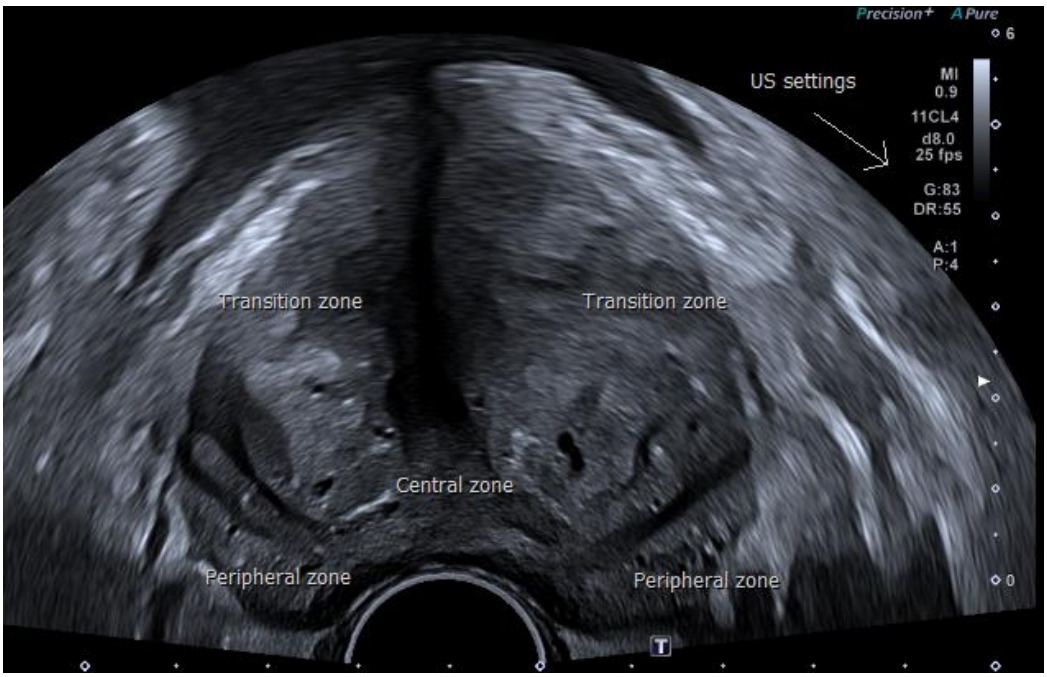

Figure 6.2 Standard US image of the mid prostate gland

6.7.1 Standard image protocol

- Seminal vesicles (where possible)
- Base
- Mid gland
- Apex
- Focal areas of change in appearance

With colour flow Doppler applied, the same set of images was stored. The probe was then removed.

6.7.2 MicroUS

The examination was then repeated using the high frequency micro-ultrasound machine and probe. Again, an optimised imaging pre-set was used and no changes to the scan frequency, or pre-processing software made. Overall gain and TCG were manipulated to further optimise the image. Imaging of the prostate using microUS was undertaken in the longitudinal plane as real time transverse imaging is not possible with this probe. Colour Doppler technology is not available on this system, but imaging was undertaken at two differing frequencies, nominally 22 MHz and 29 MHz, known as large and small views colloquially. Still images of the prostate in large view and then small view were captured in a systematic manner in accordance with the imaging protocol and stored to PACS. Figure 6.3 depicts a typical image of a normal prostate on microUS imaging.

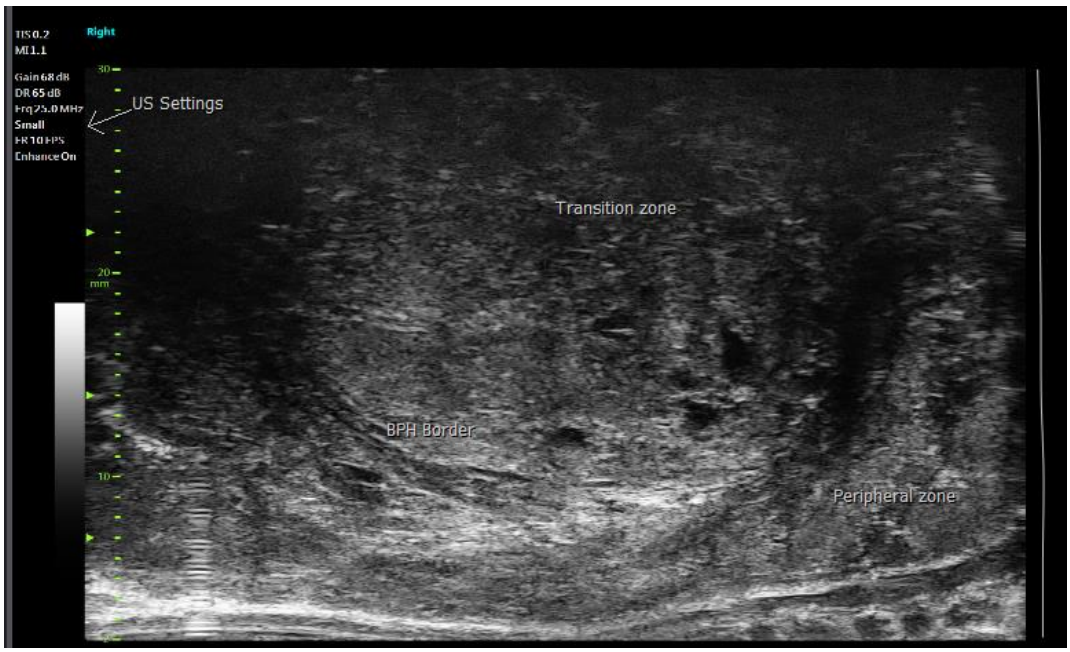

Figure 6.3 MicroUS image of the right side of the prostate gland

6.7.3 MicroUS image protocol

- Midline,
- Right mid gland,
- Right lateral gland,
- Left mid gland,
- Left lateral gland,
- Focal areas of change in appearance.

As no Doppler functionality was available on the microUS system, the examination was therefore complete, and the probe removed.

Both ultrasound examinations took no more than a maximum of 10 minutes to complete (five minutes each scan). Standard infection control procedures were undertaken to clean ultrasound equipment, the examination couch and all peripherals (HUTH, 2023b; 2023a). The image collection for the study was then complete. All scans were completed by me as lead researcher and were directly observed by a second sonographer. Once the trial images had been obtained and stored, I conferred with the second sonographer present and agreed a microUS risk prior to proceeding further to complete the TP Biopsy. As the use of microUS was untested and new, the baseline score was non-contributory and did not influence patient care or subsequent treatment, but this baseline result was recorded on the research database for each participant. The standard US was used to guide the biopsy and target tissue sample collection from any lesions identified on MRI.

The lead researcher was un-blinded to the MRI and the biopsy procedure was planned in consensus with the other sonographer in attendance. The patient proceeded to standard or fusion guided TP Biopsy under local anaesthesia, as per standard care of patients, and dependent upon the findings of the MRI. The study 1, phase 1 patient participant journey is depicted in below (Figure 6.4).

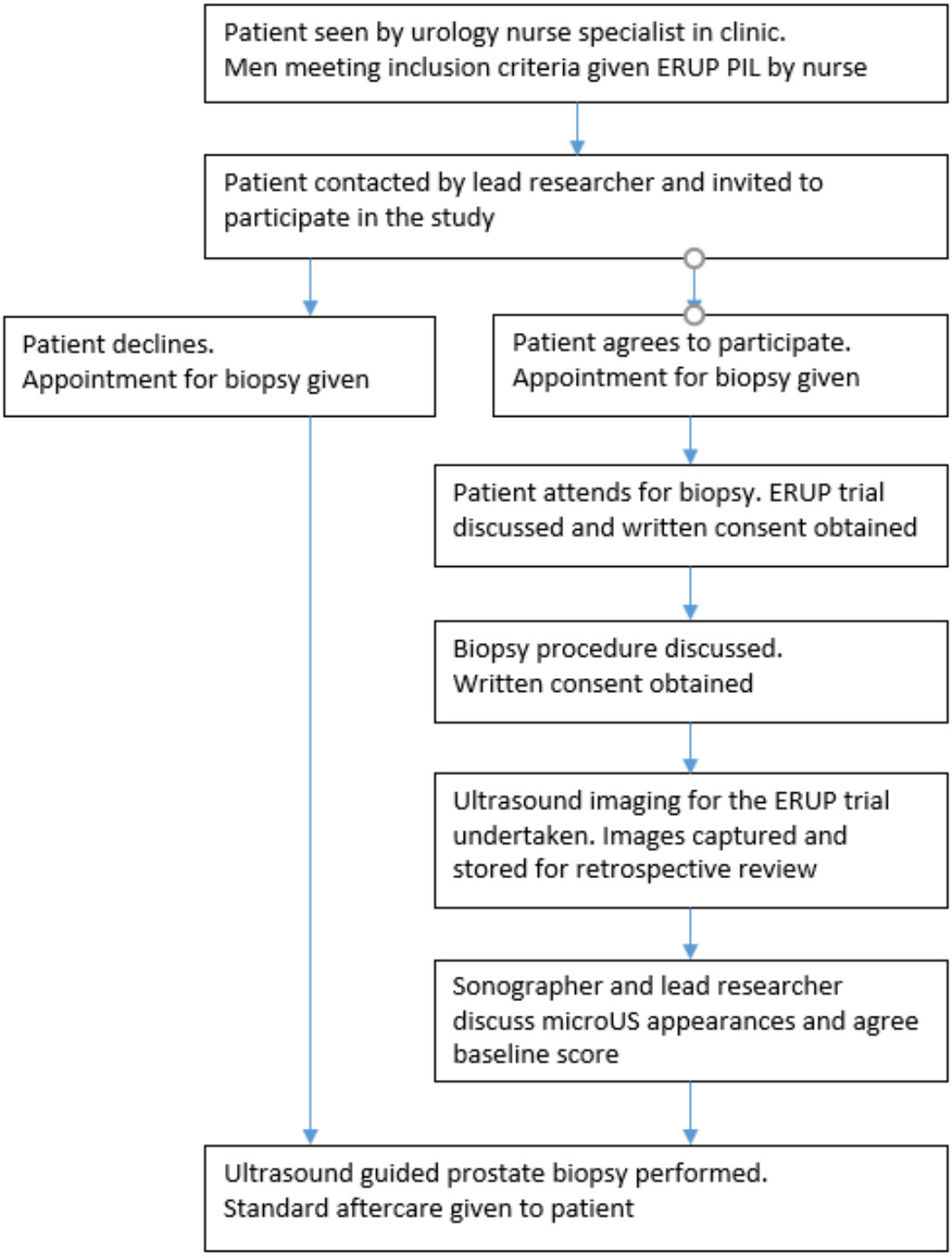

Figure 6.4 Flow chart showing participants journey in study 1, phase 1

6.8 Data collection

Each participant was given a unique study identification (UID) number. All images and data for the study were acquired and stored under this separate study UID. The images were stored on the HUTH password protected picture archiving and communication system (PACS). A password protected database, stored in a password protected network drive of Hull University Teaching Hospitals NHS Trust (HUTH), was used to hold the unique identifier number and a password protected excel database was used to record study data.

To avoid the bias that may have occurred if only a single person reviewed all the participants' scans, and to minimise reviewer fatigue, as well as minimising the time impact on the clinical workforce, a team of reviewers was required. Members of the clinical team, who had consented to participate in study 2 (Chapter 9.1) of the ERUP trial, were invited to review the ultrasound images obtained during the scans performed on the patients for the ERUP trial. All study 2 participants agreed to review images. Each reviewer was given their own unique identifier number known only to the lead researcher and supervisors. The identity of the reviewers was kept anonymous as far as possible to avoid internal scrutiny within the team. The images of both the standard ultrasound and microUS scans to be assessed for the study had all patient identifiable data removed. The images from each of the scans were transferred into a Microsoft PowerPoint® presentation (PPT) format for ease of review and assessment. The individual participant PPTs were stored on the password protected network drive.

Each participants' standard ultrasound and microUS scans were reviewed twice. As such, each patient participant was randomly allocated to two reviewers. The saved PPT were duplicated and then distributed to the allocated reviewer for retrospective assessment and scoring. Given the random allocation, the same person was occasionally both the first and second reviewer.

6.8.1 Image review

The anonymised and saved set of images were reviewed by the assigned reviewers. The reviews were completed by all seven reviewers between 15th January and 14th February 2023. The images were reviewed via a monitor with quality, and viewing

conditions, as similar as possible to the ultrasound monitors and scan rooms. The saved images were scored using a 5-point scale, similar to the published PRI-MUS™ protocol (Ghai et al., 2016). This 5-point scale provided a score of the ultrasound appearance ranging from homogeneous and mid-grey (highly likely to be benign) through to heterogeneous and echo-poor (highly likely to be malignant). The sites of any identified focal areas were documented on the data collection sheet, dependent upon where in the gland the image was taken, (Appendix 4, page IX).

Assessment of the presence of Colour flow Doppler was documented on a four-point scale ranging from no colour Doppler signal evident to florid colour Doppler evident (signal fills the imaging sample box), using a similar scoring method to that of the study by Shoji et al (2016). The scoring system data collection forms for the standard ultrasound and micro ultrasound images are provided in Appendix 5, page XI and Appendix 6, page XIII. Once reviewed, the scores submitted on the data collection forms were uploaded onto the database by the lead researcher. The process for data collection and assessment is demonstrated in the flow chart below (Figure 6.5).

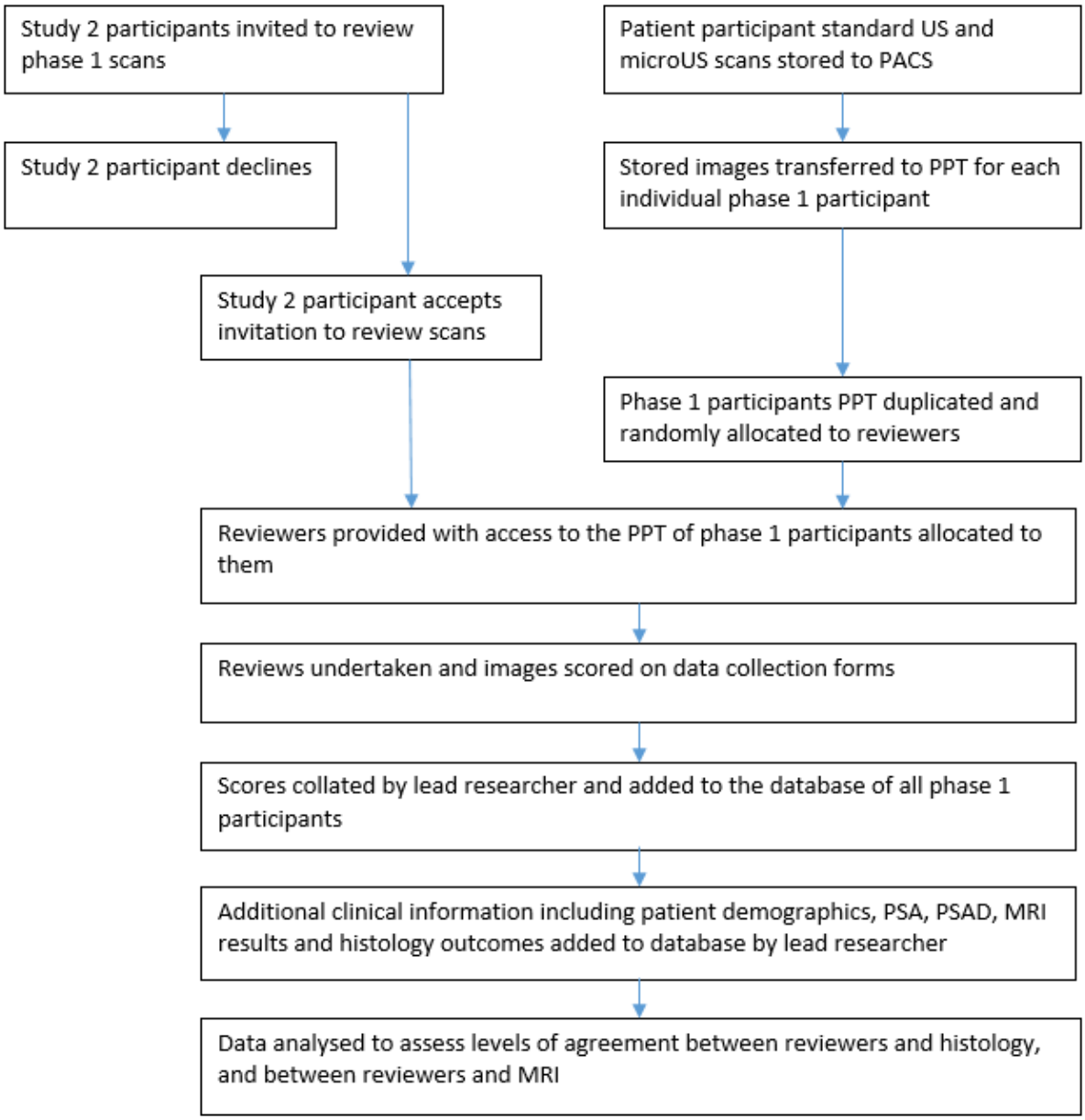

Figure 6.5 Flow chart demonstrating data collection and assessment process of study 1, phase 1

6.8.2 Data collation

Once the reviewers' scores had been uploaded onto the database, the lead researcher added the clinical information taken as part of the standard care consultation. This included the baseline microUS score agreed at the time of the examination, the PSA level, the MRI findings, and the histology results of any prostate biopsies undertaken as part of the standard care pathway.

6.8.3 Reference Standard

Histological diagnosis of the presence or absence of disease in the prostate samples taken during the TP Biopsy was deemed to be the reference standard in this study (Sonni et al., 2022). Reference standard is commonly known as the gold standard; in

accordance with STARD (Bossuyt et al., 2015) the term reference standard is used here. The TP Biopsy was undertaken immediately post image collection and, in the absence of a whole organ histological assessment, is the optimum method to identify malignancy in this patient cohort. However, it is noted that the histology is reliant on the TP Biopsy technique and accurate sampling of high-risk areas of the prostate. Histology is documented in terms of Gleason scores. The highest Gleason score for each patient was extracted from the patient records via the electronic patient administrative system (PAS). Where more than one focal abnormality was targeted, the highest Gleason score of either target or random core was recorded.

Histology outcomes were risk stratified to align with clinical management pathways utilised under the standard care of these patients, and the PRECISION study (Kasivisvanathan et al., 2018). In the PRECISION study (ibid.), clinically significant prostate cancer (csPCa) was identified dependent upon the Gleason score and length of affected core identified at histology, and commonly requires radical treatment. The PRECISION study (ibid) also identified an equivocal category, which includes insignificant prostate cancer, and high grade prostatic intraepithelial neoplasia (PIN) that requires clinical follow-up but no radical treatment. The low-risk category includes benign and low-grade PIN. To align with clinical management, I created a risk stratification system which reflected the ordinal scale of PCa likelihood utilised in the RAPID pathway trial (Eldred‐Evans et al., 2023). My risk stratification was locally agreed with the clinical supervisor of this study and the consultant radiologists reporting the relevant prostate MRI. This risk stratification was used to score image review outcomes and correlate with the reference standard (Table 6.2).

Low-risk stratification (1) correlates to histological findings of no concern and MRI findings of PI-RADS v2 scores or 1 or 2 (Vargas et al., 2016) are assigned this risk category. Published evidence related to ultrasound features of prostate cancer demonstrated at both standard ultrasound and microUS imaging (Harvey et al., 2012; Ghai et al., 2016) determine that a prostate with normal features, or evidence of benign prostatic hypertrophy (BPH) nodules align with the low-risk stratification outlined in Table 6.2 below.

Table 6.2 Locally devised risk stratified scoring system.

Risk	Low	Low	Equivocal	High	High
Risk Score	**1**	**1**	**2**	**3**	**3**
Histology	Benign/ no cancer detected	Low grade PIN; ASAP	High grade PIN; Gleason 3+3 /3+4 & cancer core length < 6mm	Gleason 3+3 / 3+4 with cancer core length ≥ 6mm	Gleason ≥ 4+3
Standard US **Colour Doppler**	Normal No flow	BPH Diffuse throughout gland	Uncertain / heterogenous Present but no focal pattern	Focal lesion present Confined to focal area	Focal lesion present Confined to focal area
microUS PRI-MUS™	1; low-risk anterior gland	2; low-risk anterior gland	3	4, High-risk anterior gland	5; High-risk anterior gland
MRI PI-RADS v2	1	2	3	4	5

High-risk stratification (3) findings at ultrasound relate to the presence of focal abnormalities on standard ultrasound (Harvey et al., 2012) and a typical “snowstorm” pattern on microUS as described by Ghai et al (2016). High-risk features of distinct abnormalities on MRI imaging are typically reported as PI-RADS v2 4 or 5 (Vargas et al., 2016). High-risk histology equates to high grade Gleason scores. Gleason classifications and scores relate to the degree of cellular change within the prostate (Stark et al., 2009). The results are presented as the most common cell pattern followed by the second most common, with cellular change ranges from 1 (well differentiated) to 5 (poorly differentiated) although 1 and 2 are no longer reported and are considered to be normal prostate tissue. The length of disease within a biopsy core is also recorded. The greater the length of the cellular change, the higher the grade of disease. In histological terms, a patient with Gleason 4 + 3 or above is deemed to have csPCa. However, Gleason 3 + 3 or 3 + 4, with less than 6mm of cellular change within one core are not deemed to be significant cancers (Kasivisvanathan et al., 2018) and are an equivocal finding despite pathology being present. Those with cores lengths of over 6mm are deemed to be at a greater risk for extra-prostatic extension (Stark et al., 2009) and treatment is advised.

This equivocal group, which includes the Gleason groups of Gleason 3 + 3 or 3 + 4 and <6mm core length, as well as pre-cancerous cell change, require active surveillance as a minimum management plan. This group is stratified into an equivocal risk (2) and includes uncertain and indeterminate imaging findings at both ultrasound and MRI. Here, appearances of imaging are neither truly normal nor obviously abnormal and most require progression to biopsy (Schoots, 2018).

Given the complexities of Gleason scores, MRI and ultrasound appearances, and the reporting systems of PI-RADS v2 (Vargas et al., 2016) and PRI-MUS™ (Ghai et al., 2016), the pragmatic approach of a three-point risk stratification has been employed for the data analysis of this study. The rationale for this is that a three-point stratification reduces subjectivity and can be used to categorise patients into at high, indeterminate, or high-risk of disease as is used in ovarian cancer assessment (Timmerman et al., 2016), discussed in Chapter 5.10.3. Importantly, the three-point risk stratification correlates with the D'Amico risk group originally developed to estimate the likelihood of prostate cancer recurrence (Rodrigues et al., 2012; Gabriele et al., 2016).

6.9 Data analysis

From the completed database, the reviewers' scores, MRI and histology outcomes were assigned a risk correlating to the stratification system discussed above in Table 6.2. Using this assigned risk, a series of comparisons were made to investigate the agreement between the ultrasound scores and the histology, and MRI, outcomes. Agreement between the individual seven reviewers was not measured as this study is designed to test the technology and not individuals' performance. The reviewers all had similar levels of experience and exposure to both standard ultrasound and microUS and is assumed they are a random sample from a theoretically bigger pool of similar ultrasound practitioners. However, the range of experience, training, and type of clinical practice was reviewed to evaluate any patterns between reviewers.

6.9.1 Inter-reviewer agreement

Initially, the histology outcomes were determined and numbers of participants with respective risk scores of 1, 2 or 3 calculated. The number of ultrasound scores in each category was then calculated. The overall rate of agreement between any one

reviewer and histology, followed by the rate of agreement between reviewers, then between both reviews and histology was calculated for both standard ultrasound scores and microUS scores. To understand the degree of agreement between the reviews and histology, a kappa statistical test was performed for both standard ultrasound and microUS. Percentage agreement rates and inter-reviewer reliability (IRR) were calculated and relative strength of agreement determined in accordance with the methods of Landis and Koch (1977). As discussed by Donnan et al (2002), kappa grading utilises a range of values between +1 to -1. The kappa coefficient calculates agreement between two observers or two tests and corrects for chance (Rigby, 2000); to aid explanation, Κ of 0 is no better than throwing a coin. The results of the kappa analysis are presented in a tabulated form throughout the results section in the next chapter (Chapter 7.1.6 to 7.1.10) and include the following criteria, explained by McHugh (2012) as:

- Percentage agreement – number of times the reviewers agree with the reference standard.
- Expected agreement – calculation of the expected or chance agreement which takes into account the insistency of how reviewers score variables.
- Kappa – calculation of interrater reliability. Results range from +1 to -1; 0 is chance agreement, +1 total agreement and -1 total disagreement.
- Standard error (SE) – 95% confidence interval and is a measure of the precision of kappa. The smaller the SE, the greater the precision and vice versa
- Z – t-test which compares the means of the two groups under investigation. The smaller the t-test result, the greater the agreement between the reviewers and the reference standard
- Prob>Z – p-value which is the probability that the results occurred by chance. A low p-value the less likely that the t-test result is related to chance.

However, the kappa test performed assumes that all categories are in proportion and that the reviewers were all rating in the same way. Kappa does not consider if there are different levels of agreement between the three risk stratifications. A weighted kappa allows ordinal characteristics, those inherent descriptive characteristics that the reviewers will have used during the reviews of the ultrasound images, to be considered. Weightings can be applied where there are three or more categories in a nominal scale and where an understanding of agreement in each category would be

useful (Sim & Wright, 2005). A weighted kappa test has been applied when evaluating the baseline microUS reviews.

6.9.2 Sensitivity and specificity

Results were further analysed to understand if there was a difference in agreement between standard ultrasound or microUS and histology depending upon the given risk stratification score. 3 x 3 contingency tables were created for the outcomes of both standard ultrasound and microUS reviews. The 3 x 3 tables take into account the risk stratification scores of high, equivocal, or low. Equivocal histology identifies pathology which may or may not be significant. The histology outcomes for all risk stratifications are provided in Table 6.2.

For the purposes of evaluating the sensitivity and specificity value of both ultrasound systems, and in agreement with my clinical supervisor who is responsible for the patients within this trial, I determined that equivocal imaging scores were deemed to be in agreement with high and equivocal risk histology scores as this cohort either have low grade malignancy or high grade, pre-cancerous benign disease. All patients with equivocal histology require further management in the clinical setting, even if this is unlikely to be radical treatment. There is agreement between histology and low-risk imaging only where low-risk benign disease was identified. The following Table 6.3 provides the agreement and true positive criteria used in the 3 x 3 tables throughout the results section to determine sensitivity and specificity within this study.

Table 6.3 3 x 3 table criteria for determining sensitivity and specificity of imaging reviews

Imaging risk category	**Histology risk category**		
	High	Equivocal	Low
High	**TP**	**TP**	**FP**
Equivocal	**TP**	**TP**	**FP**
Low	**FN**	**FN**	**TN**

TP = True positive
TN = True negative
FP = False positive
FN = False negative

$$\text{Sensitivity} = \frac{TP}{TP + FN} \qquad \text{Specificity} = \frac{TN}{TN + FP}$$

As Altman and Bland (1994a) discuss, it is important to understand how well a test performs and a common approach is to calculate the proportion of true positives that are identified by reviewing the ultrasound images as well as calculating the proportion of true negatives that are equally identified. The sensitivity of both standard ultrasound and microUS was calculated to gain an understanding as to how well each test could determine if prostate cancer, of any grade, was present. Specificity of each test was calculated to understand how well each performed at determining if prostate cancer was not present (Chu, 1999; Swift et al., 2020).

6.9.3 Predictive values

An assessment of how likely it is for the evaluation of the imaging to be correct could also be calculated as positive and negative predictive values (PPV, NPV), as recommended by Altman and Bland (1994b) and Safari et al (2015). Predictive values can be interpreted as the probabilities for performance markers for the imaging tests. Montano (2014) identifies that both high PPV and NPV's indicate that the test is either correctly identifying or excluding disease, regardless of the sensitivity and specificity calculated. However, the predictive values of the tests performed in this trial have not been calculated as they pertain to screening tests as opposed to diagnostic tests within a population likely to have a pathology. Predictive values, both positive and negative

(PPV / NPV) are affected by disease prevalence and differ dependent upon the cohort population (Safari et al., 2015). Predictive values assume a healthy population is included within the study cohort. However, as Altman and Bland (1994b) discuss, the prevalence of the disease will vary and may result in a high false positive rate when prevalence is low within a screening population. In this instance, a small cohort of at-risk patients has been recruited and the ultrasound imaging is not being used as a screening test. Calculating PPV and NPV is not indicated in this trial as these may falsely represent the usefulness of mpUS in the context of this study (Nelson et al., 2001).

6.9.4 MRI Analysis

The final analyse undertaken was the comparison between independent histology findings and MRI risk stratification. MRI is commonly seen as a reference standard imaging tool for the evaluation of prostate cancer (Turkbey et al., 2016) and microUS is being increasingly compared as both Klotz (2021) and Sountoulides (2021) have recently published. It was important to understand the reliability of locally performed and reported MRI in this study sample so that an informed comparison of practice could be made. At the time of completion of study 1, phase 1 and phase 2, no comparison between local MRI performance and national or international data had been made. However, this has since been reviewed in February 2024. Results demonstrate comparable detection rates of prostate cancer local MRI practice good correlation with histopathological outcomes. This study is currently under review for publication *(Clinical Radiology submission March 2024 - CRAD-D-24-00204: Prevalence of PI-RADS 3 lesions detected on biparametric MRI and subsequent diagnosis of clinically significant prostate carcinoma – a local experience).*

The design for the ERUP trial has been presented in this chapter with the methods for study 1, phase 1 presented. The results of phase 1 are provided and discussed in the next chapter.

Chapter 7 Study 1, phase 1: results and discussion

In this chapter, the results and discuss the findings of phase 1 of the ERUP trial are presented. The methods for data collection and analysis were presented in chapter 6.

An abridged version of this chapter was published online in February 2024:

Parker, P., Twiddy, M., Rigby, A., Whybrow, P. & Simms, M. (2024) Evaluating the Role of Ultrasound in Prostate Cancer trial – phase 1: Early experience of micro-ultrasound in the United Kingdom. *Ultrasound*, doi:10.1177/1742271X231226302

7.1 Results

7.1.1 Recruitment

In total, 106 patients were identified who met the inclusion criteria (Chapter 6.6.2) during this recruitment period (6.6.4). All were invited to participate in the ERUP trial; two declined, two patients were unable to tolerate the micro-US examination and two had incomplete datasets of images recorded and had to be excluded. Recruitment of eligible participants is outlined in Figure 7.1 below.

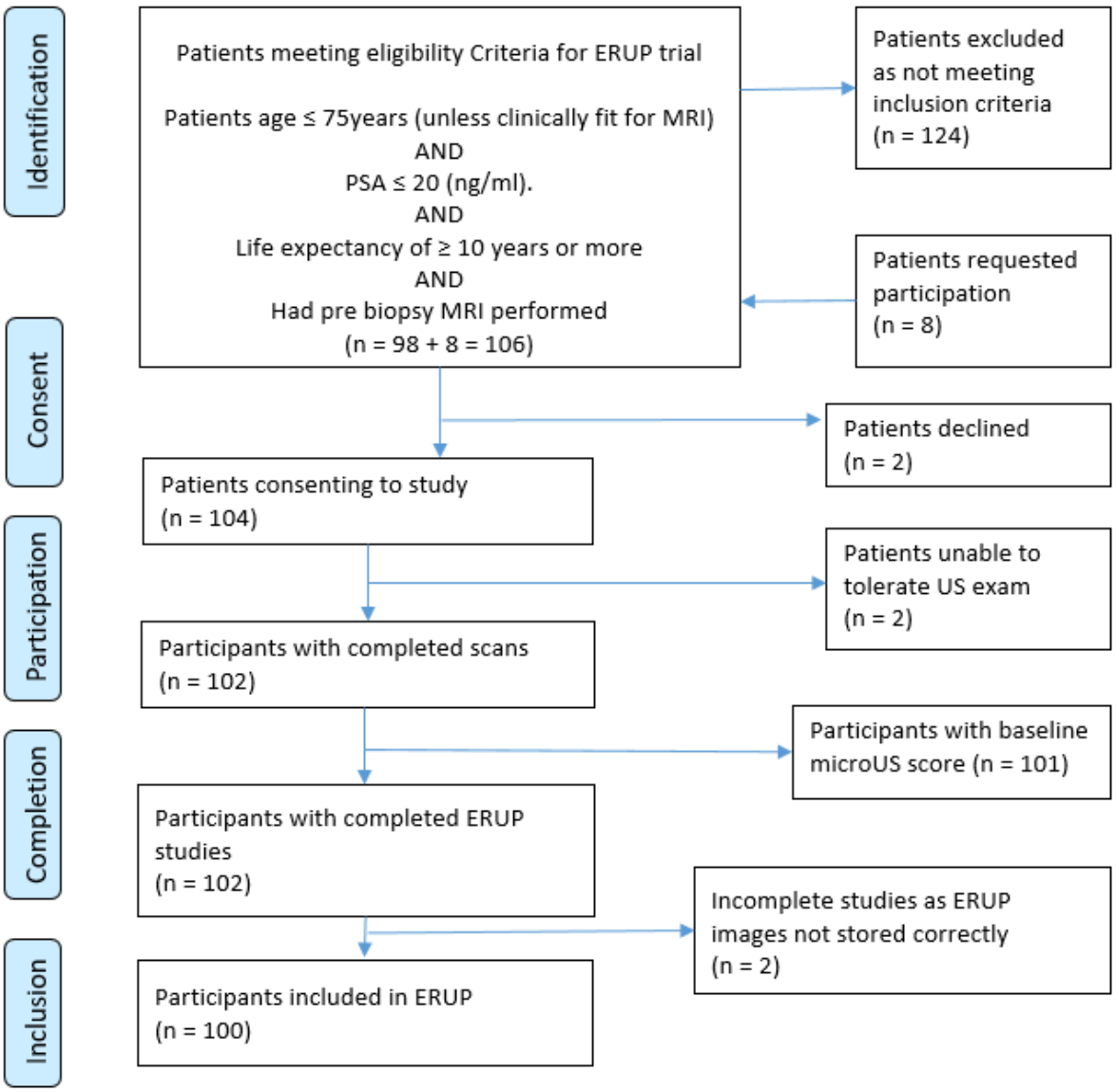

Figure 7.1 Recruitment of participants into the ERUP trial

7.1.2 Demographics

Of the 100 participants who had a completed MRI, completed the ERUP scan protocol, and had a transperineal prostate biopsy performed, their ages ranged from 47 – 84 years of age (median 67) and their PSA ranged from 0.82 – 50 ng/mL (median 6.4). Prostate volume was calculated from the pre biopsy MRI and ranged from 16 – 167 mL (average 50 mL). The PSA density (the ratio between prostate volume and PSA) was calculated in all cases and ranged from 0.04 – 0.93 (median 0.14). The normal cut off value is 0.14 with PSAD ≥ 0.15 identified as a high-risk for csPCa. Age and clinical demographics are given in Table 7.1 below.

Table 7.1 Age and clinical demographics of participants

	Age years	PSA (ng/mL).	Prostate Volume mL	PSAD
Range	47 - 84	0.82 – 50	16 - 167	0.04 – 0.93
Mean	66.4	8.1	50	0.18
Median	67	6.4	42	0.14

Eight men outside of the age and PSA criteria requested to participate in the study as they had been inadvertently given the relevant PIL at their initial urology consultation (Chapter 6.4.1). These were included in the study following discussion between the lead researcher and clinical supervisor as they were deemed fit for surgery if needed and all had had a pre-biopsy MRI completed. This approach is undertaken in normal practice following consultation between urology specialist and patient; as such, a pragmatic approach was adopted for the trial to reflect standard care pathways. There were no participants over 75 and with a PSA over 20 included. Men who did not have pre biopsy MRI were excluded. The participants unable to tolerate the ultrasound examination were both less than 75 years old and had PSA of less than 20.

Family history is identified as an increased risk factor for patients. In this cohort, 32 participants had a positive family history and 37 with no known family history. In 31 participants, family history status was not provided by the referrer or declared by the patient. Family history status is noted in Table 7.2. Given the large number of participants without this being recorded, no meaningful analysis can be made.

Table 7.2 Family history status of phase 1 participants

Status	Frequency
Positive	32
Negative	37
Not stated	31

7.1.3 Reviewers

Ten clinical practitioners were invited to participate in the review of the collected images; five of these were sonographers (including the lead researcher), two were consultant radiologists and three consultant urologists. The three urologists declined as none had active involvement in interpreting radiological imaging. Experience of the

reviewers related to prostate imaging ranged from three to ten years. The roles, experience and skills related to prostate ultrasound is outlined in Table 7.3.

Table 7.3 Role and experience of reviewers

Professional Background	Main role in prostate imaging	Years of experience in prostate imaging	MicroUS audit user level
Sonographer	involved in performing micro-US and prostate imaging	3-5	Expert
Sonographer	involved in performing micro-US and prostate imaging	3-5	Intermediate
Sonographer	involved in performing micro-US and prostate imaging	5-10	Advanced
Sonographer	involved in performing micro-US and prostate imaging	10+	Intermediate
Sonographer	involved in performing micro-US and prostate imaging	10+	Beginner
Consultant Radiologist	involved in the interpretation of micro-US as radiologist or at MDT	5-10	N/A
Consultant Radiologist	involved in the interpretation of micro-US as radiologist or at MDT	10+	N/A

All reviewers had been given access to on-line training resources provided by the microUS manufacturer. Five reviewers had external audit of their microUS interpretation performed by the manufacturer. Audit results ranged from beginner user (n = 1), intermediate user (n = 2), advanced user (n = 1) and expert user (n = 1). There was no correlation between years of experience of prostate imaging and microUS audit results.

7.1.4 Histological outcomes

Histology outcomes ranged from benign findings with no disease present through to high grade csPCa with Gleason score of 9 (5 + 4). Prostate cancer of Gleason 6 (3 + 3) or above was identified in 70 patients. However, this includes all Gleason scores. The range of disease identified, and risk stratification score this aligns to, is presented in Figure 7.2 below.

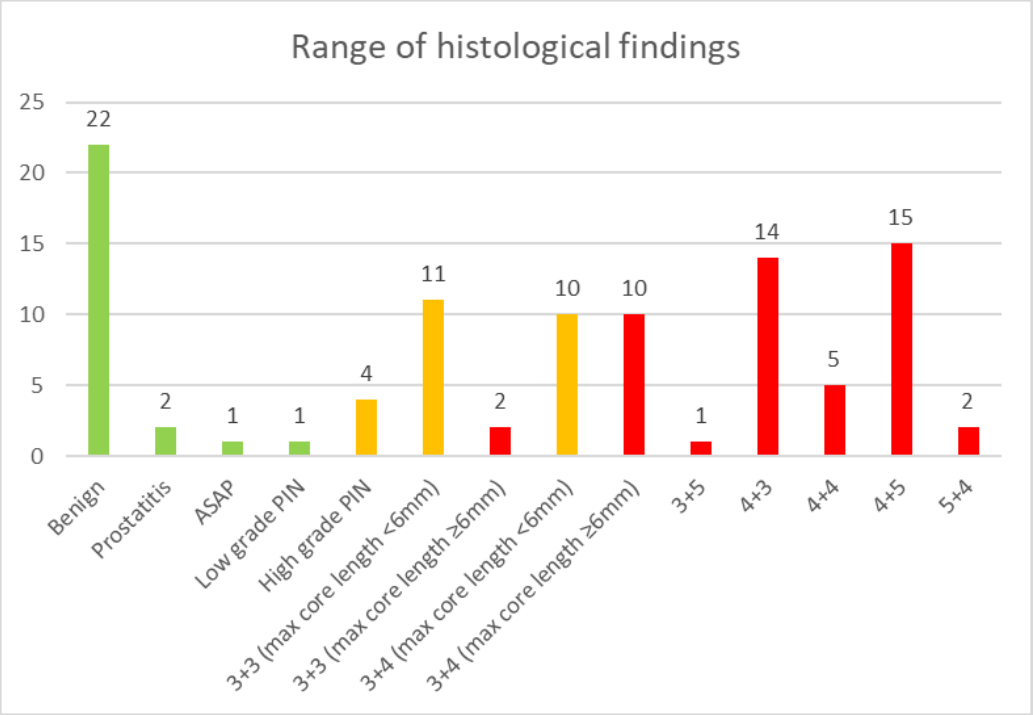

Figure 7.2 Range of histological outcomes and aligned risk stratification score

ASAP - Atypical small acinar proliferation
PIN - prostatic intraepithelial neoplasia
Gleason score – severity of cellular change. 1 normal to 5 highly abnormal and poorly differentiated

csPCa was detected in 62% (n = 48/78) of targeted LATP Biopsy procedures and in one participant with no apparent target on pre biopsy imaging. Using the PRECISION criteria (Kasivisvanathan et al., 2018) for determining significant disease, in this cohort of 100 patients, csPCa has been identified in 49 patients.

There were 49 high-risk outcomes requiring radical treatment, 25 with equivocal outcomes requiring follow-up, and 26 with low-risk of disease. The risk stratified histological outcomes are presented in Figure 7.3 below.

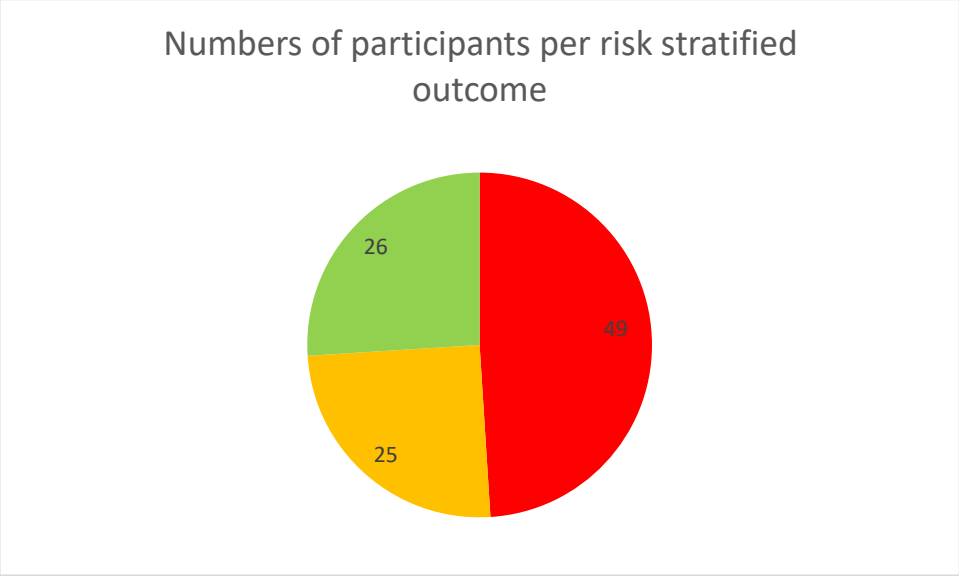

Figure 7.3 Risk stratified histological outcomes

7.1.5 Image review

A total of 400 sets of images embedded into PPT (200 standard and 200 micro-US) were reviewed by the seven reviewers. Examples of high and low-risk standard US and microUS images are provide in Figure 7.4, Figure 7.5, Figure 7.6 and Figure 7.7 below.

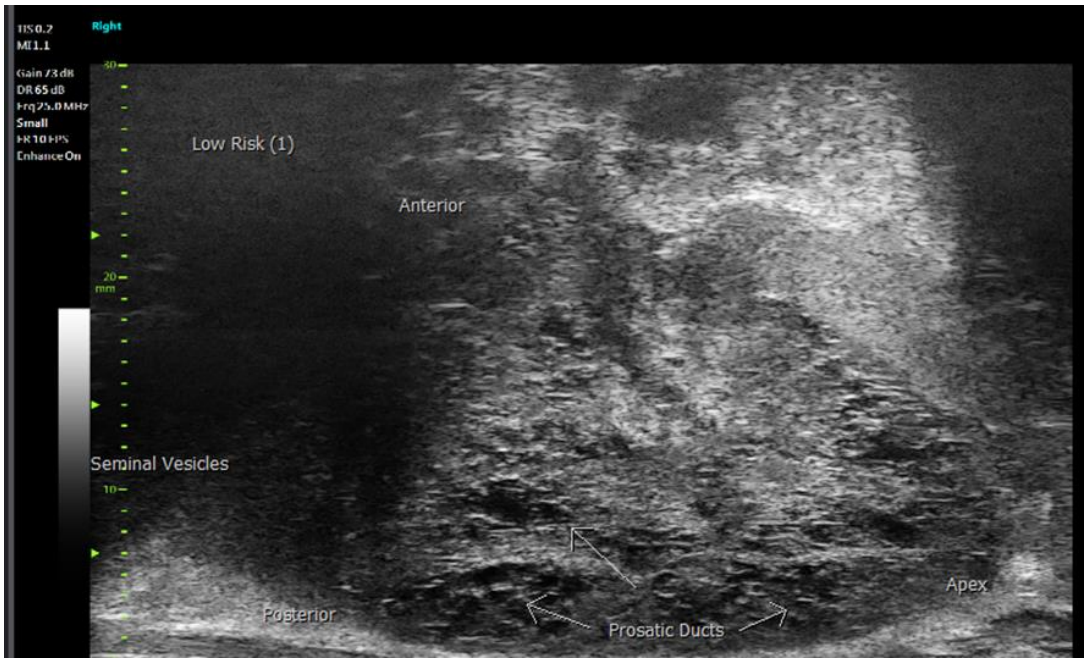

Figure 7.4 MicroUS image of low-risk prostate demonstrating ductal patches throughout. LS section

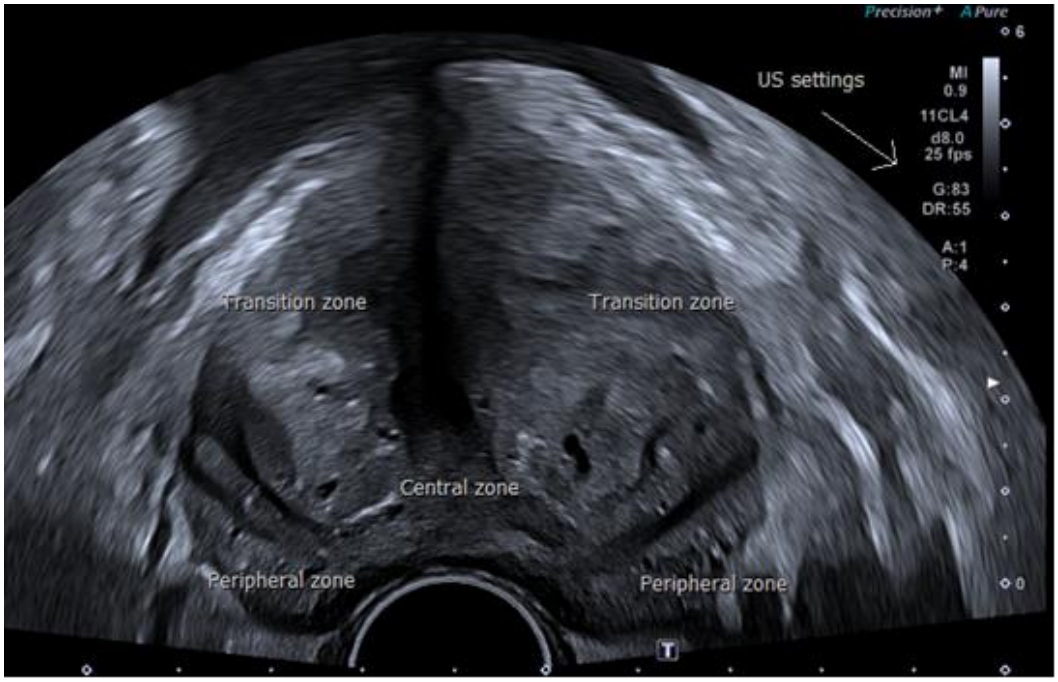

Figure 7.5 Standard US image of low-risk prostate demonstrating normal anatomy. TS section

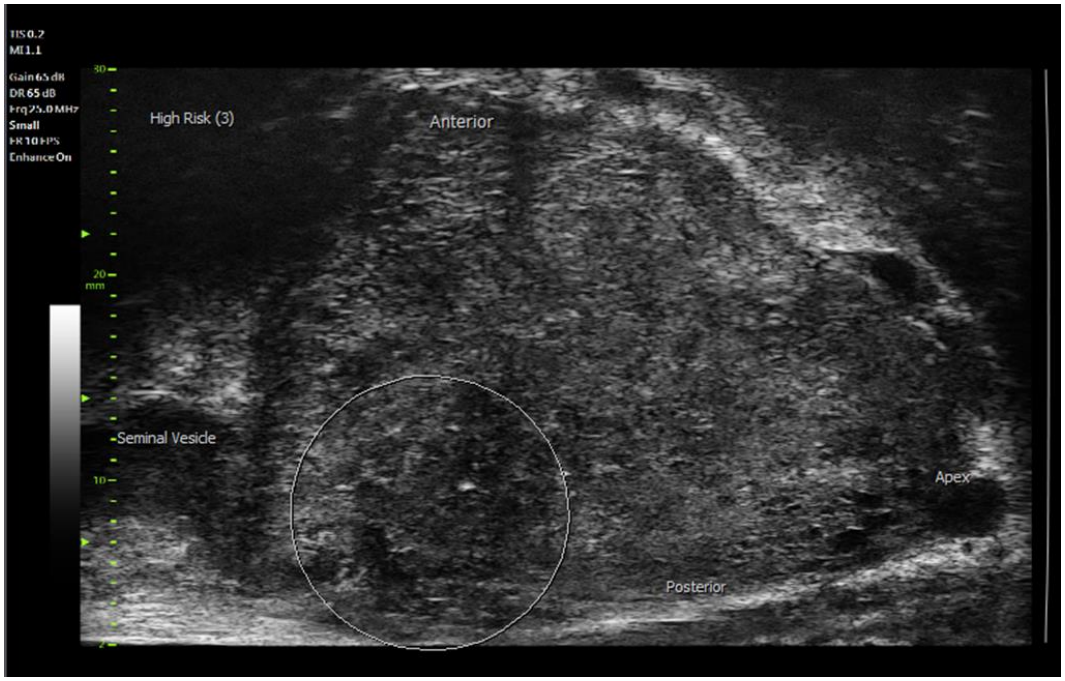

Figure 7.6 MicroUS image of high-risk prostate demonstrating focal region of interest (ROI) on right. LS section

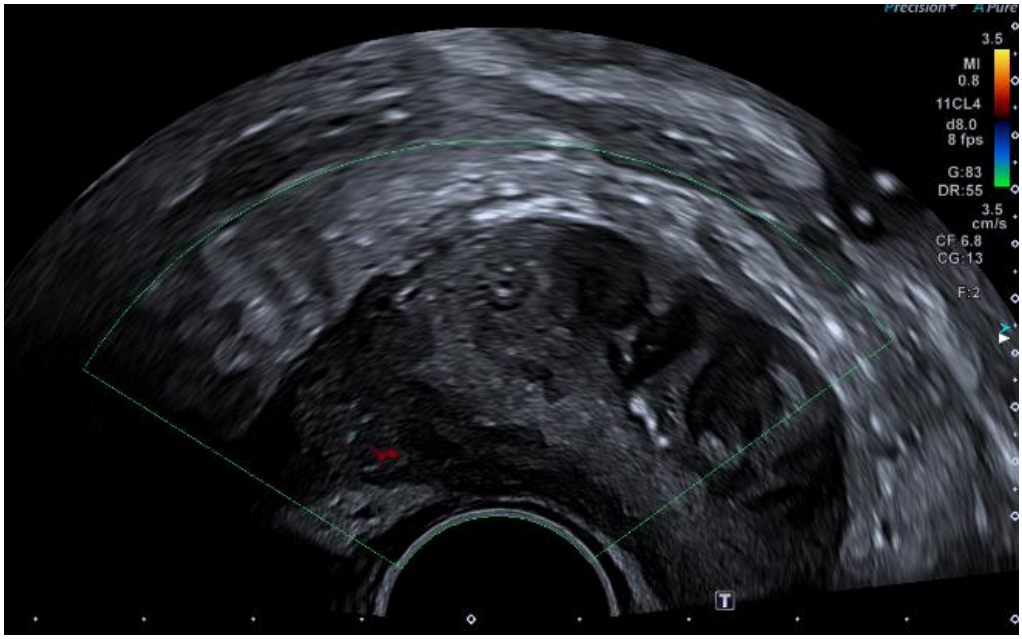

Figure 7.7 Standard US image of high-risk prostate with ROI in right peripheral zone. Small area of colour Doppler signal identified. TS section

The locally agreed risk stratification was used to score image review outcomes and correlate with the reference standard. Outcomes of the reviews are presented in Table 7.4. MicroUS identified high-risk disease in 96 of the reviews, whereas standard US only identified high-risk disease in 54 reviews. Standard US suggested a prevalence of low-risk disease greater than that identified at histology.

Table 7.4 Risk stratification outcomes of ultrasound reviews

Risk stratification score	Standard US - Numbers of reviews	MicroUS - Numbers of reviews
3	54	96
2	30	49
1	116	55
Total	200	200

The following chart (Figure 7.8) demonstrates that microUS reviews indicated the presence of high-grade disease to a greater extent than was identified on review of the standard US images. However, this broad base review does not indicate whether there is agreement between the reviewers, nor whether there is agreement between the ultrasound review and the histological outcome. From this overview, it cannot be

determined whether the ultrasound reviews deemed to be high-risk correlate directly with those patients in whom csPCa has been detected.

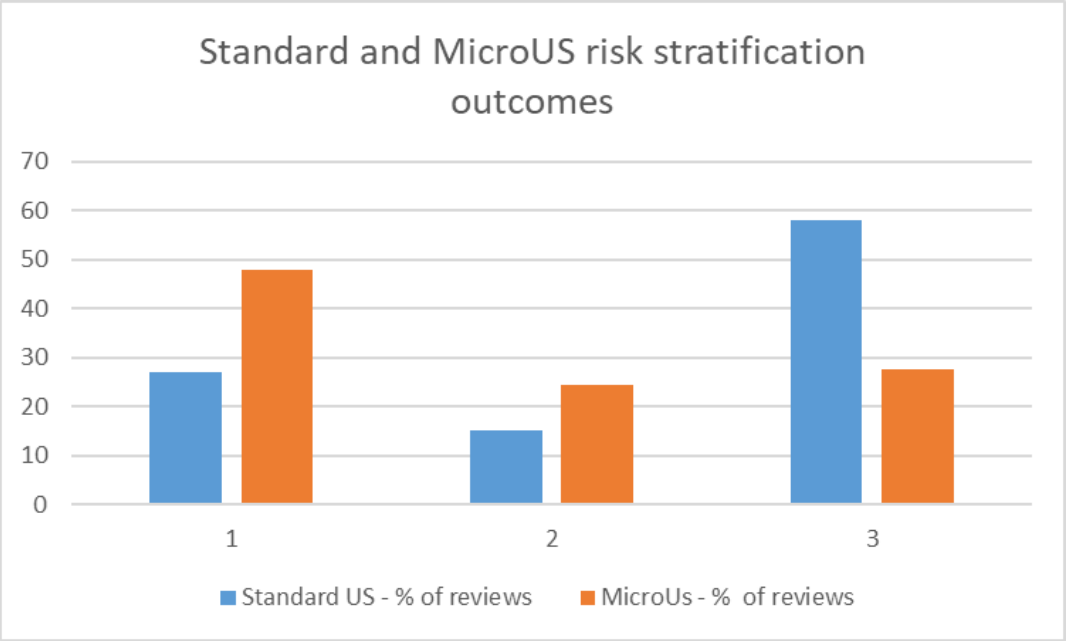

Figure 7.8 Graph depicting risk outcomes of ultrasound reviews

7.1.6 Ultrasound review and histology agreement

An overall rate of agreement between reviews and histology was determined by using the risk stratification scoring system. Agreement between the review and histology was deemed positive if the documented US risk at the review was the same as the highest histology risk score, regardless of the site or side of pathology, i.e. if histology indicated high-risk disease in any biopsy core, and the ultrasound review indicated high-risk disease then agreement was noted as positive. Agreement rates for each reviewer compared to histology for each participant was calculated.

7.1.6.1 Inter-reviewer agreement

Agreement between individual reviewers and histology ranged from 26.7% to 56.7% for standard ultrasound and, a similar range of 25.9% to 56.7% for microUS. No apparent difference between standard or microUS outcomes scored by reviewers and histology was identified. Whilst there was a range of performance between reviewers, there was no linear relationship between reviewer experience, training undertaken, manufacturer user allocation, or profession of reviewer and outcomes.

Three reviewers were consistent in outcomes with over 50% agreement between their scoring of both the standard ultrasound and microUS and histology. However, overall, agreement between reviews and histology was poor.

Table 7.5 provides the range of scores and agreements between reviewers and histology and demonstrates the range of inter and intra reviewer agreement rates. There was marginally better inter-operator agreement of standard ultrasound reviews with 48% of reviews agreeing (n=96/200) compared to 45% of microUS reviews in agreement (n=90/200) although overall inter-reviewer agreement is poor.

It is noted, that due to the random selection of participants against reviewers, only five reviewers had identical cases and, therefore, intra-reviewer agreement rates cannot be calculated for all. The number of randomly allocated identical cases to those five reviewers is also small and ranged from three to six with a maximum of only 21 cases subjected to intra-reviewer evaluation. Whilst there were low numbers of intra-reviewer reviews to analyse, standard US had better intra-reviewer agreement with an average rate of 75% (n=16/21) than the identical reviews of microUS, which agreed on average 60.8% of the time (n=13/21). Indeed, intra-reviewer agreement of standard ultrasound was improved compared to the inter-reviewer agreement rate, but numbers are too small to extrapolate further.

Table 7.5 Agreement with US review score and histology using risk stratification

	Standard US	**MicroUS**
Total number of reviews performed	200	200
Total reviews per reviewer	27 - 30	26 - 30
Range of individual reviewer % agreement with histology	26.7% - 56.7%	25.9% - 56.7%
Mean % agreement with histology	44.3%	46.5%
Median % agreement with histology	50%	50%
Inter-reviewer agreement rate		
Total number of reviews performed	179	179
Range of % agreement with histology	23.3% - 66.7%	30% - 56.7
Mean % agreement with histology	48.3%	45%
Median % agreement with histology	48.1%	46.7%
Intra-reviewer agreement rate (5 of 7 reviewers)		
Total number of reviews performed	21	21
Range of % agreement with histology	60% - 100%	33% - 80%
Mean % agreement with histology	75%	60.8%
Median % agreement with histology	60%	50%

Whilst the analysis demonstrated poor inter and intra-reviewer agreement, this has not considered whether, when both reviews agreed, there was also agreement with the histological reference standard. Agreement with both reviewers and histology was only found in 28% of standard US reviews and 23% of microUS. These outcomes are summarised in Table 7.6.

Table 7.6 Agreement between histology, reviews, and reviewers

Reviews	**Agreement of ultrasound findings between two reviewers regardless of histology outcome**	**Agreement between both reviewers and histology**
Standard US	48.3% (n = 96/200)	28% (n = 56/200)
MicroUS	45% (n = 90/200)	23% (n = 47/200)

7.1.6.2 Inter-reviewer reliability

Further analysis to understand reliability was undertaken using kappa statistical modelling to calculate the percentage agreement rates and inter-reviewer reliability (IRR) (Landis & Koch, 1977). *(Descriptors of the kappa test outcomes are noted in Chapter 6.9.1).* All analyses were performed using STATA®17.0 (StataCorp, College Station, Texas).

Statistical outcomes are detailed in Table 7.7 and Table 7.8 below. Percentage agreement and kappa values of 46.5% and 0.21 respectively for standard US were calculated (Table 7.7). Κ of between 0.21 and 0.40 indicates fair agreement between the standard US reviews and histology outcomes.

Table 7.7 Percentage agreement and IRR of standard US reviews

Percentage agreement	Expected agreement	Kappa	SE	Z	Prob>Z
46.5%	32.1%	0.21	0.04	4.8	<0.0001

The same analysis was performed for microUS with percentage agreement and kappa values were 48.5% and 0.19 respectively for microUS (Table 7.8). Κ of less than 0.2 indicates only slight between the microUS reviews and histology outcomes.

Table 7.8 Percentage agreement and IRR of MicroUS reviews

Percentage agreement	Expected agreement	Kappa	SE	Z	Prob>Z
48.5%	36.8%	0.19	0.05	3.64	<0.0001

7.1.7 Risk stratification agreement

The results thus far have reviewed the general levels of agreement between reviewers and histology. Whilst agreement is poor, further analysis has been undertaken to evaluate if there is a different degree of agreement dependent upon the histological risk score and the reviewers' outcomes. 3 x 3 contingency tables were compiled to provide an overall comparison of reviews (n = 200) and histology results for each review (n = 200) related to the risk stratification.

7.1.7.1 Standard Ultrasound risks

Table 7.9 relates to the standard ultrasound reviews.

Table 7.9 3 x 3 table of the reviews of standard US vs histology

Standard US risk category	**Histology risk category**			
	High	Equivocal	Low	Total
High	**41**	**7**	**6**	54
Equivocal	**10**	**13**	**7**	30
Low	**47**	**30**	**39**	116
Total	98	50	52	200

	Sensitivity	Specificity
	48%	75%

Sensitivity of standard ultrasound, using the true positive and true negative criteria defined in Chapter 6 (Table 6.3) was calculated to be 48% with a specificity of 75%. This indicates that the test is reasonable at detecting those patients with disease but has a higher ability to identify patients without disease.

7.1.7.2 Colour Doppler

The addition of colour Doppler imaging of the prostate was undertaken to evaluate if there were any features of perfusion that may indicate the presence of prostate cancer. Colour Doppler imaging was performed in all 100 participants. Increased perfusion of an area of the prostate was deemed to indicate hyper-vascular activity commonly associated with malignant change. As such, the agreed risk stratification

criteria, documented in Chapter 6 (Table 6.2), were used to assess agreement of colour Doppler with the standard ultrasound scores, and with the histology findings. Inter-reviewer kappa analysis demonstrated worse agreement than expected between the colour Doppler evaluation and the histology score as presented in Table 7.10 below.

Table 7.10 Percentage agreement and IRR of colour Doppler using histology as comparator

Percentage agreement	Expected agreement	Kappa	SE	Z	Prob>Z
25.5%	26.3%	-0.01	0.03	-0.34	0.63

A 3 x 3 contingency table demonstrates the small numbers of cases where there was deemed to be high-risk perfusion, with only five of the 200 reviews suspecting focal perfusion within a lesion. Approximately 70% of reviews (n = 141/200) indicated low-risk perfusion with either no flow or diffuse flow being identified. A quarter of all reviews of colour Doppler returned an equivocal finding. Using the classifications in Chapter 6 (Table 6.3), these equivocal findings may represent significant pathology and are classified as true positive when undertaking sensitivity & specificity calculations as in Table 7.11.

Table 7.11 3 x 3 table of the reviews of colour Doppler vs histology

Colour Doppler risk category	**Histology risk category**			Total
	High	Equivocal	Low	
High	**4**	**1**	**0**	5
Equivocal	**19**	**15**	**20**	54
Low	**75**	**34**	**32**	141
Total	98	50	52	200

	Sensitivity	Specificity
	26.3%	61.5%

Colour Doppler performance, as a predictor of pathology is unreliable and has poor agreement with histology. Whilst the presence of colour Doppler within a focal area of

the prostate is a specific and positive finding, the presence of perfusion is not confidently associated with the presence or absence of pathology. Indeed, the presence or absence of colour Doppler compared to findings at standard ultrasound also demonstrated poor agreement when kappa analysis was performed.

Table 7.12 Percentage agreement and IRR of colour Doppler using standard US as comparator

Percentage agreement	Expected agreement	Kappa	SE	Z	Prob>Z
25.5%	26.3%	-0.01	0.03	-0.34	0.63

As demonstrated in Table 7.12, a negative kappa score of -0.01 was achieved when looking at agreement rates between the presence of perfusion and the risk stratified findings of standard ultrasound. As such, there was a minor disagreement for this US parameter and, as demonstrated in the images (Figure 7.9 and Figure 7.10) below, there was little discernible difference in perfusion between high and low-risk glands. These findings indicate that the use of colour Doppler does not provide any useful diagnostic information and cannot be used to assess normality of the prostate gland.

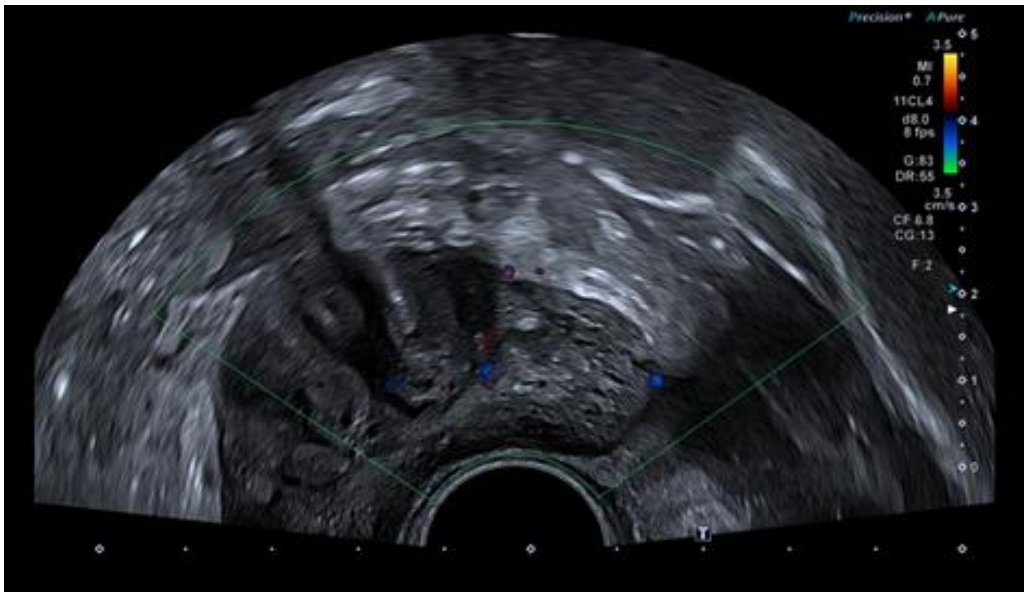

Figure 7.9 Colour Doppler image scored as low-risk perfusion; histology was equivocal.

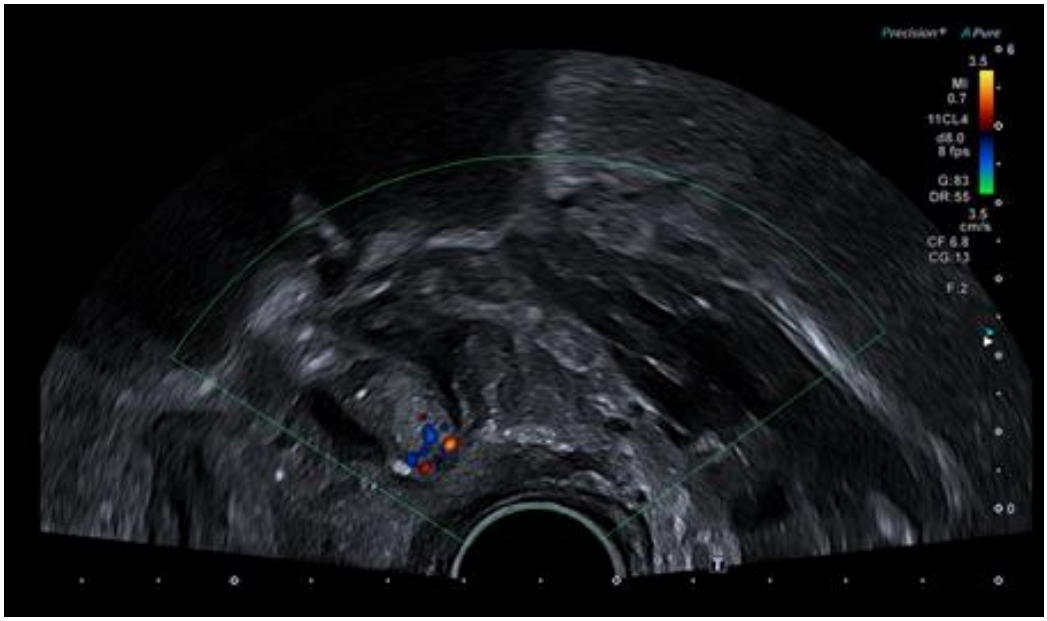

Figure 7.10 Colour Doppler image scored as high-risk perfusion due to signal being concentrated in one focal area. Histology was low-risk

7.1.7.3 MicroUS risk stratification

A similar interrogation was performed for microUS. Again, there were 200 reviews of the microUS image PPT and each categorised into a risk interpreted by the reviewer as documented in Table 7.13 below.

Table 7.13 3 x 3 table of reviews of microUS vs histology

MicroUS risk category	**Histology risk category**			
	High	Equivocal	Low	Total
High	**59**	**18**	**19**	96
Equivocal	**20**	**17**	**12**	49
Low	**19**	**15**	**21**	55
Total	98	50	52	200

	Sensitivity	Specificity
	77%	40%

The sensitivity of microUS is improved compared to standard ultrasound at 77% but specificity has shown to be reduced at 40%. This indicates that more abnormalities

were detected on review of microUS than those of the standard ultrasound images, but the test performs less well at identifying a normal prostate gland.

Whilst standard ultrasound has shown a higher specificity compared to microUS, neither test has a high sensitivity, which indicates that agreement between reviewers and histology is poor and cannot be relied upon for the detection of disease.

Analysis thus far has considered all the reviews, regardless of whether there was inter-reviewer agreement. Given the IRR and kappa scores are low, indicating poor agreement between reviewers, the results were further analysed to understand if agreement improved in those cases where the reviewers agreed with each other. There was inter-review agreement in 48.3% of standard ultrasound and 45% of microUS reviews, as described in Table 7.14, but there was no linear relationship between these two groups; the inter-reviewer agreement of the standard ultrasound did not translate to the same cases having agreement in the micro-US reviews. There were only 14 cases where both reviewers score of standard ultrasound and microUS agreed, six of these were high-risk scores and eight low-risk. Of these 14, only nine agreed with the histology reference standard.

The 3 x 3 tables of standard ultrasound inter-reviewer agreements indicate a poor agreement between high-risk histology and the inter-reviewer scores but there is better agreement where there is both low-risk disease and low-risk standard US findings on review. This analysis is presented in Table 7.14 below. Sensitivity is low at 29.4% even when reviewers agree but specificity is improved to 84.2% given the high agreement of low-risk appearances at the image review.

Table 7.14 Comparison of histology and reviews of standard US where both reviewers agreed

Standard US risk category	**Histology risk category**			
	High	Equivocal	Low	Total
High	**6**	**0**	**2**	8
Equivocal	**0**	**4**	**1**	5
Low	**14**	**10**	**16**	40
Total	20	14	19	53

	Sensitivity	Specificity
	29.4%	84.2%

Similar analysis of the microUS outcomes identify better agreement between high-risk histology and high-risk disease identified by reviewers; detail is presented in Table 7.15 below. Indeed, microUS demonstrated a sensitivity of 90% indicating that reviewers agreed with themselves and histology when abnormalities were present. However, the specificity of microUS, even where reviewers agree is less than that of standard ultrasound at 45.4%.

Table 7.15 Comparison of histology and reviews of microUS where both reviewers agreed

MicroUS risk category	**Histology risk category**			
	High	Equivocal	Low	Total
High	**17**	**1**	**2**	20
Equivocal	**6**	**3**	**4**	13
Low	**3**	**1**	**5**	9
Total	26	5	11	42
	Sensitivity	Specificity		
	90%	45.4%		

A summary of the results of the inter-reviewer agreement, reliability, sensitivity and specificity of the standard ultrasound and microUS reviews is outlined in Table 7.16.

Table 7.16 Summary of inter-reviewer agreement and sensitivity and specificity of standard and microUS reviews

Review	Sensitivity	Specificity	% agreement	Inter-reviewer reliability (kappa)
Standard US reviews (n=200)	48%	75%	46.5%	0.21
MicroUS reviews (n=200)	77%	40%	48.5%	0.18
Standard US where reviewers agree (n = 96/200)	29.4%	84.2%		
MicroUS where reviewers agree (n = 90/200)	90%	45.4%		

This summary demonstrates that the specificity of standard ultrasound remains largely unchanged whether only one reviewer agrees with the histology or where both reviewers agree. However, the sensitivity of the standard ultrasound, in detecting the presence of disease, increases where only cases with inter-reviewer agreement are analysed. The performance of microUS improves in both sensitivity and specificity in those cases where the reviewers of the imaging agree despite there being fewer cases of agreement.

7.1.8 Baseline agreement and results

The results of the retrospective review of static images demonstrate poor inter-reviewer agreement and variable sensitivity and specificity of each test, although this is improved for microUS in those cases where both reviewers' scores agreed with each other. To evaluate whether this poor agreement was due to the blinded retrospective review of static images, or more related to interpretation of the microUS imaging itself, a comparison of the microUS results, as reported at the initial baseline examination, and the histological outcome was made. At the baseline scan, there were two of the seven reviewers evaluating the microUS imaging and documenting a risk factor based on consensus following observation of the real time imaging. As such, where both observers agreed, as results of the retrospective review outlined in Table 7.15 indicate, this may translate to reasonable sensitivity and specificity in a real-life clinical scenario.

At the baseline examination, the reviewers were blinded to the MRI but un-blinded to the patient's presenting PSA. The images included a real-time scan and evaluation of static images. A baseline score was documented in 101 of the 104 patients who consented to the ERUP trial. Whilst one of these was excluded from the ERUP trial review as the static images had not saved correctly, they are included in the baseline assessment.

At baseline, there were 101 histological outcomes: 49 high-risk, 26 equivocal, 26 low-risk. Of these 101 cases, there was agreement between the microUS and histology in 57 cases.

Percentage agreement and kappa analysis of baseline micros US with histology does demonstrate improvement of performance when compared to the retrospective analysis with percentage agreement of 56.4% and Κ of 0.31, respectively. This is compared with percentage agreement of 48.5% and Κ 0.18 following the baseline review. Detail of this analysis is provided in Table 7.17 below.

Table 7.17 Percentage agreement and IRR of baseline MicroUS vs Histology

Percentage agreement	Expected agreement	Kappa	SE	Z	Prob>Z
56.4%	37.0%	0.31	0.07	4.34	<0.0001

There were delays in installing the microUS system, which resulted in limited training and skill development prior to participants being recruited and scanned for the ERUP trial. As such, practitioners performing and interpreting the baseline assessment had to gain knowledge and skills as the cases for review were being collected. Inter-reviewer agreement rates have been calculated to assess if there was any difference in performance as experience was gained. The following tables (Table 7.18 & Table 7.19) demonstrate that there was marginally better percentage agreement and IRR with the first 50 cases when compared to the second 51 cases.

Table 7.18 Percentage agreement and IRR of baseline MicroUS vs Histology for the first 50 cases recruited

Percentage agreement	Expected agreement	Kappa	SE	Z	Prob>Z
58.0%	35.6%	0.34	0.10	3.50	<0.0001

Table 7.19 Percentage agreement and IRR of microUS vs Histology for the second 50 cases recruited

Percentage agreement	Expected agreement	Kappa	SE	Z	Prob>Z
54.9%	39%	0.26	0.10	2.58	<0.0001

Whilst the IRR is greater for the first 50 cases, there is no significant difference in performance over time and only fair agreement has been achieved over all the 100 participants.

A weighted kappa test was performed so that disagreements between the differing risk stratification categories could be taken into account. The weighting assumes equal assessment and space between the high, equivocal, and low categories. Results of the weight kappa test are presented in Table 7.20 below.

Table 7.20 Weighted kappa and agreement for baseline microUS reviews

Percentage agreement	Expected agreement	Kappa	SE	Z	Prob>Z
71.8%	54%	0.39	0.08	24.67	<0.0001

The weighted kappa test demonstrates an improved agreement between the assessment of the prostate at the baseline examination and the histological reference standard. Whilst there remains only fair agreement, taking the differences between the categories into account has improved performance overall.

7.1.9 Baseline MRI agreement

Baseline, real time reviews do demonstrate some improvement in performance compared to blinded retrospective reviews, this analysis has so far not compared the agreement rates of microUS with that of the reference standard imaging of MRI. When comparing MRI with histology, interestingly, the inter-reviewer reliability is very similar to that of the microUS agreement. The reviewer of the MRI is one of the two consultant radiologists participating in the ERUP trial.

Percentage agreement and kappa analysis of MRI with histology does not demonstrate significant differences of performance compared to microUS with a percentage agreement of 58.4% and κ of 0.31 calculated for MRI, although when using a weighted

kappa test, microUS agreement is marginally improved compared to MRI. Detail of this analysis is provided in Table 7.21 below.

Table 7.21 Percentage agreement and IRR of baseline MRI vs histology

Percentage agreement	Expected agreement	Kappa	SE	Z	Prob>Z
58.4%	39.5%	0.31	0.07	4.42	<0.0001

7.1.10 Baseline risk stratification

Both tests demonstrate minimal agreement between the reviewer of either the microUS or MRI and histology. However, when evaluating whether there is better agreement dependent upon the risk score than identified at the retrospective review, a reasonable identification of both high-risk and low-risk disease is made with microUS when there are two practitioners observing the real time imaging. This is demonstrated in Table 7.22.

Table 7.22 Base line microUS vs histology

MicroUS risk category	**Histology risk category**			
	High	Equivocal	Low	Total
High	**37**	**6**	**7**	50
Equivocal	**6**	**6**	**5**	17
Low	**6**	**14**	**14**	34
Total	49	26	26	101

	Sensitivity	Specificity
	73.3%	53.8%

The sensitivity and specificity of the baseline microUS is 73.3% and 53.8% respectively, which demonstrates reduced sensitivity, but improved specificity compared to the results of the retrospective reviews when both reviewers agreed. These findings indicate that microUS performs well when there is inter-reviewer agreement. The moderate sensitivity indicates that it is a good test at identifying the presence of prostate cancer and it can reasonably indicate that there is unlikely to be disease

present. However, the test only performs well when there are two observers who agree.

7.1.11 MRI performance review

MRI remains the reference standard pre-biopsy imaging test of choice. All participants in the ERUP trial had a pre-biopsy MRI and the MRI findings were categorised according to the local risk stratification described in Chapter 6 (Table 6.2). Risk stratification scores of MRI compared to histology are outlined in Table 7.23 below.

Table 7.23 Base line MRI vs histology

MRI risk category	**Histology risk category**			
	High	Equivocal	Low	Total
High	**44**	**11**	**6**	61
Equivocal	**6**	**6**	**11**	21
Low	**1**	**9**	**9**	19
Total	49	26	26	101

	Sensitivity	Specificity
	87%	34.6%

Whilst MRI reports a higher proportion of true high-risk disease than compared to the baseline microUS (n = 44/49 compared to microUS n = 37/49), it is shown to under report low-risk disease and has a lower true negative rate than was demonstrated with microUS (n = 9/26 compared to microUS n = 14/26). However, when analysing sensitivity and specificity within these 3 x 3 tables, where equivocal results are also considered, MRI performs better than microUS in disease detection but less well with disease exclusion. Sensitivity of 87% and specificity of only 34.6% for MRI were found in this cohort. Whilst the specificity is less than that of an agreed microUS scan, the sensitivity of MRI is high and comparable with microUS when there are two observers in agreement (Table 7.15).

7.1.12 Site specific correlation

The analysis thus far has related to the broad comparison of the identification of disease within the prostate, regardless of site or size of any detectable abnormality on the imaging tests, and this agreeing with the histology post biopsy. Transperineal ultrasound guided biopsy is reliant on the practitioner identifying, targeting, and obtaining tissue cores that relate directly to the area of abnormality identified on the reference standard MRI imaging. Without whole mount prostatectomy in each participant, a comprehensive analysis of agreement of site or size of reported abnormality compared to the physical presence of disease cannot be undertaken. However, reviewers and reporters of MRI did indicate the location of the abnormality, and this can be correlated with the histological outcomes.

In the baseline microUS reviews, where there was true agreement with the histology, i.e. true positive and true negative findings used in this study, the highest-grade Gleason score was found at the reported site of abnormality in 88% (n = 61/69) of cases. When a similar review of the MRI reports compared to the highest-grade Gleason score was undertaken, the MRI correlated with histology in 89% (n = 68/76) of cases. Both baseline imaging tests perform well with no significant difference between site correlations. However, in the absence of whole mount prostatectomy, further analysis of such detail may be misleading and difficult to accurately interpret.

In this context, MRI has been shown to have a higher sensitivity and specificity compared to baseline micros US, which increases the confidence of the pre-test probability of disease. One further benefit of MRI is that is can also identify disease progression such as capsular breach of aggressive cancers, presence of lymph node involvement, and bony metastatic spread. This supports the notion that MRI remains the reference standard imaging of the prostate as a precursor to biopsy where the gold standard diagnosis can be made.

7.1.13 Results summary

Multiple factors have been analysed, which include inter-reviewer agreement between standard US, microUS, MRI and histology. To summarise:

- A three-point risk stratification scoring system improved reliability of image and histology assessment given differences in reporting systems used in US, MRI, and patient management.
- Agreement between individual reviewers and histology was poor and ranged from 26.7% to 56.7% for standard ultrasound and 25.9% to 56.7% for microUS.
- Inter-reviewer reliability was poor regardless of the ultrasound parameters used.
- Colour Doppler performed poorly with a negative kappa result of -0.01 indicating a slight disagreement. Sensitivity and specificity were 26.3% and 61.5%, respectively.
- Sensitivity of standard ultrasound was calculated to be 48% with a specificity of 75%. A kappa value of 0.21 was determined by assessing the IRR.
- Retrospective review of microUS had a sensitivity and specificity of 77% and 40% respectively with a higher, but only fair IRR kappa score of 0.31.
- Performance is improved when scored in real time by two practitioners at the base line imaging. Sensitivity and specificity were 73.3% and 53.8% respectively at baseline with an improved inter-reviewer agreement calculated as a weighted kappa of 0.38.

7.2 Discussion

This study is a proof-of-concept design to determine if the use of ultrasound in the active surveillance of prostate cancer is feasible. The study has not been designed to test the diagnostic accuracy of the new technology of microUS but to understand if there are features within a multiparametric ultrasound (mpUS) imaging protocol that could be exploited to identify pathology within a prostate gland which may indicate disease progression. As Tranquillo et al (2023) discuss, a proof-of-concept study allows testing of study designs, new technologies or theories before either a wider study is performed or the new technology is more widely utilised. This proof-of-concept study is advocated by research councils (United Kingdom Research and Innovation, 2022) to gather initial data from a small sample to evaluate and inform the continual development of the new technology within the prostate pathway. The study protocol for the ERUP trial was designed so that data could be collated to use to plan the future scope of mpUS within the active surveillance population. Study 1, phase 1 of the ERUP

trial, has evaluated the use of mpUS in the identification of disease; an essential component of the study if this technology is to be used to detect disease progression.

7.2.1 Patient inclusion

Within the local heath economy, there are approximately 550 referrals received on the 28-day faster diagnostic standard prostate pathway (NHSE, 2022) each year, although there is a constant growth in demand year on year as awareness in the population grows (Prostate Cancer UK, 2024b). This NHSE (2022) pathway advocates initial imaging with MRI where capacity allows. In my institution, capacity within MRI was restricted, prior to the Covid-19 pandemic, and prostate MRI was reserved for men most likely to be suitable, and require, surgical intervention in the advent of them having csPCa. This stratified use of MRI resource not only predetermined the inclusion criteria for the ERUP trial, but also was a key influence for the purpose of this study. Should ultrasound technologies demonstrate some diagnostic reliability, then there may be an opportunity to offer imaging to men on AS as the limited MRI capacity in 2019 prevented access for this cohort.

7.2.1.1 Age criteria

The rationale for restricting patient inclusion to phase 1 of the ERUP trial is based on the prostate imaging pathways employed in my institution. Whilst this has ensured all men participating underwent the required imaging, it has limited the findings to men younger than 76 and with a PSA of less than 21 ng/mL. There were eight men who were outside of these criteria who requested to join the study but, despite this, the mean age of participants was 66 with a mean PSA of 8 ng/mL. However, whilst the risk of mortality due to prostate cancer is known to increase with age, as discussed by Brawley (2012), the median age at diagnosis of prostate cancer is falling and is now 67. The population of the ERUP trial correlates to this known median age. The incidence of prostate cancer is also known to increase with age with 60% incidence in men over 65 years of age (National Cancer Institute, 2023) but it is noted that a younger demographic at diagnosis is not associated with worse outcomes for patients (Magheli et al., 2007).

7.2.1.2 PSA and Ethnicity

A raised PSA is also an indicator of the presence of prostate cancer and levels are deemed to be elevated at a PSA > 4 ng/mL (Rawla, 2019). In the ERUP trial cohort, the

PSA ranged from 0.82 – 50 ng/mL with a median value of 6.4 ng/mL. Men with a PSA of a normal value were included in the eligible cohort as risk factors such as positive family history and raised PSAD initiated investigation under the standard prostate care pathway. Men deemed to be clinically at risk of PCa and on the appropriate imaging pathway were included. However, a risk factor for prostate cancer not mentioned in the eligibility criteria is ethnicity.

Prostate cancer incidence rates vary widely across the globe with peak rates in the Americas, Africa, Australasia and North and Western Europe (including the UK); prevalence is much lower in Asia (World Health Organisation, 2023). It is known that African-American men have the highest incidence of prostate cancer worldwide (Kheirandish & Chinegwundoh, 2011) and one limitation of the ERUP trial population is the lack of diversity within the cohort. All participants were white Caucasian, and this is purely a reflection of the local hospital pathway demographics as opposed to a selection bias. It does, however, skew results towards a Northern European demographic but prostate cancer morphology is unchanged between ethnic groups; it is purely the incidence and risk factors that vary (Rawla, 2019).

7.2.2 Retrospective image review – still vs cine formats.

Ultrasound imaging is a widely used diagnostic tool that requires interpretation of the acquired images. As Ihnatsenka and Boezaart (2010) discuss, the advantage of US over other imaging modalities is the ability to view structures in real time and adapt technique to improve assessment of structures. However, the ERUP trial protocol required a double review of the prostate images with reviewers blinded to each other to prevent bias in interpretation and scoring and, as such, images needed to be captured, stored, and retrospectively assessed. Most ultrasound image interpretation studies utilise a retrospective review with success, as Freeman et al (2022) demonstrated with their review of 3731 cases. Retrospective analysis of still image data is also commonplace in the development of machine learning and artificial intelligence in ultrasound (Liu et al., 2019). In the vast majority of studies, the retrospective review is of still stored images, despite the limitations of the lack of a dynamic view, which Cantin and Knapp (2013) acknowledge hinders direct comparison with a real time study.

The optimum ERUP trial design would have been to store cine clips of both the standard ultrasound and microUS scans undertaken for study 1, phase 1 and phase 2. However, the microUS image files for each study were approximately one GB of data, which needed to be transferred from the ultrasound machine to the hospital PACS. This block of data proved too large for the network within the ultrasound department. The network was rebuilt in May 2022, and engineers from the hospital IT and microUS development team attempted to resolve the data transfer issues relating to time-outs but with minimal success. Cine loops would not transfer reliably and a pragmatic approach to sending still images was taken. The limitation of this was mitigated within the team of reviewers as still image review is well embedded into the clinical practice of the team. Indeed, a study by Parker & Byass (2015) describes a retrospective peer review audit process originating within the ERUP trial site ultrasound department. This process has been adopted by the British Medical Ultrasound Society (2023) and advocated by Smith (2022) as a valid method to assess ultrasound examinations. As such, the inability to review cine loop dynamic imaging has not significantly hindered the retrospective review of the images collated for study 1, phase 1 of the ERUP trial.

7.2.3 Reviewer selection, training, and experience

Seven reviewers participated in the evaluation of the standard and microUS images collated for phase 1 of the ERUP trial. Whilst these seven practitioners were the main team performing or interpreting prostate imaging as the study was designed in 2020/2021, they do provide a representative sample of the wider imaging community. Inter-rater reliability kappa analysis is performed to compare a pair of outcomes (Landis & Koch, 1977), however, as Gwet (2014) discusses, the number of reviewers can be multiple providing they represent a subset of a larger population using the tool being assessed. The ERUP trial requires a subset of reviewers to analyse the large number of images that had been collated. It is acknowledged by Gwet (ibid) that fewer reviewers reduce the likelihood of chance agreement, but having too few reviewers may have led to inaccuracies in scoring. Hlabangana et al (2021) identified that reviewer fatigue can impact on scoring and needs to be taken into account when designing a study. The maximum number of reviews undertaken was 30 per reviewer but this still amounts to 60 sets of images being scored by reviewers on top of their regular clinical practice. The number of reviewers utilised was pragmatic in this real-life clinical study.

Five of the seven reviewers were sonographers who were involved with imaging and interpreting both standard ultrasound and microUS techniques. Two further reviewers were radiologists who were involved with interpreting MRI and ultrasound imaging despite not actively acquiring the ultrasound scans on a regular basis. MicroUS training was available online to all reviewers. Five of the reviewers were externally validated as users of microUS by the manufacturers of the system. A study by Cash et al (2022) identified that the rate of csPCa detection, and quality of biopsy, were improved following the microUS training programme. However, in this ERUP trial, the results demonstrated no linear relationship between experience or training and agreement of reviewers' scores with histology, although it is noted that a larger cohort of procedures were performed by Cash et al (ibid.) (n = 1190 participants) compared to the ERUP trial (n = 100). Further experience and training are indicated prior to undertaking a larger trial.

7.2.4 Multiparametric ultrasound

The concept of multiparametric imaging is derived from MRI where several imaging parameters are used in conjunction to assist in the evaluation and interpretation of anatomy and disease (Barrett, 2015). As Dias (2022) discusses, multiparametric ultrasound (mpUS) comprises several functionalities of ultrasound that can be combined, as in MRI, to improve the accuracy of diagnosis. Within the field of ultrasound, those modalities include standard B-mode imaging, Doppler imaging, contrast enhanced imaging, elastography, and with emerging technology, microUS. A pragmatic approach to the range of parameters available for the ERUP trial was taken; parameters that were available in rea- life clinical use, and that did not raise the risk of harm to the patient, were employed. In this study, standard ultrasound, colour Doppler and microUS imaging parameters were employed. Ghai and Toi (2012) describe the features of standard ultrasound that are associated with prostate cancer although these can also be seen in benign tissue and, as such, this imaging parameter is reported to have a PPV of between 18% and 42% (Dias et al., 2022).

Colour Doppler imaging was used to evaluate the presence of blood flow as it was suggested by Harvey (2012) that assessing perfusion of the prostate may indicate areas of malignant change due to the angiogenesis, a frequent sequelae of tumour growth. Colour Doppler was chosen over contrast enhanced imaging as it is widely available on

all standard ultrasound systems, and practitioners are well versed in its use as it is ubiquitous in all areas of scanning (Hoskins et al., 2019). Contrast enhanced imaging is shown to increase sensitivity of tumour detection over colour Doppler (Halpern et al., 2001) but requires the intravenous injection of a contrast agent into the patient. Whilst the use of contrast is becoming more widespread (Sidhu et al., 2018) it remains unlicensed for non-hepatic use within the UK. Sonographers, as non-medical practitioners, would be unable to administer the contrast agent and, practically, contrast was excluded from the ERUP trial design.

MicroUS was available within the clinical department and was taken advantage of for the ERUP trial. MicroUS, as previously discussed, is a novel and emerging technology. The study site is only the second centre in the UK to have this technology available. A recent systematic review by Sountoulides et al (2021) concluded that comparable detection rates of PCa were obtained using microUS guided biopsy compared to MRI guided biopsy but that further trials are warranted. The ERUP trial was designed to evaluate if there were any features evident on ultrasound imaging that could be identified by reviewers which correlated with disease at histology. Therefore, agreement between the reviews of the mpUS imaging pragmatically and practically chosen for the ERUP with histology outcomes post biopsy have been analysed.

7.2.5 Inter-reviewer agreement

7.2.5.1 Individual agreement

As presented in Table 7.5, there was a range of individual reviewer agreement with histology but even the best performance had only 56.7% of reviews agree with the pathological outcome. As mentioned, there was no linear relationship between performance and experience although, as lead researcher, I did obtain the highest agreement rates for both standard ultrasound and microUS reviews. As Pannucci and Wilkins (2010) discuss, there is recognise bias in research related to lead researchers having a vested interest in the subject. This has been mitigated in the ERUP trial by employing multiple reviewers and undertaking blinded retrospective reviews, despite the limitations of not observing real time dynamic studies and discussed previously.

7.2.5.2 Collated performance – standard ultrasound and colour Doppler

Another method to mitigate bias was to collate all the reviews undertaken, rather than assess individual performance. The collated reviewer scores were compared to the

histological outcomes using the kappa inter-reviewer agreement test. The kappa values of Κ = 0.21 for standard ultrasound, Κ = 0.19 for microUS demonstrate only fair agreement when using criteria outlined by Landis and Koch (1977).

This fair agreement was further analysed to evaluate if either standard ultrasound or microUS performed better when detecting or excluding the presence of disease. The locally agreed risk stratification tool, whilst not a five-point scale utilised in MRI reporting (Vargas et al., 2016) or advocated for microUS (Ghai et al., 2016), is closely aligned to patient management and correlates with the critical review published by Rodrigues et al (2012) which stratified PCa into three similar categories. Using this three-point risk stratification score, standard ultrasound was shown to have sensitivity of 48% with a specificity of 75%. The results are comparable with that reported by Harvey (2012), who indicates that these can range from 50 to 92%, and 46–91% respectively. Despite the technological advances in standard ultrasound in the past decade, the ERUP trial data has not demonstrated any significant improvement in sensitivity or specificity of standard ultrasound imaging.

Colour Doppler performance was poor, and this study has confirmed the findings of Halpern and Strup (2000). These authors reported a kappa agreement of Κ = 0.12 for B-mode, Κ = 0.11 for colour Doppler. The findings in the ERUP trial are marginally improved for standard ultrasound with Κ = 0.19 for B-mode. However, performance is much worse for colour Doppler with Κ = -0.01.

7.2.5.3 Collated performance – mircoUS

The collated analysis of the microUS reviews compared to histology demonstrated that the sensitivity of microUS is improved compared to standard ultrasound at 77% but specificity has shown to be reduced at 40%. This is comparable with a study published by Pavlovich et al (2021), which identified a sensitivity of microUS of 60.8% but a reduced specificity of 63.2%. This study (ibid.) identified that performance improved over time and that training and increased experience did improve performance. The results of the ERUP trial corroborate these findings, although sensitivity is greater than in this published study but is lower than a sensitivity reported by Zhang et al (2019) in their meta-analysis of microUS. Zhang et al (ibid) report a pooled sensitivity of 91% and a pooled specificity of 49% of microUS from seven studies of a total of 769 patients. Given the known limitations of the blinded retrospective review of still images, a

further analysis of microUS was warranted to evaluate if agreement was improved when this novel imaging was assessed during real time imaging.

7.2.6 Baseline imaging agreement

7.2.6.1 microUS

During the collection of the images for the retrospective review, the two sonographers undertaking the scanning and biopsy assessed the real time microUS imaging and agreed a PRI-MUS^{TM} (Ghai et al., 2016) score. This was transposed into the risk stratification and compared to histology. Analysis of the results considered any change due to increased experience or additional training but there was no improvement over time; indeed, agreement was better for the initial 50 participants than the latter recruits. However, overall, there was improved agreement than for the retrospective review with a kappa agreement of $\kappa = 0.31$. It is noted that when a weighted kappa test was employed, which takes into account the differences in scoring between the three criteria, the agreement improved to $\kappa = 0.39$ and future studies investigating where microUS best agrees with histology may be of value. The specificity determined in this study would indicate it have a role ruling out disease in patients who are unable to undergo MRI.

Using the local three-point risk stratification, sensitivity, and specificity of the baseline microUS was found to be 73.3% and 53.8%, respectively. Data published within a recent review of microUS by Basso Dias and Ghai (2023) reports a study by Lugehzzani et al (2021), which found a sensitivity of 89.7% and a specificity of 26.0% for microUS in detecting PCa. Another study by Klotz (2021) identified that microUS had a sensitivity of 94% and a specificity of 22%. The sensitivity demonstrated in the ERUP phase 1 study is lower than both previous studies, but specificity is improved.

The sensitivity of the baseline microUS compared to that of standard ultrasound (73.3% compared to 48% respectively) demonstrates that microUS is better at identifying the areas of abnormality within the prostate. This study has shown performance of microUS to be less sensitive than published studies and that this is not related to the retrospective review of still images. Indeed, performance of microUS, when undertaken in real time with two practitioners observing and conferring, does not demonstrate any notable improvement in sensitivity and specificity compared to the results of the retrospective review. Despite an improvement in IRR being

identified, sensitivity and specificity remained poor. Compared to studies reported by Basso Dias & Ghai (2023) and Klotz et al (2021), the sensitivity of microUS determined by the ERUP trial is only moderate and, if the use of microUS is to be considered, a comparison with the agreement of local MRI practice with histology was necessary.

7.2.6.2 MRI performance

MRI is integral within the prostate cancer pathway. Indeed, the ERUP trial is not aiming to replace MRI; its aim is to identify if it can supplement MRI in patients under active surveillance. If mpUS in any of its formats is to be used, its performance will need to be comparable with the imaging reference standard of MRI. It is well documented that there is variability in the current use of MRI (Richenberg et al., 2019) although a study published by Greer et al (2019) reports excellent agreement between radiologists regardless of level of experience, in part due to the advent of the PI-RADS V2 guidance (Vargas et al., 2016). Using the three-point risk stratification, local MRI was found to have sensitivity of 87% and a specificity of 34.6% when compared to histology. These results are comparable with the findings by Klotz (2021) who also compared mpMRI with the identification of csPCa. He found a sensitivity of 90% and a specificity of 22% for MRI undertaken in a similar cohort of patients who underwent microUS and biopsy. Our local results are equivalent and non-inferior to published data.

7.3 Limitations

7.3.1 IT Infrastructure

There are limitations of phase 1 of the ERUP trial, not least the network and IT issues experienced which prevented the transfer of dynamic cine loops. The use of cine loops may have improved the performance of the retrospective reviews. However, the results have demonstrated no significant difference in levels of agreement between the analyses of the baseline microUS undertaken in real time with that of the retrospective reviews.

7.3.2 Experience

The second limitation was the overall lack of experience in microUS before data collection commenced. This was largely due to the delays in getting the microUS machine installed but also a need to not delay the PhD timeframe any further. Unfortunately, the relevant engineers and applications specialists were unable to travel to the UK to set the equipment up in time for pre-trial scanning to be

undertaken due to the Covid-19 pandemic. The majority of experience was gained during the data collection period of the study. Unfortunately, to date, there are only two systems installed in the UK and, despite multiple attempts, there has been no ability for cross site learning. As the world has now opened up post pandemic, it is envisaged that there will be opportunities for greater engagement with European partners.

7.3.3 Ultrasound parameters

A further limitation was the limited standard ultrasound parameters that were available for this trial. Contrast imaging was contraindicated as it remains unlicensed for non-hepatic use in the UK. Elastography was unavailable as a software option on the standard ultrasound system and there were no available resources to purchase. Its use in prostate assessment is untested in my local practice. The evidence for its use (Correas et al., 2013) was balanced against the resources required to purchase and the potential invasive nature of the test; no compelling argument could be made to progress.

The use of low-flow Doppler technology could have been exploited, as could the use of power Doppler but, as the published evidence suggests and these results have demonstrated, the assessment of perfusion in the prostate is unreliable.

7.3.4 Tissue collection

Finally, a limitation relates to the method employed for tissue collection for histological analysis. For true correlation between focal abnormalities evident on imaging and histology, comparison with whole mount prostatectomy would be required (Callejas et al., 2022). However, this would be radical for patients under investigation of PCa and remains only viable in patients requiring curative treatment. This limits a more definitive correlation between site and size of abnormality identified on imaging compared to histology results and remains an unresolvable limitation for any diagnostic study. Given this limitation, this entire cohort, quite reasonably, had an ultrasound guided transperineal prostate biopsy performed for tissue diagnosis. However, the limiting factor for this study is that these were undertaken using a standard frequency ultrasound probe and machine, and targeted MRI identified lesions, not those areas of abnormality identified at the microUS examination. As such,

focal abnormalities that may have been identified on microUS alone have not been sampled, and this may have contributed to the reduced specificity identified in this study. Studies by both Sountoulides et al (2021) and Dariane et al (2022) have identified that microUS guided compared favourably with standard ultrasound guided biopsy for the detection of clinically significant PCa. Indeed, Sountoulides et al (2021) identify that microUS guided biopsy may detect fewer non-significant cancers that the more traditional MRI targeted procedures. Greater experience with this technology is required to improve confidence in biopsy technique performed under local anaesthesia within our local practice.

7.4 Conclusion

The phase 1 question posed was

> "Could the use of multi-parametric ultrasound identify significant prostate pathology?"

The results of phase 1 have indicated that there is no role for standard ultrasound or colour Doppler in the assessment of abnormality within the prostate due to the poor sensitivity and the low kappa agreement identified. The inter-reviewer agreement of microUS improves from $\kappa = 0.18$ to $\kappa = 0.31$ when imaging is performed in real time and there are two practitioners observing and collaborating but the sensitivity of microUS in this study remains lower than published studies would suggest.

This phase of the study has addressed the measurable objectives one, three and four (Chapter 5.4.1). It has identified that microUS may have a role in screening for normality particularly in men contraindicated for MRI. It has identified that a local risk stratification tool may provide a more confident, standardised, reporting tool than the reliance on modality specific reporting systems, and it has demonstrated that performance of microUS is improved when there is active, real-time consensus between practitioners, particularly when undertaking new and complex imaging.

With these results, I conclude that multiparametric ultrasound, including microUS, cannot reliably identify significant prostate pathology. However, the specificity of microUS in this study of 53.8% does indicate it may continue to have a role and be able to confidently identify when no disease is present. Continuation to phase 2 is indicated.

In this chapter, the results of phase 1 have been presented and discussed with conclusions drawn. In the next chapter, the methods, and results of phase 2 are detailed and the findings from this longitudinal aspect of the study are discussed.

Chapter 8 Study 1, phase 2: methods, results and discussion

The chapter presents phase 2 of the ERUP trial, designed to test the concept of using ultrasound to monitor patients on an active surveillance pathway. A small cohort of patients identified through the study 1, phase 1 recruitment were studied and the rationale for this phase of the study, the methods used to collect data, the results of image review is provided, and the relevance of these findings discussed.

8.1 Rationale

Phase 1 of this study has identified that mpUS cannot be confidently used to identify significant prostate pathology as an independent diagnostic test. However, its role to guide biopsy is essential to ensure optimum tissue retrieval for histological assessment. Once a histological diagnosis has been made, the management of the patient is determined by the significance of the pathology identified. The risk stratification employed in study 1, phase 1, detailed in Chapter 6 (Table 6.2) is aligned to the patient management pathways employed to care for patients who have been under investigation for prostate cancer. Those patients with benign disease or with insignificant cancer of Gleason 3 + 3 (core length <6mm) are unlikely to benefit from radical treatment as Wilt (2020) discusses in the updated findings of the PIVOT trial. Wilt et al (ibid.) identified that radical treatment was only associated with a small increase of life length gained and that these gains are further reduced in men with low-risk disease. Wilt et al's (ibid.) findings have been further supported by the latest outcomes of the ProtecT trial (Hamdy et al., 2023), which has undertaken a 15-year monitoring programme of patients who had been randomised to either surgery, radiotherapy or active surveillance (AS) at initial PCa diagnosis. Hamdy et al (ibid.) have demonstrated that, even after 15 years, the prostate cancer specific mortality was low regardless of the arm of the trial the patient was initially assigned. Incidentally, it is noted that the metastatic progression rate of the disease was almost double in the AS group when compared to prevalence in either treatment option.

Whilst the rate of metastatic disease in the monitoring group of the ProtecT trial (ibid.) has been identified as 9.4%, Klotz et al (2015) found that adverse oncological outcomes were identified in only 2.8% of their cohort of patients being monitored with low-risk disease. As such, whilst immediate treatment for low-risk disease is not

necessarily advocated, AS of prostate cancer is most effective, as discussed by (Tosoian et al., 2016), when there is a monitoring programme associated with rates of adverse oncological outcomes that are comparable with those of radical treatment.

8.1.1 Disease detection and AS pathway selection

Whilst NICE (2021) recommend that AS is offered to men with low-risk disease, the risk and benefits of both treatment and monitoring have to be discussed so that an informed choice can be made (Merriel et al., 2019; Vickers et al., 2023). Histological diagnosis of prostate cancer is reliant on the skills of the practitioners performing the biopsy to ensure appropriate samples of the gland are obtained. Fusion guided targeted procedures aid performance of the biopsy and, as Rai et al (2021) state, there is little evidence comparing the previous transrectal technique with the increasingly common place transperineal (TP) approach. There is a current assumption that that a TP biopsy is as accurate as previous techniques, as the single centre study by Fulco et al (2021) identified, although sensitivity and specificity of biopsy outcomes in the majority of published studies relate to transrectal biopsy techniques. The initial diagnostic biopsy in my institution is now performed using a fusion guided TP approach where a focal abnormality has been identified at MRI, in line with published best practice. Studies such as the PRECISION study (Kasivisvanathan et al., 2018) have demonstrated that the use of MRI guided procedures are superior at diagnosis of csPCa, although the confirmatory biopsy was performed using a trans-rectal procedure.

Despite using a fusion guided method, in a small percentage (9%, n = 10/113) of men, csPCa is detected in areas of the prostate with MRI inconspicuous disease (Hansen et al., 2017), and, as Fulco et al (2021) also identify, 9.6% (n = 26/74) of csPCa may be missed with a target only approach to biopsy. The standard care pathway for patients in my institution is to offer AS to all men referred to urology for suspected prostate cancer who have benign findings or low-risk, clinically insignificant, prostate cancer following initial MRI and biopsy. AS is offered in these cohorts of patients, regardless of an initial benign biopsy, due to the known risk that csPCa could be missed at biopsy either as it may not be evident at MRI and not targeted, or may not be sampled with systematic, non-targeted biopsy.

8.1.2 Imaging during AS

Identifying, and implementing, a monitoring programme that ensures there are low rates of progression, and adverse outcomes, is difficult as there is limited consensus on what constitutes an affective AS regime, as discussed in Chapter 1.9. NICE (2021) advocate an initial MRI if one has not been undertaken during diagnosis, and a subsequent MRI at 12 – 18 months post commencement of monitoring. Nieboer et al (2018) report that centres in the USA recommend MRI for the first three years of monitoring and then subsequent MRI between every 1 – 3 years. PSA doubling time was a measure used by Klotz et al (2015), primarily as MRI was not widely available during their 15-year data collection period, and Nieboer et al, (2018) also identified that a wide use of PSA and re-biopsy was advocated in monitoring. Of all tools utilised, adherence to AS is variable and repeat biopsy is most likely to reduce compliance with this management regime (Kalapara et al., 2020). The incorporation of microUS into a monitoring programme is discussed by Avolio et al (2023) as a possible effective tool in predicting the presence of disease which has progressed beyond the prostate. A study of 100 men by Maffei et al (2023) identified that microUS would have reduced the re-biopsy burden in a small cohort study of men on AS and concluded that microUS may offer a viable alternative to MRI due to their negative predictive value (NPV) of 88.9%. The phase 1 data of the ERUP trial did not calculate NPV but found a sensitivity of only 77% compared to Maffei et al (2023) who report sensitivity of 94.1%. The study designs are different with the cohort of men in the study by Maffei et al (ibid) all being previously diagnosed with low grade disease and being part of a monitoring programme, whereas the cohort in phase 1 of this study had a range of disease severity detected.

A previous feasibility study, by Eure et al (2019), concluded that microUS had better sensitivity than standard ultrasound, and that it may provide an office-based imaging tool that could aid an AS programme. The specificity of microUS was 53.8% in phase 1 of my study, which has indicated that this technique may be valuable to identify if no disease is present and, as such, study 1, phase 2 was designed to test this concept.

8.2 Hypothesis

The key question for study 1, phase 2 of the ERUP trial was to identify if there were features of multi-parametric ultrasound that could be used to identify changes within

the prostate in men on AS. As such, the hypothesis for phase 2 was that there were features of multiparametric ultrasound (mpUS) that could identify disease progression on imaging alone.

8.3 Phase 2 – Method

8.3.1 Study population

The 100 men were included in phase 1 of the ERUP trial, as described in Chapter 7 (Figure7.1) and were the cohort of patients from whom participants for phase 2 were recruited. There was no planned sample size; the number of participants was dependent upon their initial diagnosis, individual management plan, and meeting the inclusion factor. It was anticipated that a maximum of 20 patients would be eligible based on the anticipated and current conversion rates from investigation to AS in the Hull University Teaching Hospitals NHS Trust prostate pathway. Following their initial diagnostic investigations, phase 1 men with either low-risk or equivocal histology results were identified. Their hospital records were reviewed to further identify whether they were deemed potentially suitable for AS rather than radical treatment following consultation with their urology specialist. Participants clinically suitable for AS were consequently eligible for phase 2 of the study, provided they met the requisite inclusion criteria.

8.3.2 Inclusion criteria for study 1, phase 2

The inclusion criteria used for this study were as follows:

- Consented and participated in phase 1 of the ERUP trial.
- Were suitable for an AS monitoring pathway.
- Were on an AS monitoring pathway which is regularly reviewed by a consultant urologist.
- Were able to attend Castle Hill Hospital for 6 monthly multi-parametric US examinations.
- Able to tolerate a rectal ultrasound examination.
- Able to provide informed consent to the study.

8.3.3 Exclusion criteria

The exclusion criteria used for this study were as follows:

- Men who met inclusion criteria for AS but have elected to undergo active treatment (hormone treatment, prostatectomy, or radiotherapy)
- Men who met inclusion criteria for AS but had additional intensive biopsies which may have led to changes to the prostate not related to cancer.

- Men who had complications following their biopsy due to risk of spurious changes to the prostate unrelated to cancer
- Men who were eligible for inclusion but who could not tolerate rectal ultrasound examinations.
- Men who do not have regular PSA or clinical reviews arranged.
- Men who are unable to attend Castle Hill Hospital for ultrasound imaging within study time frames.

8.3.4 Recruitment

Recruitment for study 1, phase 2 commenced in May 2022, two months after the start of phase 1. The clinical notes stored on the hospital patient administration system (PAS) were searched to identify histology results and the patients' eligibility for phase 2. A review of their agreed management plan and subsequent follow-up appointments was made to ensure men who met the eligibility criteria were identified, prior to being verbally approached to participate. PAS was integrated on a maximum of three separate occasions following the patients' initial consultation to ensure that all relevant information was available and had been recorded as a delay in follow-up for some men was noted.

8.3.5 Ultrasound appointments and consent

Eligible men were approached by telephone and phase 2 of the study explained to them. Those interested in participating were sent a patient information leaflet (PIL) via the post for them to consider further (Appendix 7, page XVI). After a suitable period to allow for postage and consideration (2 to 3 weeks), the men were contacted again, and participation offered. Where verbal consent was gained, and mutually agreed appointment times were made for ultrasound imaging to coincide with their planned PSA test and urology review. This ensured clinical support was available should any untoward findings become evident during the imaging performed for this study. Phase 2 scans were also planned to coincide with any appointments for repeat TP biopsy in any patients who had this arranged as part of their AS management plan.

Phase 2 monitoring scans were planned to be undertaken at no less than three-month, and no more than six-month, intervals for the first-year post phase 1 inclusion depending upon individual participants AS management plans. A second phase 2 scan was planned for each patient, again correlating to their planned follow-up between further three-to-six-month periods. At each review point, the latest PSA test result was noted. At 12 months from the final participant being recruited, the phase 2 results

were reviewed, and a decision made by the lead clinical supervisor, based on their perceived reliability of microUS, as to whether to continue with the proof-of-concept study. A third follow-up scan was arranged for any participant who had management plans arranged within the study 1, phase 2 initial data collection period.

Upon arrival for any follow-up scan, the participant had a face-to-face consultation with me, as the lead researcher, and time was taken to discuss the phase 2 aims of the ERUP trial and written consent obtained. Previous imaging, histology and their management plan was discussed with the patient to ensure participants were aware of next steps following these research scans.

8.3.6 Scan protocol

The scan protocol utilised in phase 1 of this study was repeated and this is detailed in Chapter 6.7. Two sonographers were in attendance, one to perform the scans on both the standard ultrasound machine and microUS machine, and the other to manipulate the image and capture the images as per the protocol. Where possible, cine loops were captured in a bid to optimise retrospective review but given the known network issues, still images were saved in accordance with the phase 1 protocol. At this point, the examination was completed unless the patient had a planned TP biopsy procedure, which then was undertaken as per routine patient care. Captured images were stored on the hospital PACS for retrospective review. An initial comparison with baseline imaging was made within seven days of the phase 2 scan so that any areas of concerning change could be flagged up to the patients' urologist and discussion at the multi-disciplinary team (MDT) meeting arranged to agree any follow-up care required. A report of the imaging was issued on the radiology reporting system to ensure timely communication with the clinical team and PAS.

8.3.7 Agreement of significant change

A trigger for significant change was agreed with the lead urologist (who is also clinical supervisor) and radiologists to avoid unnecessary concerns for patients but also to ensure appropriate follow-up was arranged. It was agreed that patients would require discussion at MDT if any of the following occurred during phase 2 monitoring:

- MicroUS scores progressed risk group from low to equivocal, equivocal to high, or, more concerning, low to high.

- MicroUS PRI-MUS™ (Ghai et al., 2016) scores changed within a stable risk group but with an associated rise in PSA of ≥ 1.0 ng/mL.
- Patients stated they had concerns about their management plan and requested clinical review.

8.3.8 Image review

To ensure consistence between phases, stored images were later retrieved from PACS and viewed on the same PC workstations as used to review phase 1 images. All previous ultrasound images for the participants were retrieved and comparison with baseline and subsequent imaging performed. Imaging from each participant was reviewed by me and a second reviewer, who had been identified to have the highest agreement between reviews and histology during the phase 1 data analysis. Both reviewers had comparable agreement rates in phase 1. Independent of each other, reviewers were asked to compare all available images for each phase 2 participant. Images were assessed it identify any areas of change in the prostate between the baseline and subsequent scans. An assessment of PRI-MUS™ score, normality, or comment on appearance was required for any areas of suspected change; this was not required if no change was detected. All reviews were completed within two months of the monitoring scan being performed. Reviewers had access to previous MRI and histology reports to ensure consistency with real-life clinical settings, and to be able to make comparison with perceived reference standard imaging of MRI (Turkbey et al., 2016). Once reviews were complete, scores of changes or no change were documented on a password protected database for each participant and stored under their original unique study ID number. Only anonymised data was stored.

8.3.9 Data analysis

Scores from each reviewer of each monitoring scan were compared and any difference noted. Where differences occurred, comparison with the baseline PRI-MUS™ score and imaging was made. Where there was any upgrade in risk stratification score, this was noted against the PSA test results and subsequent clinical actions where applicable. A review of the PSA tests over the duration of the phase 2 collection period of all participants was made and any changes were compared to any notable changes in imaging appearances.

Due to the small, as anticipated, cohort size of this phase 2 study, no meaningful statistical analysis could be performed as such a narrative assessment was made.

8.4 Results

8.4.1 Recruitment

Recruitment for study 1, phase 2 commenced in May 2022 and continued until December 2022. During this time, histology results and patient management plans of all the 100 study 1, phase 1 participants were reviewed until the final phase 1 participant had a documented outcome. Fifty-one eligible patients were identified due to their histological outcomes as being potentially suitable for AS and therefore eligible for phase 2 recruitment. Of the 51 eligible patients, information from the PAS records identified that 39 had to be excluded from phase 2 due to the following reasons:

- 3 remained undecided about treatment options.
- 18 requested radical treatment rather than AS
- 2 required additional intensive biopsy as there remained a high suspicion of csPCa despite low-risk histology obtained at TP biopsy
- 1 had post biopsy prostatitis which required extensive treatment.
- 5 were discharged from urology care without any care plan in place.
- 10 had no urology follow-up arranged, or management plan in place after the third review of PAS.

This resulted in 12 patients meeting the inclusion criteria. A flow chart of participant selection outlines the steps involved in recruitment is provided below (Figure 8.1).

Twelve men were initially approached, and 11 men verbally stated they were interested in participating. One man declined the invitation to participate as he had found the phase 1 scan and biopsy procedure uncomfortable and with undesirable side effects, which he did not want to repeat. Following receipt of the PIL (Appendix 7, page XVI) and consideration time, the 11 men were contacted again, and all agreed to participate. However, one was unable to commit to a mutually agreeable appointment time for follow-up scans due to his work schedule and, therefore, declined further involvement. Mutually agreed appointment times were made for the remaining 10 patients. The first follow-up scan was performed in October 2022 and the final follow-up scan was performed in October 2023; a total of 20 follow-up scans were performed. The review of the baseline, and subsequent images taken throughout the monitoring period, was completed for all participants in November 2023.

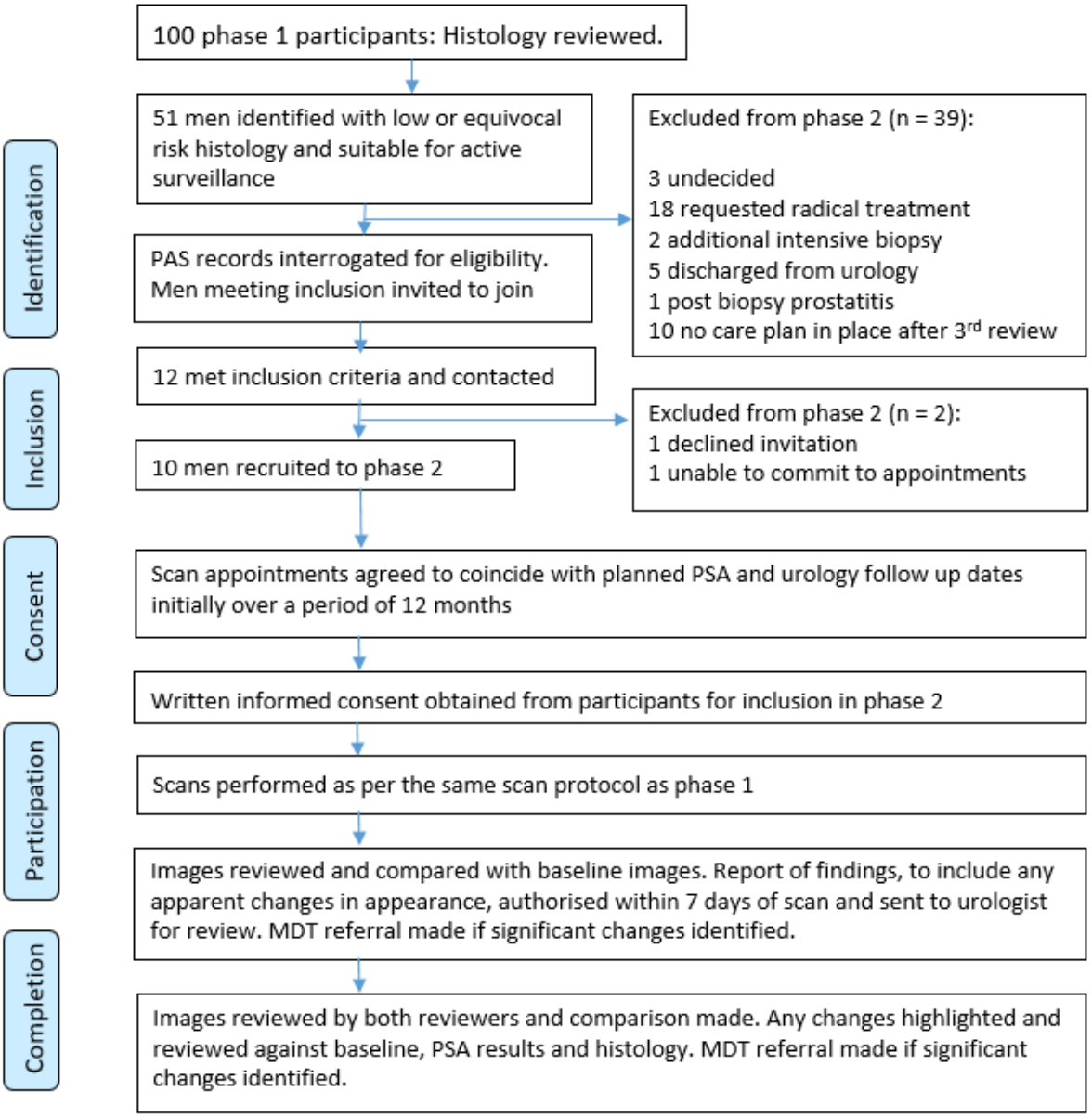

Figure 8.1 Recruitment of participants into Study 2, phase 2 of the ERUP trial

8.4.2 Phase 2 monitoring scans

Ten patients had a first monitoring scan performed at between four-to-seven-month intervals following the initial investigation, with an average time to first review of six months. All patients were offered an appointment for a second monitoring scan, nine attended with one failing to attend or contact the department. The second scan was performed at between four and seven months following the first review with an average gap between scans of five months. One participant had an agreed management plan within the initial phase 2 period which enabled a third monitoring scan to be performed. An overview of the monitoring timeline is given in Table 8.1 below.

Table 8.1 Timeline of monitoring scans for phase 2 cohort

UIN	Age at baseline	Time from baseline first scan (Months)	Time from baseline to second scan (Months)	Time from baseline to third scan (Months)
ERUP4	57	4	4	5
ERUP22	64	7	5	
ERUP26	67	4	7	
ERUP27	66	6	5	
ERUP44	56	6	5	
ERUP50	66	6	4	
ERUP58	66	6	6	
ERUP88	60	7	DNA	
ERUP95	62	7	6	
ERUP104	69	7	6	
Mean	63	6	5	

8.4.3 Demographics, PSA, and histological outcomes of cohort

Ages of the men participating in study 1, phase 2 ranged from 57 to 69 with an average age of 63. At baseline, their PSA levels ranged from 0.9 - 11 ng/mL with a mean of 7.0 ng/mL and median of 6.4 ng/mL. The average PSA level changed during the monitoring period with the means reducing to 5.1 ng/mL at the first review and 4.3 ng/mL at the second, although the ranges were stable and were between 0.51 - 9.9 and 0.53 – 12 ng/mL, respectively. The demographics of the cohort is provided in Table 8.2 below.

Table 8.2 Demographics of phase 2 participants

	Age years	PSA (ng/mL) at baseline	PSA (ng/mL) at first review	PSA (ng/mL) at second review
Range	57 - 69	0.9 - 11	0.51 – 9.9	0.53 – 12
Mean	63	7	5.1	4.3
Median	65	6.4	4.3	4.2

There was a range of histological outcomes following biopsy in the phase 2 participants. Benign tissue was found in four men, atypical small acinar proliferation

(ASAP) was found in one, one man had prostatitis, three were found to have low grade Gleason 6 (3 + 3) prostate cancer with cores lengths of less than 6mm, and Gleason 7 (3 + 4) with core length <6mm in one participant. Those with a diagnosis of prostate cancer were classified as ISUP grade group one or two (Table 1.1) and deemed clinically suitable for active surveillance at MDT.

There was no correlation between the PSA level at baseline and the findings of benign compared to low grade prostate cancer at histology. The highest PSA was seen in a man with a benign histological outcome, and the PSA levels in men with low grade disease ranged from 0.9 – 11 ng/mL at baseline. All participants had an initial follow-up PSA monitoring although in two participants, the PSA was not tested again in the monitoring period. A more detailed overview of the PSA and the histological outcomes of the prostate biopsy for the study 1, phase 2 participants is provided in Table 8.3 below.

Table 8.3 PSA levels (ng/mL) over phase 2 and histology outcomes

UIN	PSA Baseline	PSA Review 1	PSA Review 2	PSA Review 3	Highest Gleason Score on histology post biopsy
ERUP4	11	9.9	12	11	3+3 (0.5 mm core)
ERUP22	8.4	2.8	4.4		ASAP
ERUP26	16	3.6	4		Benign
ERUP27	7.2	8.1	6.6		Benign
ERUP44	3.2	3.1	3.4		Benign
ERUP50	3.7	3.9	3.9		3+3 (1mm core)
ERUP58	0.9	0.51	0.53		3+3 (3mm core)
ERUP88	5.6	6.1			Benign
ERUP95	4.6	4.6			Prostatitis
ERUP104	8.9	7.9	8.5		3+4 (2mm core)

No alternative imaging was performed throughout phase 2 on any of the participants despite MRI being advocated by some AS protocols (Merriel et al., 2019). Two participants (ERUP26, benign at baseline, and ERUP50, Gleason 6 (3 + 3) with 1mm core at baseline) had repeat TP biopsy at around 12 months following baseline

investigations, but no obvious trigger for these was evident on PAS and the referral for biopsy was likely due to adherence to NICE (2021) by their urologist rather than a clinical concern. Neither had had a consultation beyond the initial post biopsy attendance when their AS management plan had been agreed. In both cases, the histological outcomes were unchanged following the second biopsy.

8.4.4 Histological outcomes and baseline ultrasound assessment

A review of the baseline images, and risk scores, as per the locally agreed stratification (Table 6.2) employed in phase 1 revealed a range of appearances and scores. There was agreement between the histology and the baseline microUS assessment in eight participants, but agreement between histology and standard US and colour Doppler imaging in only two within the cohort. There was agreement between histology, microUS and standard ultrasound in two participants. Two of the cohort were scored as high-risk at baseline microUS and, therefore, in disagreement with the subsequent low or equivocal histology outcomes. The baseline scores are outlined in Table 8.4 below.

Table 8.4 Risk stratified baseline ultrasound appearances and histology outcomes

UIN	Histology Risk Category	Highest microUS PRI-MUS™ score at BASELINE imaging	Overall opinion standard image at BASELINE
ERUP4	equivocal	equivocal	high
ERUP22	low	low	high
ERUP26	low	low	equivocal
ERUP27	low	low	high
ERUP44	low	low	Normal
ERUP50	equivocal	equivocal	Normal
ERUP58	equivocal	high	high
ERUP88	low	high	Normal
ERUP95	low	low	Normal
ERUP104	equivocal	low	Normal

8.4.5 Phase 2 image review – baseline comparison

A retrospective review of all baseline microUS scans was performed by the two reviewers. Both reviewers noted a wide range in appearances of microUS scans across the participants, which likely accounts for the risk stratification originally documented. Representative images from baseline scans, and first follow-up scans, of all participants

is provided in Appendix 9, page XXII. Images of the region of highest risk stratification score are provided.

8.4.6 Monitoring scan review

A total of 40 reviews of follow-up images were performed by the two reviewers; each participants scans were reviewed by both reviewer A & B. Results from the reviews of the standard US imaging monitoring scans performed identified that no change was seen between baseline and subsequent scans in any of the reviews of the 10 patients. Given the poor agreement between histology and standard US, the relevance of this finding was deemed to be insignificant.

Of the 40 microUS reviews performed (20 by each reviewer), change in appearance was noted by one reviewer (B) in the first monitoring scan of participant ERUP88. No change was evident in any of the other review scans and appearances of the prostate was seen to be stable overtime.

Reviewer B provided comment on the perceived change on the image of the left mid gland stating the PRI-MUS^{TM} score was now 2. Reviewer B felt there to be a loss of the descriptive “ductal patches”, described by the PRI-MUS^{TM} score (Ghai et al., 2016) as being grade 1 findings. Reviewer B noted that, on their review of the baseline scan, this area had more PRI-MUS^{TM} 1 features than the follow-up imaging displayed. Reviewer A felt there was no change in microUS appearances between both scans and, as such, did not provide an updated PRI-MUS^{TM} score. The original ultrasound imaging, MRI, and histology of participant ERUP88 was reviewed by both reviewers A & B and a radiologist involved in the ERUP trial. Histology demonstrated benign prostate tissue with no evidence of malignant change. It was noted that the original baseline microUS had been scored as PRI-MUS^{TM} 5 (high-risk) and that the PI-RADS v2 (Vargas et al., 2016) score of their MRI was 4 (high-risk) with an area of concern in the left gland. It was noted that, although a full data set of images had been collected for microUS at both baseline and follow-up, the images were not precisely replicated. However, on review of all the images of phase 2 for this participant, it was mutually agreed that the gland had been fully imaged, and a comparison could be made. On comparison with MRI, histology and the PSA levels, it was mutually agreed that the perceived change

did not meet the significant criteria outlined above (8.3.7) and that no action was required.

Comparative images for ERUP88 are provided below (Figure 8.2, Figure 8.3, & Figure 8.4) and demonstrate the MRI findings on the axial and sagittal T2 weighted imaging, the area of concern on baseline microUS, and the comparative area of concern at follow-up. The patient's agreed AS management plan was to be continued rather than immediate referral to MDT. Unfortunately, this patient did not attend for a further follow-up phase 2 monitoring scan. However, as a safety net, PAS was interrogated, and his PSA was seen to be stable with a four-month review with his urologist planned.

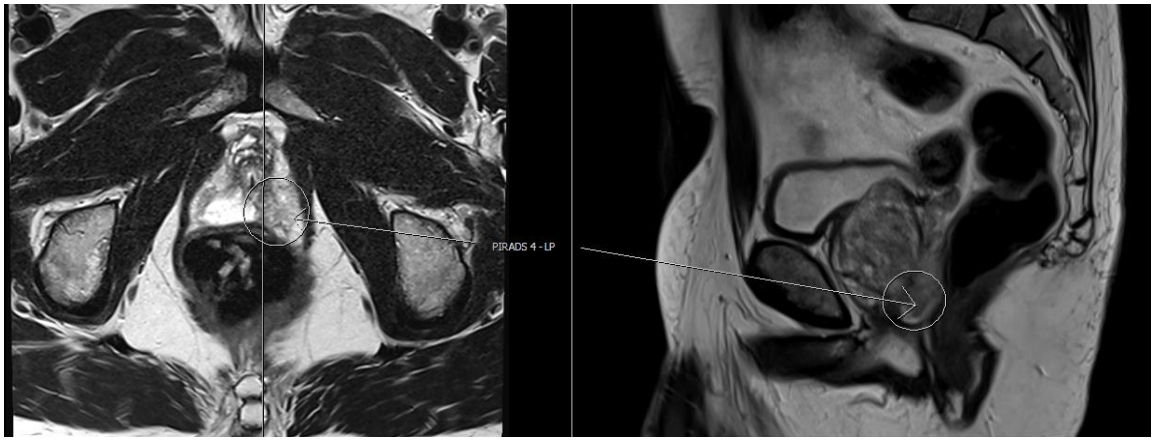

Figure 8.2 ERUP88 Baseline MRI – PI-RADS 4 lesion, Lt posterior peripheral zone at the apex

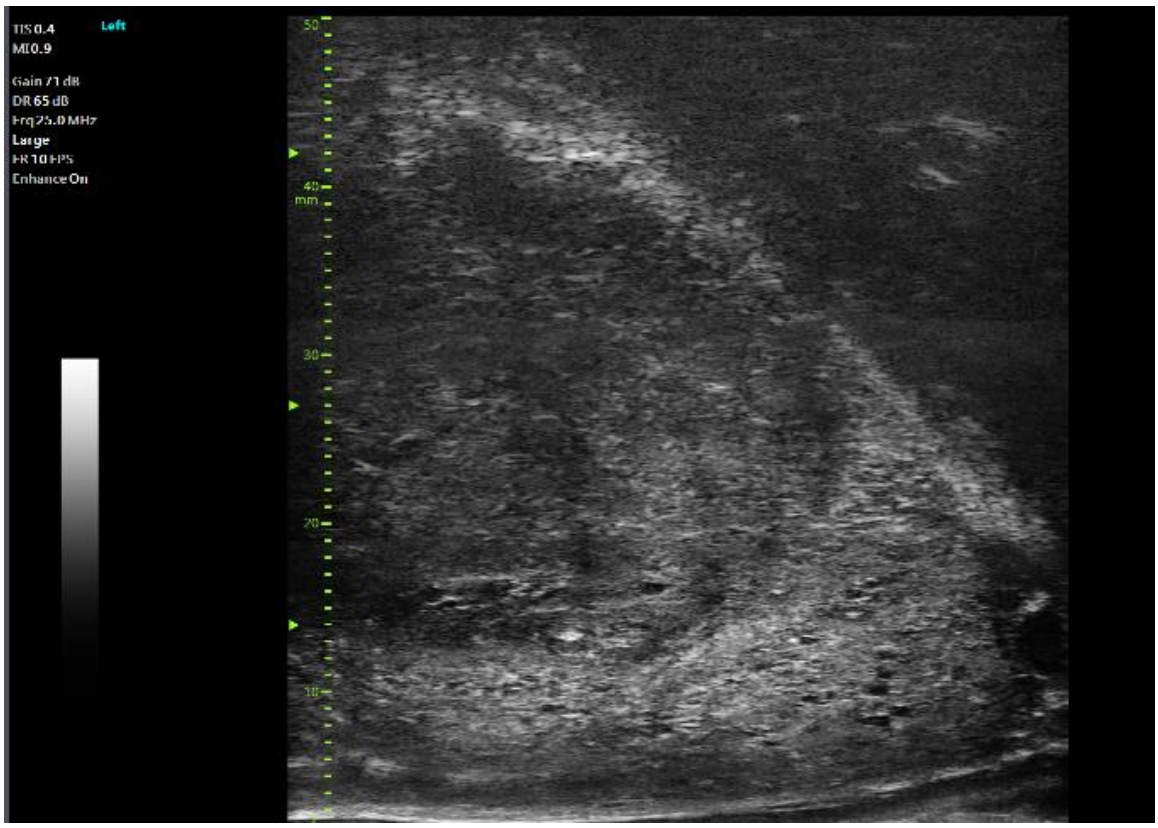

Figure 8.3 ERUP88 Baseline scan 27/09/2022 – scored as PRI-MUS^{TM} 5 (high-risk) at baseline but PRI-MUS^{TM} 1 (low-risk) at phase 2 review by both reviewers

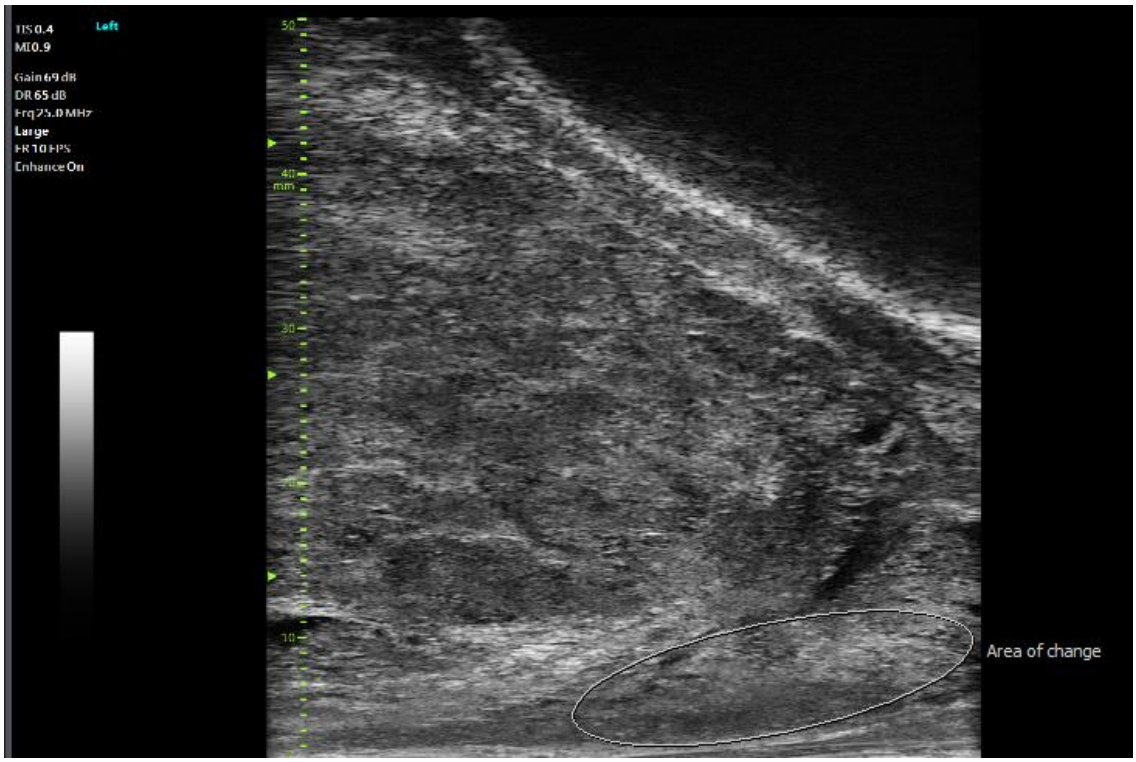

Figure 8.4 ERUP88 First monitoring scan 03/05/2022 – scored as no change by reviewer A but an increase to PRI-MUS^{TM} 2 (but still low-risk) by reviewer B

8.4.7 Results Summary

- No changes were noted in the appearances of standard US or colour Doppler imaging, but the wide range of risk stratification and poor agreement with histology at baseline (two of ten participants) reduced confidence in this being a viable assessment of the prostate.
- Change in appearances at microUS was noted by one reviewer in one follow-up scan, but the PRI-MUS^{TM} score assigned was low-risk compared to the high-risk score given at baseline and at MRI. Although reviewer B felt the PRI-MUS^{TM} score, of the follow-up scan, had progressed from 1 to 2, this remained a low-risk score and agreed with the histological outcome. As such, this was not deemed to be a significant finding and no further action was required. No change was recorded in any of the other nine participants.
- No histology changes were found in the two patients who had repeat biopsies during the monitoring period, and there was no overall significant change in PSA levels across the cohort.

8.4.8 Clinical Outcome

The results of the phase 2 monitoring imaging were reviewed by me and my clinical supervisor in January 2024. Each participants' prostate imaging and histology history were reviewed and, whilst we tried to remain objective, the results of the phase 1 study were considered with regards the clinical context and impact on patient management. Within this small cohort, perceived change of microUS in one scan was noted by one reviewer but not the other and, on review of baseline imaging, the assigned risk was reduced. Whilst we acknowledged this is only one case, it highlighted inconsistency in interpretation between reviewers and over time between imaging, which was evident from the poor inter-reviewer agreement rates demonstrated from the results of study 1, phase 1. In terms of the clinical consequence, this inconsistency was felt to be a risk for patients as it may trigger unnecessary MDT referral and patient follow-up biopsy. As such, the decision was made to terminate this proof-of-concept study and close phase 2 of the ERUP trial. All participants were contacted by letter, outlining the decision, and thanking them for their participation. They were advised to contact me or their urologist if they had any concerns regarding their AS management plan in the future.

8.5 Discussion

Study 1, phase 2 of this ERUP trial was designed to test the concept of whether there was a role for ultrasound in the AS pathway. When the ERUP trial was designed, it was anticipated that features of both standard and micro ultrasound imaging may be combined to provide a multi-parametric approach to prostate imaging, with the addition of microUS as a novel parameter. The study by Correas et al (2021) identified that the use of multi-parametric (mpUS) was more powerful than standard B-Mode imaging alone but did acknowledge that, even an approach that combined contrast enhanced ultrasound and elastography, it did not obviate the need for mpMRI in men with a suspicion of PCa. Men on an AS pathway will already have a diagnosis and low-risk of csPCa (Dall'Era et al., 2008) and the role of mpUS, therefore, is concerned with recognising change rather than diagnosis. Nevertheless, the purpose of continued investigations during AS is to identify disease progression with a view to initiating early curative treatment if required (Ip et al., 2011), and should be approached with the same suspicion of the presence of prostate cancer. If mpUS is to be used, it would need to perform to the standard as the current reference standard of mpMRI. Results of the first phase of this ERUP trial indicated that the sensitivity and specificity of standard ultrasound, even with the inclusion of colour Doppler, was too poor to be considered as an imaging test for the identification of significant prostate pathology and, as such, has not been investigated in depth in study 1, phase 2. However, the specificity of microUS of 53.8% suggested that this test, when using the criteria outlined by Altman and Bland (1994a), was reasonable at detecting true negative or normal prostates. As such, with a higher specificity than was found of the MRI in the study 1, phase 1 cohort, continued investigation of the role of microUS, as a tool to monitor patients, was indicated.

8.5.1 Considerations for the use of microUS in AS

Not only does any imaging investigation need to perform comparably to the reference standard, but, as discussed by Tosoian et al (2016), the AS pathway needs to ensure the rates of adverse outcomes are less, or at most equivalent, to those of radical treatment. Developing a pragmatic mpUS protocol that can identify disease progression, but with a minimal false positive rate, is necessary to avoid overcalling the presence of disease, which could then lead to the burden of additional invasive

biopsies for patients. The specificity of microUS determined in study 1, phase 1 was higher than that of Klotz et al (2021) and indicates that our true negative rate was reasonable. However, the sensitivity determined by the phase 1 study was 73.3% and lower compared to Klotz et al's (ibid.) study, which found theirs to be 94%. With this lower sensitivity, my study could not confidently identify the presence of disease and a positive, or high-risk result, may lead to diagnostic intervention to confirm progression, but with a high false positive rate. Notwithstanding the limitations of microUS discussed in Chapter 7.3, the study 1, phase 1 sensitivity indicates that, in our current practice, microUS did not perform well enough to confidently rule out csPCa but could be specific enough to confirm normality.

As identified in Chapter 2.6.2, and subsequently published (Parker et al., 2021), the evidence of the systematic review indicated that microUS is comparable with MRI. Subsequently, Albers et al, (2022) identified that microUS detected PCa at a comparable rate to MRI in patients undergoing biopsy during AS. Eure et al (2019) identified, microUS has an added benefit of being relatively low-cost and can be performed in real-time in a clinic setting. Given the challenges related to MRI capacity, and the consideration that any changes to the AS monitoring regime need to be of limited impact to the patient and fiscal resources, the advent of microUS, as a potential imaging tool, for surveillance could have proved advantageous to our local population. Whilst this was the rationale for the ERUP trial, the inconsistencies identified between the study 1, phase 2 reviews, and importantly the varied appearances of the prostates of the phase 2 participants, resulted in a lack of confidence in the use of microUS in this setting.

8.5.2 Study design considerations

As a proof-of-concept study, study 1, phase 2 was designed to test whether microUS could be used to monitor patients. The aim of phase 2 was to determine whether the technology was acceptable in terms of patients tolerating the procedure, and whether it became accepted practice for practitioners. This latter consideration is investigated and discussed in full in Chapter 9. The study was designed to minimise the burden on participants by running in parallel to routine care. As such, phase 2 imaging was planned to coincide with the regular PSA monitoring and biopsy that is recommended as an AS protocol by NICE (2021). Given the evidence I found during the scoping review

of Chapter 3.4.10, I aimed to reduce the number of hospital visits, health care encounters, and tests that patients had during their period of AS. In addition, it was essential that participants had planned access to urology following any imaging performed. Evidence suggests between 24-40% of men on AS progress to active treatment (Tosoian et al., 2016), either due to their own choice or due to disease progression, and clinical support would be required. The study was also designed to consider any findings at the follow-up imaging that may suggest significant change in the prostate or disease progression. In accordance with NICE (2021), any suggested changes were seen to be a raised clinical concern and could lead to MDT discussion, where the failsafe would be to repeat the prostate biopsy. Whilst TP prostate biopsy has less risk than the previous transrectal biopsy procedures (Newman et al., 2022), and thereby reduces the risk of adverse outcome of the AS regime (Tosoian et al., 2016). It is still an uncomfortable procedure for patients, and, before undertaking the biopsy based purely on the findings of a novel imaging technique, a urology consultation would be necessary.

The study 1, phase 2 study design met the criteria for an effective follow-up pathway discussed by Tosoian et al (2016), although it restricted the cohort available to invite to participate. Following review of the PAS, it became apparent that there was little consistency between the local urologists as to the AS pathway adopted for patients. As presented in the results section (Figure 8.1), some potentially eligible patients were discharged from urology following histology results, whereas others, with similar presentation and histology, were offered AS. However, even in this eligible cohort, there were patients with no follow-up planned, despite this being agreed following the initial diagnosis. Whilst it is out-with the remit of this thesis to determine the reasons for the lack of a standard, NICE (2021) concordant, AS pathway locally, it is likely that demand for urology services has impacted on the ability for patients with low-risk disease to be followed up. As discussed by The King's Fund (2024) waiting lists are growing and there are simply more people being referred than can be treated. Demand to meet the 28-day faster diagnostic prostate timed pathway (NHSE, 2022), and meet NHS standards for recovery post the COVID-19 pandemic (NHSE&I, 2022), are highly likely to have contributed to many of the patients within the study 1, phase 1 cohort not having the planned care that would meet the NICE (2021) AS guidance.

However, a cohort of 12 patients were identified as eligible which represented approximately 10% of the study 1, phase 1 group. Whilst small, this is an appropriate number to meet the needs of this proof-of-concept study, before wider research is performed (Tranquillo et al., 2023).

8.5.3 Phase 2 cohort considerations

Of the 100 patients within the study 1, phase 1 cohort, 51 were identified who met the AS criteria used by Wilt et al (2020) in the PIVOT study and, therefore, potentially eligible for phase 1. As discussed, of these, only 12 had appropriate urology follow-up to meet recruitment criteria for phase 2. For AS to be effective, it needs to capture eligible patients and have a consistent approach, but I found that locally, 35% (n = 18) of the 51 suitable phase 1 participants were either discharged, undecided about their option, or had no follow-up arranged. As discussed above, this is likely indicative of wider issues with urology capacity and NHS waiting times (The King's Fund, 2024) rather than a lack of clinical decision making. However, it has highlighted that there are pathway issues within urology leading to inequalities in care across the team of urologists. Adding a new test into the already non-standard and varied AS pathway, which in itself may create more follow-up due to the inconsistency between practitioners and poor inter-rater reliability (IRR) evident with microUS, may create additional demand, rather than be part of the solution of improving imaging capacity on AS.

The additional burden for patients also needs to be considered. Indeed, even in this small 12 patient cohort, two patients declined transrectal imaging as part of their follow-up, although I acknowledge that they were being invited for research purposes as opposed for imaging with proven clinical benefits. Regardless, one man declined inclusion as he had difficulties tolerating the transrectal examination and did not feel able to have an additional scan. The second man was unable to commit to attend for imaging due to work commitment; a significant consideration when adding any additional tests into a pathway where most men in this cohort were of working age.

8.5.4 Reflections on phase 2 image review

Unlike study 1, phase 1, in this second phase, only two practitioners reviewed the images of the participants. The two practitioners with greatest agreement with

histology of the phase 1 reviews were included. The rationale was to limit the variation between reviewers where possible. In this phase, both still and cine loop images were captured for retrospective review but, unfortunately, the previously encountered limited network speed prevented the utility of this. Only still images could be reliably retrieved for review. There was a notable improvement in subjective image quality of the follow-up images with the gain settings (image brightness) markedly optimised. As commonly demonstrated in clinical practice, and particularly noted in the learning of fusion guided transrectal prostate biopsies (Mager et al., 2017), imaging quality does increase with confidence. The improvement in imaging reflects the findings of Cash et al (2022) in their investigation of the learning curve of novice users of microUS.

The retrospective review was undertaken un-blinded to any previous imaging and the histology outcomes. This method of review was consequently not consistent with that employed in phase 1, and thus, results are not directly comparable. However, being un-blinded to relevant information better reflects a near real-life clinical setting where comparative image review is expected if disease progression is being monitored, and also reflects the locally agreed peer review processes (HUTH, 2023c). Given that there had been some disagreement between the microUS score and histology at baseline, and the fact that the best agreement between these two top reviewers and histology in phase 1 was only 56%, it was reasonable to only assess for change in appearance of the prostate rather than to estimate a PRI-MUS^{TM} (Ghai et al., 2016) score at each review. As demonstrated in Appendix 9 (page XXII), despite the similar low-risk histology scores, a variation in appearances of individual prostates on microUS imaging was evident. It was agreed between the reviewers that assessing for change within an individual prostate was a pragmatic approach and that a PRI-MUS^{TM} score would be given if any change was noted. In this way, a region of interest could be identified for any potential future biopsy. However, the confidence of the reviewers in their ability to interpret microUS, which is discussed in Chapter 9, is likely to have influenced their ability to review objectively. Had a wider group of practitioners been trained, experienced, and available, it may have been prudent to have had the phase 2 imaging reviewed by practitioners' independent of study 1, phase 1 and study 2.

Despite this potential bias inherent in the review process, only one change was noted during one scan of an individual participant. The reviewer stated that, in their opinion,

the PRI-MUS™ score increased from 1 to 2 between the two scans. However, when compared to baseline score which was initially PRI-MUS™ 4 and high-risk, the risk now documented by both reviewers had reduced. It is hard to understand why such a difference was exposed, but again, is likely to be due to the transition from novice to expert as discussed by Cash et al, (2022). One plausible reason for the difference between the reviewers at this more advanced stage is likely to be exposure and training. Throughout the ERUP trial data collection and analysis period, I had regularly undertaken online microUS training packages as supplied by the manufacturer, Exact Imaging™ Markham, Canada (2023) and achieved their "Expert User" status. The second reviewer completed only the basic training modules and chose to learn by doing during the study 1, phase 1 data collection and review period. This may account for a delayed learning curve in Reviewer B, but, again, highlights inconsistencies. Due to the perceived change remaining within the low-risk category and comparable with known histology, following discussion with the lead urologists and clinical supervisor, a consensus decision to continue to monitor with a no biopsy strategy was agreed for this patient.

Other studies performed by Maffei et al, (2023) and Albers et al, (2022) have looked at appearances of the prostate at the time of a single scan performed to guide biopsy and have not apparently compared with previous imaging. Suspicious areas have been biopsied in both studies, guided by microUS, but it is not clear in either study as to whether these are new regions or ones previously dismissed or indeed sampled at an earlier time. This reflects imaging is not an exact science but relies on interpretation and inherent margins of error and risk. An advantage of phase 2 of this ERUP trial is the longitudinal approach with comparative reviews of sequential imaging performed and, as such, margins of error can be minimised. However, a limitation consistent with that of phase 1, is that most of the cohort only had imaging performed and the apparent stability of the prostate was not confirmed by biopsy. In the absence of clinical concern, and with stable PSA, a repeat biopsy was not indicated at the time of the monitoring scans. However, in two patients, repeat biopsy was requested in line with the NICE (2021) AS protocol at 12 months post the initial diagnosis. In both patients, no change was evident on the image review and the histology remained stable. These findings, whilst from a small cohort, support the findings by Maffei et al, (2023) that

suggest biopsy could be prevented where no high-risk PRI-MUS™ score is evident on follow-up imaging.

8.6 Limitations

8.6.1 Sample size concerns

A key limitation to this second phase of the study is the small sample size. This limits the conclusions that can be drawn about prostate cancer detection and monitoring. However, the small sample has been useful to inform this proof-of-concept study and, despite being smaller than anticipated, is justifiable. Despite there being a reasonable potential cohort eligible for AS, only 10 were identified who met the inclusion criteria for phase 2. As discussed, there are wider issues within the NHS in terms of capacity and demand (NHSE&I, 2022), which likely influence how patients are managed, particularly across the team of urologists. The faster diagnostic standard (NHSE, 2022) concentrates on achieving a cancer diagnosis and decision to treat within 28 days of referral, but consequently, capacity is skewed to achieving this target as opposed to managing patients on a longer-term plan. A standardised AS regime across the local service, in line with NICE (2021), may have resulted in more phase 1 participants being eligible for onward monitoring, and is certainly a desirable action to take from this research. There is a clinical need for standardisation for all patients on a prostate pathway prior to changes in how they are monitored can be implemented safely.

8.6.2 Reviewer experience and exposure

The second limitation is that the phase 2 reviews are likely to have been influenced by the reviewers' experience of microUS in terms of its use and interpretation during data collection and reviews of phase 1. The ERUP trial was not testing the primary diagnostic abilities of microUS, but its use to guide biopsies, as the system was used outside of the ERUP trial protocol, has had a clinical influence and subsequent lack of diagnostic confidence, which is discussed further in Chapter 9. To achieve an objective review as possible relies on reviewers not being biased by their own experience. In this instance, due to the limited exposure to microUS, neither reviewer may not have felt themselves to be expert, despite achieving "expert" status on the on-line training (Exact Imaging, 2023). Certainly, from my own experience, I did not feel I had sufficient confidence in my own judgement, which potentially introduced bias into the image review. With this possible biased perspective, there is a risk subtle changes may be

discounted due to a perceived lack of experience or lack of confidence in the reviewers' knowledge and skill. Equally, changes could have been perceived as significant that more experienced, or confident reviewers, would have discounted.

Whilst the ERUP trial protocol and study design was scrutinised for a risk of bias, as advocated by Faille et al, (2017), it is acknowledged that possible reviewer bias, born from negative experience, was not taken into account. That said, as a single centre study, and with only one other system in the UK, the option for independent review by experienced external practitioners was not practicable in this proof-of-concept study. It will be an essential consideration for future research design.

8.6.3 AS biopsy protocol

A further limitation is that this second phase of study 1 is not directly comparable to others, such as those by Eure et al, (2019), Albers et al, (2022) and Maffei et al, (2023), as no confirmatory biopsy was performed using microUS as guide. In the ERUP trial, the assessment of disease progression was undertaken purely by evaluating changes within an image. However, for experienced sonographers, whose primary training and role is to interpret and report from ultrasound imaging, this assessment by the reviewers is within their agreed scope of practice (BMUS & SCOR, 2023). I anticipated this to be relatively easy to incorporate into practice, and, as such, it was felt that confirmatory invasive biopsy was not indicated for inclusion in the study design. As discussed previously, there is a lack of consistency in how patients are managed locally under AS, with few patients being referred for confirmatory biopsy at 12 months, despite NICE (2021) guidance. Given this inconsistency in management, an invasive TP biopsy was not included within the study protocol despite the fact this would have provided histological comparison against the images acquired during the monitoring period. However, whilst there is no histological confirmation of a lack of disease progression in most of the phase 2 cohort, where biopsy was performed, this was consistent with the image review results. Ultimately, a pragmatic approach to local pathways and clinical management plans for this cohort of patients was adopted and biopsy only performed on the request of the clinician managing the patient.

8.7 Conclusion

The role of mpUS within AS remains unanswered. Results of study 1, phases 1 and 2 have indicated that standard ultrasound, even with the addition of colour Doppler is too unreliable to be a predictor of the presence of disease and cannot be used to effectively monitor disease progression. These results of study 1, phase 2 have indicated, that within local practice and this cohort of patient, the appearances of the prostate on microUS are too varied to be confident to make a diagnosis. As such, the second measurable objective (Chapter 5.4.1) cannot be answered. There is no evidence to suggest microUS doesn't work within this AS pathway, but in the current climate, in terms of clinical pressures for faster diagnosis and managing the waiting list backlog for elective care, it is difficult to advocate its continued use.

Within the context of this PhD, there was insufficient confidence in this technique to enable study 1, phase 2 to continue. Whilst the role of microUS may not be implemented in AS, developments within the prostate pathway, as a concomitant result of the PhD process, have resulted in significant improvements in patient care and service delivery. These outcomes will be discussed later in Chapter 11.

The second phase of the ERUP trial was presented in this chapter. Despite the reasonable specificity identified in study 1, phase 1, reviewers found the appearances of the prostate to be too varied to be confident in its use for AS. In the next chapter, the feelings of practitioners regarding the use of microUS is explored, and the process of normalisation of new technologies into real-life practice is evaluated.

Chapter 9 Study 2 methods, results and discussion

The previous two chapters presented the results of the clinical components of Study 1: phases 1 and 2 of the ERUP trial. This chapter presents the participants, the data collection method used, and the NPT tools utilised for Study 2. The results of this longitudinal study are presented, and their relevance in relation to the role of ultrasound in the active surveillance of prostate cancer are discussed.

9.1 Study 2 – Introduction

My research into the role of ultrasound in prostate cancer not only included the clinical evaluation of diagnostic imaging, but also considered the professionals who were key to delivering this service and to decisions about the presence or absence of disease. As identified in Chapter 4 (Parker et al., 2023), sonographers are eminently suitable professionals to embed change in this pathway. How they, and their medical consultant colleagues, adapt to, and adopt, new technologies, is crucial if change is to be successful (Gillespie et al., 2018). In this third phase, I asked the question:

> "How successfully could new technology be embedded into real-life clinical practice?"

Normalisation process theory (NPT) informed the study of factors affecting implementation and assessed the success of integrating technology into clinical practice.

9.2 Normalisation Process Theory

In Chapter 5, I explored different methods that could be used to facilitate an understanding of these challenges and how likely this new technology could be embedded into real-life clinical practice (Gillespie et al., 2018). Normalisation process theory (NPT), developed by May and Finch (2009), provides a framework that can be used to understand how practitioners have perceived, and adapted to, the introduction of microUS in the setting of prostate cancer assessment. NPT was selected as a tool to assess implementation primarily as it provides a framework for analysis that delivers a gain in knowledge about the process incrementally throughout the study (De Brún et al., 2016). NPT is grounded in the empirical studies about implementation from authors such as May et al (2009; 2011; 2016; 2018), Finch et al (2015) and McEvoy et al (2019), which have shown NPT to be a useful framework to

enhance the understanding of how, or if, new interventions are embedded into clinical practice. Gillespie et al (2018) found NPT to be a reliable and effective way of identifying how a new technology impacts on how people work but does not intervene or interfere with interventions as they are being developed in clinical use.

Using the NPT constructs, information is gathered from participants around three main issues which interrogate the relational integration of this new intervention - a second aspect of NPT as described by May et al (2009). The three main issues that I set out to investigate were:

- Could microUS be accepted by practitioners and clinicians as a novel intervention within the AS pathway?
- Did practitioners have confidence in their knowledge and skills of micro-US?
- Was there sufficient time and resources to implement novel intervention within the AS pathway?

May et al (ibid.) identified two dimensions of confidence and accountability which define the practice and knowledge of the new intervention under scrutiny; an understanding of these dimensions will assist me in addressing the issues I identified here in this thesis. May et al (ibid.) recognised that confidence relates to the credibility of the new intervention; how well it is understood and how well it is agreed within the team. The dimension of accountability includes validating the knowledge associated with the new intervention and understanding the degree of expertise required of the practitioner delivering the new intervention (Gillespie et al., 2018). NPT provides an optimum model to explore and evaluate these three issues, and the implementation of novel ultrasound techniques, in a complex and commonly emotive cancer pathway (Shah et al., 2021).

9.2.1 NPT Constructs and tools

As I describe in Chapter 5.14.5, NPT has four constructs used to provide the understanding of normalisation. These constructs are coherence, cognitive participation, collective action, and reflexive monitoring, and as May et al (2015) describe, represent the different kinds of work involved with implementing a new intervention or practice. These are then further broken down into sub-constructs from which responses are sought, and these are described in Chapter 5 (Table 5.1).

Finch et al (2018) recognised that the practical utility of NPT needed to be extended to improve implementation success and, as such, devised and validated an instrument for assessing interventions. A **No**rmalistion **M**e**A**sure **D**evelopment questionnaire (NoMAD) was created to provide a structured assessment of activity related to implementation and normalisation (Finch et al., 2015). The questionnaire is a set of 23 survey items devised around the four constructs of NPT. This questionnaire led to a 16-statement interactive toolkit (May et al., 2015), validated in study undertaken by Finch et al (2018), and consequently demonstrated the NoMAD tool provides consistency in the assessment of normalisation. The NoMAD tool has been used in many other studies, such as one by Gillespie et al. (2018) evaluating the implementation of a complex surgical safety checklist, and one by Hindi et al (2023) who used NPT to understand the implementation of pharmacy technician training. This ERUP trial is, however, the first known use of NPT in the normalisation process of an ultrasound intervention.

Using the ERUP NoMAD instrument enabled me to understand if the new technology made sense to participants, and to assess if their perceptions changed over time (May et al., 2015). Data was collected from participants using the NoMAD instrument longitudinally, with collection points spaced over time during the Study 1, phase 1 and phase 2 image data collection and review periods, as advocated by May et al (2015) and Lamarche et al (2022). An adaptable framework for evaluating the implementation of new interventions and technologies is provided by NPT and therefore, as discussed by Huddlestone et al (2020), was the ideal tool to provide the understanding of the role of ultrasound in the prostate pathway that was required in the ERUP trial.

9.3 The intervention in question

In Chapters 7 and 8, I reported the reliability and attributes of multiparametric ultrasound. This included standard B-mode, colour Doppler and microUS imaging. Standard ultrasound and colour Doppler are not new technologies; indeed, they have been in clinical use for over 60 years (Campbell, 2013). However, in this ERUP trial they have been employed in a different manner in assessing the prostate gland. Therefore, whilst the reasons for using this tried and tested imaging modality were new, investigating how well standard and Doppler ultrasound were perceived or normalised was unnecessary due to its ubiquitous use by sonographers. In contrast, microUS is

novel and its imaging parameters are very different to even the most modern standard ultrasound transducer. As discussed in Chapter 5.6.4, the microUS system creates an image of great detail. It is this increased resolution and differing representation of anatomy which is the new intervention and raised the need for a new interpretation of the ultrasound image by practitioners. The high resolution required a revision of the appearances of normality for practitioners when interpreting the ultrasound images and a consequent understanding of what the displayed image actually means. For microUS to become normalised, there was a requirement for the appearances of the prostate to be interpreted and understood with confidence. This would then support the embedding of this new intervention into practice, and for the findings of microUS to be a valued part of the prostate cancer pathway.

9.4 Clinical Setting

MicroUS is a novel technology in the field of urology and, despite it being promoted within prominent publications and conferences (Klotz et al., 2021; Dias et al., 2022; Ghai et al., 2022), it is new to clinical teams and pathways in the UK. Having received funding to purchase the microUS machine, an implementation process was required and, as such, the relevant practitioners within the team were included (Gillespie et al., 2018). The clinical team of sonographers and radiologists were included as they brought the expertise and experience in prostate imaging and had previous experience of developing new ultrasound practices without apparent implementation issues. Relevant urologists were invited as they are responsible for patient care in this pathway. I led the implementation process as lead researcher and service lead and was supported by the lead consultant urologist who was also my clinical supervisor.

9.5 Methods - Sample and setting

The practitioners undertaking, interpreting, and making patient management decisions based on imaging findings are critical in any diagnostic pathway. Indeed, imaging practitioners can support the best use of resources by championing appropriate tests and reducing unnecessary examinations (Porembka et al., 2021). As such, their views and perception of new technologies is invaluable if new imaging is to be embedded into practice. Inclusion as a participant in to study 2 required current and practical experience of prostate cancer imaging, diagnosis and / or treatment.

9.5.1 Inclusion criteria for study 2

The inclusion criteria for participation in this phase of the study were as follows:

- Health care practitioner working as a urologist, radiologist or sonographer and employed within radiology of Hull University Teaching Hospitals NHS Trust
- Hold a recognised qualification awarded by the Royal College of Radiologists, the Royal College of Surgeons, or a recognised post graduate ultrasound qualification undertaken at a Consortium of Sonographic Education (CASE) approved higher education institute.
- Participates in the current radiology prostate cancer assessment care pathway.
- Able to provide informed consent to the study.

9.5.2 Exclusion criteria

The exclusion criteria used for this study were as follows:

- Health care practitioners not employed in Hull University Teaching Hospitals NHS Trust
- Sonographers, radiologists, or urologists not directly participating in the current radiology prostate cancer assessment care pathway.
- Sonographers, radiologists, or urologists who do not hold relevant qualifications listed within the inclusion criteria.
- Sonographers, radiologists, or urologists who do not consent to participate in the study.

9.5.3 Lead researcher considerations

In addition to being the lead researcher, I also had a key role in the small clinical team and integral in ensuring NHS service delivery can be maintained, as well as the role of clinical lead sonographer for the ultrasound service within the NHS Trust. This conflict between researcher and team member was acknowledged and was managed by open communication, and by ensuring eligible participants clearly understood that they had the option to withdraw consent to participate at any time with no adverse effects.

There were two dimensions to consider related to my position as both researcher and team leader. As leader, there was a chance that staff might not be open about their feelings about, and adoption of microUS, particularly as they may perceive that I had a desire for positive outcomes to my research (Greene, 2014). The Hawthorne effect, which was first identified during a series of observational studies at the Hawthorne, Illinois, plant of the Western Electric Company between 1927 and 1932, (McCambridge et al., 2014; Tulchinsky & Varavikova, 2014) recognises that practitioners, for example,

behave differently because they know they are being observed. This effect had to be considered and I had to facilitate unobserved independent practice using the new technology so that practitioners could make their own, independent assessment.

In addition, as Fleming (2018) acknowledges, there may have been a potential for implicit coercion to participate as team members felt duty bound to be involved. However, as an 'insider' I could understand and empathise with the team and how they encountered challenges in implementing the new technology. (ibid.). A further benefit of being an insider researcher, which Greene (2014) discusses, was the knowledge of the clinical context that I possessed due to my lead practitioner role; although this was countered by the risk of bias I may have inadvertently projected due to the value I placed on the research in this pathway. Objectivity in the research process was required despite being a team member providing additional value and benefit. The established interaction and relationships I had with the team, and, importantly, the access I had to the team was a significant benefit of being an insider researcher (Greene, 2014); although this access could also be seen as a disadvantage due to the risks of coercion. Due consideration was given to this conflict as the results were analysed and is discussed later in this chapter.

9.5.4 Study tool and data collection

The published NoMAD (Finch et al., 2015) was modified to reflect that the intervention under investigation was that of microUS, (Appendix 10, page XXV). Revision of the original NPT tool is allowed and encouraged by the original authors (Finch et al., 2018) to ensure it best fits individual studies, and to provide clarity to participants as to what aspect of the imaging pathway they were being asked to reflect upon. The revisions made in this study were checked for clarity by the academic supervisory team. Comparison was made across all four NPT constructs in the NoMAD tool by using a five-point Likert scale to indicate level of agreement: strongly agree, agree, neutral, disagree, and strongly disagree. The three general questions about the intervention from the NoMAD were rated using a response scale of 0–10 where: 0 = not at all, 5 = somewhat and 10 = completely (Finch et al., 2015).

9.5.5 Baseline NPT Questionnaire – T1

Recruitment for study 2 of the ERUP trial commenced in January 2022, prior to the commencement of the first phase of study 1 of the ERUP trial. The flow chart below (Figure 9.1) outlines the key timeline of the study 2 recruitment and data collection. All practitioners who met the study 2 inclusion criteria were approached via email and given a participant information leaflet (Appendix 11, page XXXI) outlining the purpose of the study and the method of data collection. Each potential participant was asked to respond within 14 days to the email if interested in being recruited into the study. A follow-up email was sent asking for response within seven days and acknowledged that if no response, it would be assumed the practitioner declined the invitation. Once a response was received, consent forms were distributed (Appendix 12, page XXXV) and a verbal approach made to all eligible members of the team. It was explained to the team that participation was voluntary. Upon receipt of a signed consent form, (Appendix 12, page XXXV), the ERUP NoMAD questionnaires (Appendix 10, page XXV) were distributed in both paper and electronic forms to the relevant practitioners. Responses were requested within 14 days of receipt of the forms so that a baseline assessment (T1) could be made prior to the trial starting.

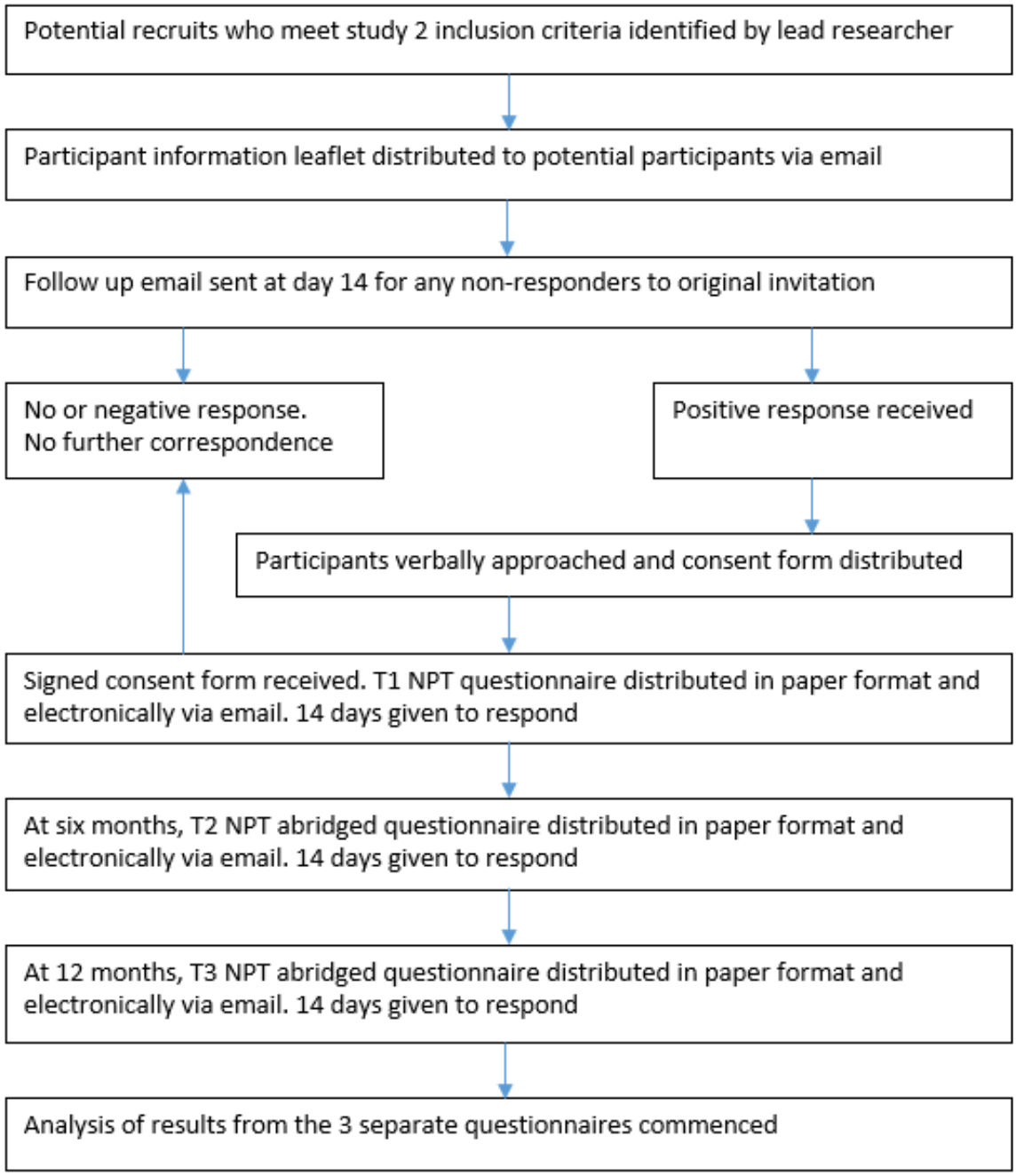

Figure 9.1 Flow chart outlining the key timeline of recruitment and data collection points in study 2

9.5.6 Interim NPT Questionnaire – T2

A shortened version of the ERUP NoMAD questionnaire, aligned with all four NPT constructs, was circulated with the purpose of recording practitioners' perceptions to microUS prior to the inter-reviewer agreement results of study 1, phase 1 of the ERUP trial being available. This shortened version of the questionnaire (Appendix 13, page XXXVI) was used to minimise time impact for practitioners who were all fully clinically committed in their substantive posts, and all participating in reviewing the phase 1 images. At the time of the mid-point (T2) questionnaire, approximately 90 patients had been recruited and images reviewed as per the trial protocol, but results had not been circulated.

The questions were chosen to gain as much insight into potential gaps in knowledge, training, or support that the team may have that could have potentially hindered implementation. From the coherence construct, the question related to the value, benefit, and importance of microUS was chosen. A negative score could have indicated that participants had insufficient understanding of the purpose of microUS, and more information could be provided. The question from the cognitive participation construct was chosen to understand whether practitioners remained willing to be involved with microUS with a view to identify if any participants had felt coerced to be involved and wanted to withdraw. To understand if the correct level of training had been provided, the question specifically asking this was chosen from the collective action construct. Finally, a question to determine if the introduction of microUS was having a negative impact on the team was chosen.

9.5.7 Final NPT Questionnaire – T3

At 12 months from the commencement of study 2, the results of the study 1, phase 1 reviews had been shared with the team. To better understand the views of the practitioners involved at the end of the phase 1 data collection period, the full ERUP NoMAD tool was re-circulated to all who had consented to their involvement (T3). The purpose of this final data collection was to achieve an understanding of practitioners' feelings and commitment to the use of microUS following their greater exposure to this intervention. Data collection was completed in April 2023.

9.5.8 Data analysis

Responses from the baseline (T1), interim (T2), and follow-up (T3) ERUP NoMAD questionnaires were collated on a password protected database. All participants were anonymised and given a unique trial identification number. A comparison of the five-point Likert scale responses provided at the three data collection points was made. Initially, radar plots comparing response from the three separate questionnaires were produced. Radar plots are used primarily to visually display the strengths and weakness of different components within multivariate data. As Saary (2008) explains, radar plots not only provide detail for each construct, they also provide a sense of the data. Radar plots are used here to demonstrate the spread of the variables across the NPT constructs.

As discussed by Gillespie et al (2018), it is noted that one item within the collective action construct (C3.2 - microUS disrupts working relationships) required a reversed scored due to its negative connotation.

9.6 Results

Five sonographers, two consultant radiologists and three consultant urologists with special interest in prostate intervention met the inclusion criteria and were invited to participate. Responses were received from the five sonographers and two radiologists. One of the consultant urologists returned a signed consent form but incomplete questionnaire so was excluded from the study. No responses were received from the two other consultant urologists, and they were also excluded. Recruitment, completion, and inclusion in outlined in Figure 9.2 below.

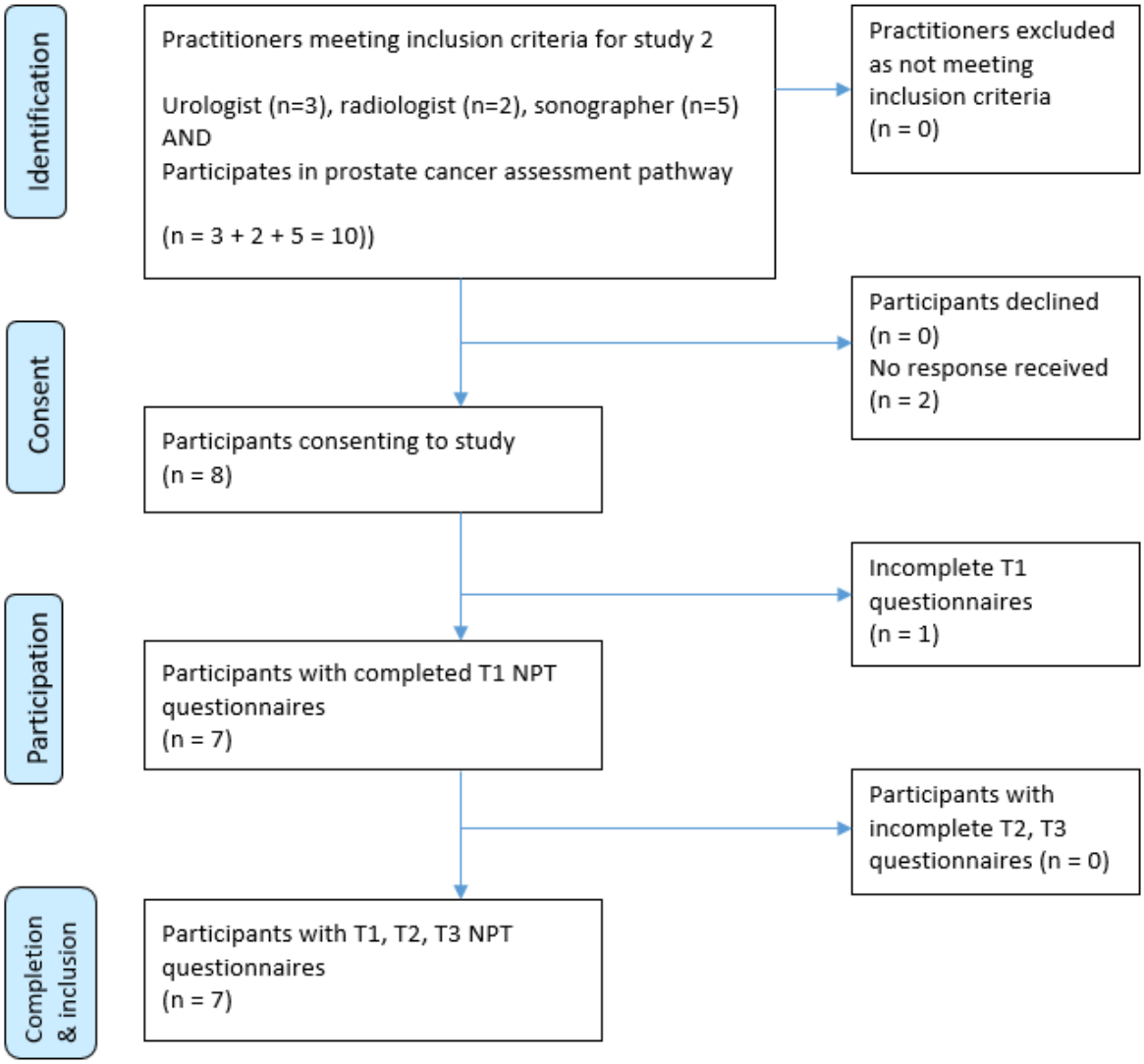

Figure 9.2 Recruitment of participants into study 2

In total, seven practitioners were included in the study 2 study cohort. The length of experience in imaging of the prostate in any profession ranged from three to over ten years. Demographics of the study cohort is outlined in Table 9.1.

Table 9.1 Study 2 participant demographics

Professional Background	**Experience**		
	3 – 5 years (numbers in group)	5 – 10 years (numbers in group)	10+ years (numbers in group)
Sonographer	2	2	1
Consultant Radiologist	0	1	1

The initial question asked participants about their involvement with microUS (Table 9.2). At baseline, no respondent indicated that they were managing microUS and is a reflection that this technology had yet to be introduced. Responses related to performance and interpretation were predominantly unchanged over the duration of the survey with sonographers indicating they were involved with performing microUS and radiologists interpreting this at both T1 and T3.

Table 9.2 Main role of participants with microUS

Main role with microUS	**T1 - baseline (numbers in group)**	**T3 – 12 months (numbers in group)**
I am, or will be, involved in managing micro-US in prostate assessment	0	1
I am, or will be, involved in performing micro-US and prostate imaging	5	4
I am, or will be, involved in the interpretation of micro-US as radiologist or at MDT	2	2

The range of current tasks undertaken within the prostate imaging and biopsy service was explored in question three and responses detailed in Table 9.3. The majority of participants indicated that they only used ultrasound to identify the prostate to guide biopsy either with or without MRI fusion imaging at the baseline, but the majority indicated their role had changed to identify target lesions suitable for biopsy but did not provide comment on this at the time of the T3 questionnaire. This reflects the overall change of role of the sonographers throughout the period of the study.

Table 9.3 Participants main tasks within the prostate imaging and biopsy service

Main task within prostate imaging and biopsy	**T1 - baseline (numbers in group)**	**T3 – 12 months (numbers in group)**
I provide a diagnostic interpretation of the prostate in my reports	1	1
I identify target lesions suitable for biopsy but do not provide comment on this in my report	1	4
I only use ultrasound to identify the prostate to guide biopsy either with or without MRI fusion imaging	4	2
I currently do not perform any transrectal ultrasound in my clinical practice	1	0

There was very little indication of prior experience of microUS at T1, with only 3 participants having had some hands-on training and the remaining either having undertaken the core online training or only viewed images, as detailed in Table 9.4. However, at the time of the T3 questionnaire despite the technology being in use within the department for 12 months, the reported experience of microUS had only marginally increased with one additional participant reporting hands on training and only one using it in a trial basis and learning to interpret images.

Table 9.4 Participants' experiences of microUS

Experience of microUS	**T1 - baseline (numbers in group)**	**T3 – 12 months (numbers in group)**
I am regularly using this technology in my everyday practice and am confident in its use and interpretation of the images produced	0	0
Yes – I am using it on a trial basis and am learning to interpret images produced	0	1
I have undertaken the online core training modules and hands on training but have limited experience in clinical practice	3	4
I have undertaken the online core training modules only	1	0
I have seen some images but have not undertaken any specific training or procedures	1	2
I have very limited or no experience of micro-ultrasound to date	2	0

Part B of the NoMAD questionnaire is three broad questions investigating how participants feel about microUS. The pooled responses are detailed in Table 9.5 below.

Table 9.5 NPT Part B - Participants feelings of microUS

B1	When you use or interpret micro-ultrasound how familiar does it feel?		T1	T3
Scale 1 - 10 (1 very unfamiliar – 10 very familiar)		Range	**1 - 3**	**2 - 6**
		Mean	**2**	**4**
		Median	**2**	**3**
		Mode	**3**	**3**

B2	Do you feel the use or interpretation of micro-ultrasound **is currently** a normal part of your work?		T1	T3
Scale 1 - 10 (1 very abnormal – 10 very normal)		Range	**1 - 1**	**3 - 7**
		Mean	**1**	**4**
		Median	**1**	**3**
		Mode	**1**	**3**
B3	Do you feel the use or interpretation of micro-ultrasound **will become** a normal part of your work?		T1	T3
Scale 1 - 10 (1 very abnormal – 10 very normal)		Range	**1 - 8**	**2 - 7**
		Mean	**5**	**5**
		Median	**5**	**6**
		Mode	**5**	**6**

At T1 none of the participants reported being familiar with microUS, and it was not part of their current practice. At 12 months (T3) the majority still felt it was not part of their normal practice, with the minority (n=2) feeling it was in regular use. Most participants felt microUS would become normal practice in the future, although views were notably varied (Table 9.5 B3).

Section C of the T1 & T3 ERUP NoMAD questionnaire interrogates the four NPT constructs using the 20 NPT questions. The NPT online tool labels the four constructs as follows:

NPT Construct	**NPT Online tool**	**NoMAD questions**
• Coherence	Sense-making	C1.1 – C1.4
• Cognitive participation	Participation	C2.1 – C2.4
• Collective action	Action	C3.1 – C3.7
• Reflexive monitoring	Monitoring	C4.1 – C4.5

A radar plot was compiled to visually compare the baseline, interim, and follow-up responses and presented in Figure 9.3 below.

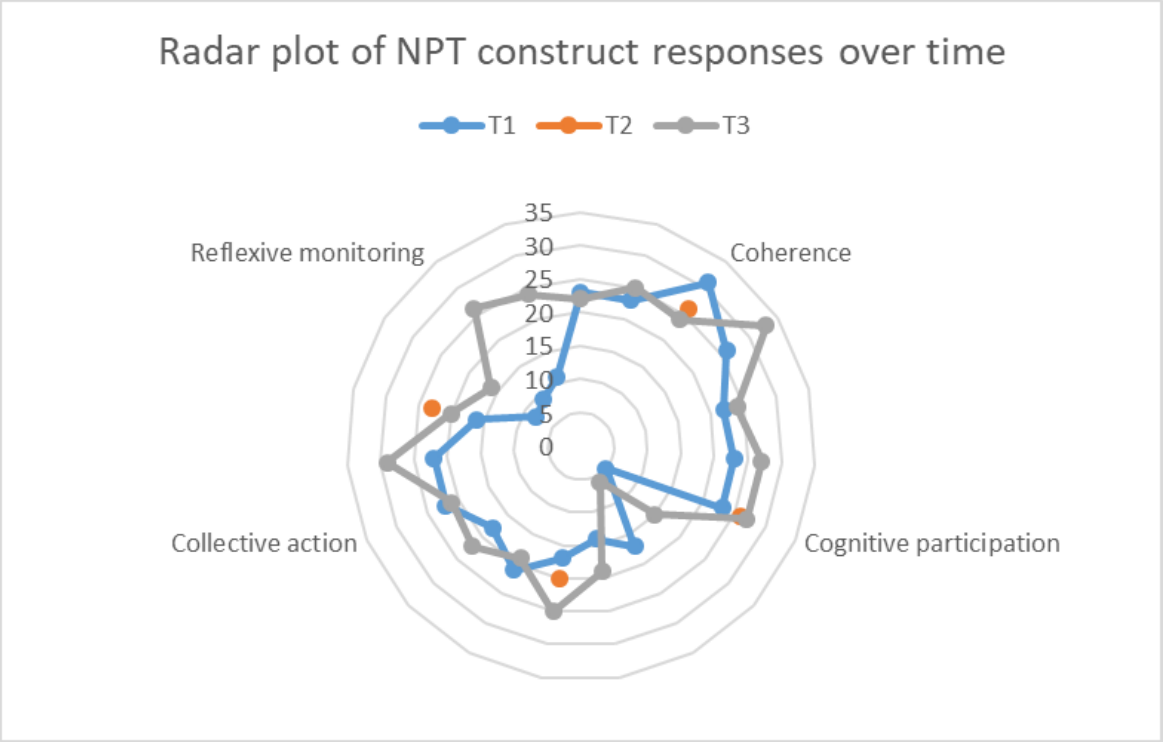

Figure 9.3 Radar plot of NPT constructs for T1, T2, and T3. Scores range 0 - 35

The T1 radar plot indicates that there was a reasonable understanding of, and willingness to participate in, microUS. A reasonable understanding and willingness to participate is demonstrated in the radar plot (Figure 9.3), and an increase in positive responses to microUS' long-term use is demonstrated at T2. The T3 questionnaire elicits a very different pattern of responses. There is a clear understanding of what microUS is and the team have identified that there is a key driver of this intervention. However, there is a marked reduction in the teams' collective action towards, or sense of value of, microUS by the time of the follow-up questionnaire.

Collated results of the ERUP NoMAD are outlined under each construct and sub-construct in Table 9.6 below

Table 9.6 Results of ERUP NoMAD: construct and sub-construct

Construct **Coherence**			
Differentiation Whilst most (n=5) identified that microUS was different at T1, all (n = 7) differentiated microUS from usual practice by T3	**Communal specification** At T1 most (n = 5) understood the purpose of microUS but at T3, that was reduced with fewer agreeing (n = 4)	**Individual specification** At T1 some (n = 4) understood what microUS meant for their role but at T3, that was unchanged despite 12 months experience	**Internalisation** At T1 the majority (n = 6) could see the value of microUS, and this was unchanged at T2, but, at T3, this had reduced with only 5 seeing the potential value
Cognitive participation			
Enrolment The majority (n = 6) identified that there are key people driving microUS at TI with all feeling this way at T3	**Legitimation** At T1 some (n = 4) felt microUS to be a legitimate part of their role, but this had reduced by T3 with only a few (n = 2) agreeing to this	**Initiation** Most (n = 5) were open to working with colleagues in new ways to support the use of microUS at both T1 and T3	**Activation** Despite the responses which indicated that microUS was not a legitimate part of their role at T3, support for this was unchanged between T & T3 with most agreeing (n = 5)
Collective action			
Interactional workability MicroUS was not seen to be easy to integrate into existing clinical work at either T1 or T3 with none agreeing this initially and only 1 at 12 months. The majority felt it would be difficult to integrate at T3 and after 12 months experience	**Relational integration** MicroUS was not seen to disrupt working relationships with some (n = 4) agreeing that it didn't. There was no confidence in other's skills at T1 or T2 but at T3, there was marginally improved confidence (n = 2) in the ability of the team	**Skill set workability** At T1 some (n = 4) felt that there was sufficient training and resources available to implement microUS, but this had reduced (n = 1) by T3 and after 12 months use of microUS	**Contextual integration** MicroUS was felt to be supported by management at T1 with some agreeing (n = 4) but this feeling of support had reduced to just two respondents agreeing by T3
Reflexive monitoring			
Systemisation Some (n = 4) were aware of published reports of microUS at T1 but by T3, all (n = 7) were aware of publications and able to make judgements based on others experience	**Individual appraisal** There was little agreement that the effectiveness and value of microUS could be identified or judged by individuals at either T1 (n= 1) or T3 (n = 3)	**Communal appraisal** Initially, some (n = 4) felt that the team thought that microUS was worthwhile. This feeling was reduced at T2 (N = 3) and at T3 (n = 3)	**Reconfiguration** At T1 few (n = 2) felt that they would be able to modify practice in response to microUS but, by T3, most (n = 5) felt that they could modify how they work with microUS

Analysis of findings from the responses to the ERUP NoMAD questionnaire is provided, under headings of the four constructs, below.

9.7 Questionnaire analysis

9.7.1 Coherence (Sense making)

At T1, the radar plot (Figure 9.3) demonstrates that practitioners could distinguish the new intervention from current practice, and that they had some agreement about the use of microUS. From the ERUP NoMAD survey data, a good agreement (n = 6) by all participants to understanding the potential value of this technology in their work was identified. Whilst there was a clear positive response to the respondents understanding of how microUS differs from usual practice (n = 5), and an appreciation of its purpose (n =5) at T1, the results demonstrate that respondents did not change what they thought microUS meant for their role despite greater experience in this technique over the 12 months. The understanding of the purpose and value of microUS reduced between the T1 and T3 questionnaires despite this not being indicated at the interim, T2, data collection point. However, by T3, all respondents could see how microUS differed from usual ways of working despite them not valuing this as a test as much as they had done at the start.

Overall, there is indication that the team could make sense of microUS and the rationale for its use even if its purpose in the pathway was questioned following increased experience of its use.

9.7.2 Cognitive participation (Participation)

The second NPT construct evaluates the relational work that participants do to sustain a new intervention. The T1 radar plot (Figure 9.3) demonstrates that, overall participants bought into the idea of microUS as a new intervention, that they felt this should become part of their work, and that they supported the intervention. This was mirrored at the T2 review but had diminished by the time of the T3 questionnaire. All respondents (n = 7) recognised there were key people who drove micro-US forward and, at T1, some (n = 4) felt participating in micro-US was a legitimate part of their role. However, this had reduced to only two respondents by T3, despite the additional 12 months experience. Regardless of this feeling, support for microUS remained high with most (n = 5) stating they supported this new technology at T1 and T3.

Despite the small cohort, respondents had a reduction in cognitive participation between T1 and T3, and the NoMAD responses provide a sense that the team felt less personally invested in microUS as the study progressed. However, all respondents continued to feel there was an individual leading this implementation and most (n = 5) remained in support of the new technology.

9.7.3 Collective Action (Action)

The collective action NPT construct is the largest of the four with seven items providing data related to how participants enacted the new practice determined by the new intervention. It looks at how the intervention affected the work of the participants and how compatible this work was with existing practices.

At T1, most of the respondents (n=5) felt that microUS was not relevant to their role and could not see how they could integrate micro-US into their existing work. Additionally, at T1, none of respondents felt that it would be easy to integrate microUS into their clinical practice. This lack of confidence persisted throughout the study with only one respondent identifying how they could use the technology at T3. Furthermore, there was no indication from respondents that they had confidence in other people's ability to use micro-US at T1 and this only marginally increased to two respondents feeling they had confidence in their team by T3.

By the end of the study, participants were less likely to feel that microUS disrupted working relationships and instead reported that they were more open to working together with colleagues to implement changes. Most respondents (n = 6) at T3 felt that microUS was assigned within the team to those who had appropriate skills, whilst at the same time there was a reduced feeling that there were sufficient training and interpretation resources available when compared to T1. At T1, 5 respondents felt that there were sufficient resources available to, but this had reduced to only two at the end of the study. Likewise, the feeling that microUS was supported by managers had also diminished from four to just two respondents agreeing support was there by T3.

Overall, as the radar plots (Figure 9.3) shows, participant's collective action towards the implementation of microUS declined.

9.7.4 Reflexive monitoring

New interventions are more likely to be successfully implemented if the users perceived them to be advantageous and the effects on patient pathways and care is clear (Tazzyman et al., 2017). This NPT construct evaluated participants' opinions about how microUS impacted on patient care and how they perceived this new technology. As demonstrated in the T3 radar plot (Figure 9.3), respondents disagreed about the value of microUS and the effect it had on their role.

However, when looking at the responses to the questionnaire over time (Table 9.6), it is evident that there was more engagement with the technology at the T3 that at T1. All respondents were aware of published reports of microUS at T3 and this in alignment with the increased understanding of how microUS differs from usual practice as demonstrated in the coherence construct.

At T1, most respondents (n=6) did not feel that microUS was relevant to their role, but this had increased by T3 with three respondents agreeing it was now relevant. However, despite this increase in a feeling of relevance, there was a reduction in the feeling that microUS was worthwhile between T1 (n = 4) and T2 (n =3), and T3 where the feeling of worth remained low (n = 3). Initially, at T1 only a few (n = 2) respondents felt they would be able to modify their practice in response to microUS, but this had increased to most (n = 5) by T3.

Data from this construct demonstrates that respondents had a greater awareness of microUS, and that they received feedback which enabled them to modify and change practice. However, this is coupled with a reduced feeling that microUS was worthwhile and reflects the outcomes of the collective action construct where there was an overall sense that microUS was not easy to integrate into practice. Only two of the seven respondents felt that microUS was valuable in their role, which may have influenced the ability to embed this new technology into clinical practice.

9.8 Team engagement

The use of NPT and a questionnaire had benefits as it allowed participants to respond anonymously and, it was anticipated, provide responses candidly without pressure from peers or from me as an insider researcher (Greene, 2014). However, one of the benefits of being an insider researcher was the empathy I had with the team regarding

the challenges of introducing microUS. A reduction in the feeling of potential value and worth of microUS was identified during the T2 interim survey (Reflexive monitoring construct, Table 9.6) and this triggered a need for further enquiry.

9.8.1 MicroUS in clinical practice

In addition to the research data collected, my understanding of normalisation and acceptance has inevitably been shaped by my experience working with the team in my professional capacity. In particular, discussions with team members and my consultant medical colleagues, as an aspect of my clinical lead role, related to our progress with microUS and how the team were dealing with this is in everyday practice. This everyday practice included its use to guide transperineal biopsy in patients out-with the ERUP trial. The team frequently talked about the challenges we were all experiencing related to interpretation and biopsy technique, and about the changes to their practice and confidence. Whilst not formal data collection, these discussions were insightful. The NPT aspect of this research did not include staff interviews due to practical and capacity limitations but the awareness I gained through discussions with my team helped inform the analysis of the study 2 data.

9.8.2 NPT Constructs and team feedback

9.8.2.1 Coherence

Coherence of microUS was evident from the NPT results with all colleagues agreeing that it differed from usual practice. The team engagement provided an opportunity to discuss the difference in resolution that microUS provides. A main discussion point related to the structures that appear to be displayed on the microUS system but at a level that the team felt was unlike any normal ultrasound image they were used to. Overall, there was a sense from the team that the images could not be easily interpreted and, as demonstrated in study 1, phase 2, my colleagues felt there was a lack of consistency between patients. The level of anatomical detail displayed by microUS is unique in prostate imaging but colleagues felt it difficult to interpret as they felt there was a great deal of overlap between the US images and the PRI-MUS™ grade descriptors (Appendix 14 and 15, pages XXXVIII and XL). Overall, the team felt that the appearance of many prostates they had scanned with microUS could correlate with a range of PRI-MUS™ scores, particularly those that were not obviously PRI-MUS™ 1, described Ghai et al (2016) as “Swiss cheese”.

Whilst it could be anticipated that increased detail would lead to higher fidelity for this new imaging, overall colleagues appeared to have a lack of confidence in their interpretation, mainly due to the difficulty in being able to assuredly assign an US real-life prostate appearance to the published criteria (ibid.). This correlates with the NPT response (9.7.3) that identified additional training and interpretation resources were required.

9.8.2.2 Cognitive participation

A concern that I had identified before study 2 commenced was the conflict that may occur between me as researcher and me as clinical team lead. The responses related to the cognitive participation construct indicate that this conflict was also evident within the team, and a desire to support the research may have influenced responses. There was a general feeling of support from all colleagues, as is indicated in the NoMAD results (9.7.2) and this emerged from the team discussions. All my colleagues stated they wanted to support me in my research, provided I was available to work with them when microUS was used, or at least be available to review images. However, this raised concerns that their efforts to adapt to the new technology were made to support me, rather than because of genuine confidence in the technology. This implies that my closeness to the team compelled them to try and use the technology more than they may otherwise have done. It also highlights that NPT findings of this study may not be generalisable to other service providers.

Conversely, there was discussion from most of the team about the benefits to patients that microUS may provide, particularly for those in whom MRI was difficult or contraindicated. Overall, there was a sense from the team that microUS was worth progressing with if this led to benefits to patients and indicates a dichotomy about choosing a new intervention because it is perceived to be better for patients and rejecting a new treatment because of a lack of confidence in it or its use. This research has indicated that both exist and have yet to be reconciled.

9.8.2.3 Collective action

Related to both the cognitive participation and collection action constructs is a theme of teamwork, which is evidenced in the NoMAD data. Unanimously, the team felt they were working together to overcome the technical and interpretative challenges of microUS. A theme from the team discussions was one of shared learning and

togetherness as all were grappling with the new technology and supporting my research goal.

This sense of teamwork is a positive finding from within an emotionally taxing cancer pathway. The context of the patient population under investigation by this technology may add to the teams' desire to work together to improve diagnostic outcomes, and influence the NoMAD responses, even though they verbalised concerns about the use of this system to guide biopsies.

9.8.2.4 Reflexive Monitoring

The team engagement highlighted concerns from colleagues about what was being asked of them in terms of diagnostic decisions due to the prescribed PRI-MUS™ grading associated with microUS, and in terms of the need to use the system for guided biopsy of high-risk areas. The role of the sonographer in this new technique was advocated in the review performed in Chapter 4 (Parker et al., 2023), but the additional responsibility of the need to make a diagnostic decision cannot be underestimated. My colleagues discussed how using microUS brought an added level of responsibility not usually experienced within the prostate pathway scope of practice. My professional observation was that these concerns indicated a feeling of insecurity, which I also encountered in my own practice, and this may well have influenced the implementation process.

9.9 Discussion

This chapter presents findings from the second study of the ERUP trial, designed to evaluate how successfully new technology could be implemented into practice. Using NPT has provided the tool to enable an understanding of this question within this proof-of-concept study. By utilising the ERUP NoMAD instrument as an NPT questionnaire, an insight into how participants, as individuals and as a collective, attempted to embed microUS into their practice has been gleaned. In this section, I discuss the conflict of my role as an insider researcher, the use of NPT, and the strengths and limitations of study 2 of the ERUP trial.

9.9.1 The use of NPT and the proof-of-concept study

A systematic review by May et al (2018) identified that NPT had been employed in 108 identifiable studies; of these, five were feasibility studies. One purpose of NPT is to

provide a conceptual tool to gather an insight about the changes that need to be made in practice to enable implementation (McCrorie et al., 2019). Changing clinical practice can be challenging, and a degree of behavioural change by practitioners is advantageous for success. Connell et al, (2019) discuss how behaviour can be modified to aid implementation of change by understanding mechanisms related to behaviour change techniques (BCT's). BCT's may have been helpful in this study, particularly to support the more experienced or less engaged practitioners move away from their entrenched positions related to the use of ultrasound. However, this strategy would not have provided the wider understanding of the role of microUS, whereas NPT has been a useful framework. NPT has facilitated a review of the purpose of microUS and how best to engage with practitioners to support its use.

The NoMAD-informed qualitative data results are aligned with the sensitivity and specificity data that were identified in study 1, phase 1, and lack of clinical confidence in microUS identified in study 1, phase 2. The ERUP NoMAD data reflects the quantitative data of study 1; microUS in this study did not confidently identify areas of abnormality within the prostate. This likely reduces confidence in the technology, leading to the reluctance to find this a valuable or legitimate part of the practitioners' role. Using NPT in this proof-of-concept study identified that practitioners found microUS was not easy to integrate into practice and support was lacking. Identifying these significant issues early on, prior to microUS being fully implemented within a patient pathway, has been a benefit of using an NPT informed approach, and will enable the use of this technology to be reviewed and amended should a role for microUS in the pathway be identified in the future.

9.9.2 Use of NPT and longitudinal data collection

In this study, the data collected from the ERUP NoMAD questionnaire has been reported in terms of agreement to the sub-construct items. McEvoy et al (2019) discuss this as an advantage of NPT as analysing in this manner can progress the understanding of the implementation processes needed to normalise the intervention in the pathway. The ERUP NoMAD questionnaire was accepted by participants; it was designed to be simple and take no more than 10 minutes to complete. As McCrorie et al (2019) discuss, NPT is useful to explore participants' expectations of new interventions and provide understanding of how these could be managed throughout

the initial adoption phase. Studies using NPT informed methodology, (De Brún et al., 2016; Gillespie et al., 2018; McCrorie et al., 2019; Shaw et al., 2023) commonly concern adaption to new technologies (or processes) that are already proven to be better or more efficient. These studies were designed to evaluate institutional adoption rather than whether the new technology worked. In my thesis, however, I have done both; the technology was tested in study 1, and study 2 used NPT to test the implementation process to support a better understanding of the clinical components of the trial. The ERUP trial piloted whether the use microUS was possible and studied adoption of this technology by practitioners through NoMAD-informed qualitative data collection. The data collected indicates a lack of confidence and reluctance to implement microUS. However, this could be contributed to unfamiliarity as much as a rational reaction to a technology that intended to support practitioners' work but was found to be difficult to use and interpret.

The rationale for using a shortened ERUP NoMAD survey mid-point through the trial was to assess if this reluctance was evident early on irrespective of the findings of the clinical study. A previous study into behavioural response bias has indicated that participants perceptions change if they are aware of disagreement, and I mitigated this by not sharing study 1, phase 1 outcomes at this mid-point in the study (Layng, 1995). A shortened survey was also used to minimise burden to participants, but, on reflection, this limited the usefulness of the responses and likely added very little value to the longitudinal study. However, combining NPT with another implementation tools may have identified the reluctance of adoption earlier. De Brún et al (2016) recommends the utilisation of Participatory Learning and Action (PLA) alongside NPT as it can be used by groups to better focus on areas of joint concern and identify challenges that can be addressed in a positive manner. However, PLA would have been challenging in this small team where I was both researcher and practitioner, and may have, again, biased outcomes due to my involvement. Despite the reported benefits in healthcare of using a similar Participatory Action Research framework (Kjellström & Mitchell, 2019), both this and PLA were excluded from the study design as, regardless of the challenges, time for group discussions would have been required and their use in this study may have added additional burdens to the clinical team participating in the project.

In essence, the longitudinal approach, using the ERUP NoMAD questionnaire at three points in time, was practical and not too burdensome on participants, whilst remaining relevant to capture data. Holtrop (2016) advocates NPT to be used in this manner, as they found it was helpful and explained the differences they observed in normalisation across their study group. However, there is no one way to use NPT (May et al., 2018) and a more flexible approach, using the NPT tools more frequently for instance has been used in other studies, (Tazzyman et al., 2017). These authors (ibid.) successfully employed NPT at multiple points throughout their qualitative study and found that this aided their understanding of implementation in a more dynamic manner. However, increasing interactions in the ERUP trial may have increased the burden on the clinical team and, whilst this approach may have identified the lack of acceptance of microUS earlier, the consistent support for, and coherence of the use of, microUS may have outweighed the changes in responses seen at the time of the T3 questionnaire.

9.9.3 Normalisation

The data collected and analysed indicates that, whilst a greater coherence of microUS has developed through the duration of this study 2, in contrast to evidence presented by Basso Dias and Ghai (2023) and Klotz (2021) suggesting microUS is a valuable tool, the team using it in the present study did not find this to be the case. Indeed, the results indicate that microUS has not been normalised. My findings suggest that microUS was not embedded into routine practice, and there were concerns about the increased responsibility and implications of its use that have not been addressed during the study. As Rich (2002) reported, there are known barriers to implementation, one of which is “physician-related” and includes a lack of knowledge and experience of new technology which the participants will have encountered as the study started. However, results from the NoMAD tool show that participants felt their knowledge of microUS increased between T1 and the T3 questionnaire 12 months later and, as such, the barrier that Rich (ibid.) reports is an unlikely influence in this study. However, a lack of confidence in new technology caused, in part by the lack of experience, and participants negative experiences of its use to guide biopsies, will have been a barrier.

Hunter (2019) describes that the known “know-do” gap in embedding new initiatives into healthcare may be due to entrenched practices which impede changes being

implemented. The experience of prostate imaging and biopsy of some of the participants in this study phase exceeded 10 years, and the required deviation from well-established practices may have contributed to the overall response identified. However, it is unlikely to have been the main contributor to the lack of normalisation given the consistent responses to the cognitive participation construct where support for microUS was unchanged throughout the duration of the study. However, my experience of working with the team and speaking to my colleagues was that there was a lack of personal investment in the new technology reducing a desire to change, particularly from some of the more experienced practitioners, and this may have created the "know-do" gap that Hunter (ibid.) discusses.

9.9.4 Conflicts in research

As De Brún et al (2016) discuss, NPT can provide researchers with enhanced knowledge about the implementation process and help close the know-do gap by engaging practitioners working in the real-life clinical setting with the research process. However, engagement in the research process within the clinical setting of an ultrasound room potentially led to participants feeling observed and, consequently, this may have changed how they performed (McCambridge et al., 2014). The study 2 results indicate that participants were engaged with microUS but not necessarily invested, which supports this theory. Another finding that may explain this level of engagement was the unanimous feeling from the responses that I was the driving force behind microUS and, as I reflect on my discussions with my team, it was evident that they were invested in me to lead this new technology forwards.

My position as lead researcher, and service lead of the small team who were also respondents, may have caused a performance bias and artificially driven a willingness of the team to succeed as a collective. Due to their investment in me as a member of their team, there may also have been a failure to fail by participating individuals. As Hughes et al. (2016) discuss, interpersonal relationships can make failure difficult and there was a risk of a biased positive assessment of microUS by participants rather than them stating their true feeling and consequently feel they were letting me down. This was the challenge of being an insider researcher within the team and, given the nature of a small cohort study, remains an unresolved limitation.

My experience of speaking to colleagues about microUS highlighted that there was a desire to try and make the technology work because it was being led by a member of their own team (9.8.2.2.). This became evident with colleagues indicating support but framed in manner that suggests they were participating collectively rather than for personal interest. However, the data collected from study 1, phases 1 and 2, indicate that microUS is not a good test in the active surveillance pathway and this is unrelated to individuals' opinion of this technology. Clearly, a lack of confidence in the technique will have a negative impact on performance (Hughes et al., 2016), but an objective assessment of microUS is required to highlight to the team that success of this technology was not about the effort they put in to make it work; the objective measure was whether pathology could be detected and the clinical phases of the ERUP trial indicate it couldn't. Galson et al (2021) discuss similar reasons for this failure to fail and identify that critical objective assessment is needed if an impact is to be made by research. Indeed, this is essential if the ERUP trial progresses from this proof of concept (feasibility) study into a formal prospective research project.

9.9.5 Time implications on normalisation

Using NoMAD to monitor the implementation of microUS indicated that, whilst between T1 and T3 participants agreed to continue supporting microUS, by T3 they no longer felt it was a legitimate part of their role and had little confidence in its use (9.7.2). Responses indicated that most within the small team did not feel confident in the interpretation and reporting of microUS, either individually or collectively, and this appears to have made them hesitant to use it due to the risk of misdiagnosis and impact this would have (if implemented) on patient care.

Discussions with staff indicated they were influenced by the fact that, outside of this ERUP trial, microUS has been used to guide biopsy procedures. The lack of time to learn and practice imaging with microUS before it was more widely used in clinical practice will have had an impact on the data collected for the ERUP trial. The use of microUS for both imaging, and in the more complex biopsy concurrently, resulted in data being collected during the initial learning curve for both practices. With more available time, the team would have had opportunity to gain experience in the imaging interpretation, and the use of microUS would have been limited to this feasibility study prior to a wider roll out which included biopsy. Had this been the case, NPT would

have been more useful as gaps in practitioners' knowledge, engagement, and confidence would have been identified and addition training and interpretation resources made available. Unfortunately, the obligatory social distancing during the Covid-19 pandemic, and the subsequent pressure to recover lost activity caused by the hiatus in normal service, resulted in a multi-use trial introduction of microUS into clinical practice and this has clearly impacted on the ability to confidently implement this technology.

9.9.6 Study Strengths

9.9.6.1 Study design

Taking into account the different approaches that authors such as De Brún et al (2016), Tazzyman et al (2017) and Gillespie (2018) have taken in their studies, the design of this study 2 was appropriate and has focussed on how the team attempted to integrate microUS into routine practice. Whilst results have identified that microUS has yet to be normalised and fully embedded, the use of NPT has been successful as a framework that facilitated a systematic and robust exploration of why microUS has not been implemented successfully (Tazzyman et al., 2017).

The study design, using a linear time point triggered questionnaire, has identified that the area where implementation has failed is within the collective action construct. This reflects the study 1 quantitative data that likely led to a lack of confidence in the technology. The responses indicate practitioners felt that microUS had a negative effect on their role and responsibilities, and that they were unable to identify the value of this intervention. The use of NPT has enabled future work to deliver successful implementation to be focussed primarily on these two important aspects. However, in future studies, the concurrent use of PAL (De Brún et al., 2016) to develop a deeper understanding of the joint concerns of the team, and / or the use of BCT (Connell et al., 2019) to support practitioners to change practice away from entrenched ideas, may aid normalisation and identify issues earlier in the process. A study design with a combined theory approach would be advantageous and could promote a more confident implementation of new technology, particularly if there was opportunity to involve clinical practitioners external to the local team where the challenges of being the insider researcher remain.

9.9.6.2 Data analysis

The data analysis was of responses collected using a pragmatic five-point Likert scale. Despite coding for NPT being advocated by May et al (2022), there was insufficient qualitative data from this small team to code effectively. As Holtrop et al (2016) identify, applying coding to NPT components can be difficult, particularly as there is overlap between constructs as De Brún et al (2016), Gillespie (2018) and McCrorie (2019) all discuss. The use of the five-point Likert scale of agreement made the data easy to understand and analyse, and assisted in explaining the success, although in this case the failure, of microUS implementation (May et al., 2018). The results will help formulate future research in microUS emerging from this proof-of-concept study.

9.10 Study 2 Limitations

9.10.1 Sample size

The main limitation of this study is the small sample size with participants exclusively working within the imaging sector. Responses from the consultant urologists would have added a different perspective to the data and may have viewed the imaging output in a more positive light. However, within the busy real-life clinical setting, a questionnaire related to a new imaging technology is unlikely to be prioritised over their routine clinical practice of urology surgeons and it is understandable why there was no participation. A second limitation is that the participants are from a close group of colleagues. Prostate imaging and biopsy are a niche within radiology, and it would be irrelevant to obtain participation from practitioners not involved in this patient care pathway. Despite me being mindful to avoid coercion or mandate involvement, there remained a risk of socially desirable responding and bias within the team towards performance and implementation of the new technology under investigation. However, results indicate that although some of the responses to the cognitive participation construct may have been influenced by the demographics of the small team, there was a general agreement in the team that microUS was difficult to use.

9.10.2 Response bias

As Börger (2013) discusses, a response bias can exist in a situation where there is either a perceived social norm or a desire for social approval. My role in the team may have introduced the possibility of artificial favourable responses to the questionnaire. Indeed, behavioural response bias was first identified by Azrin & Goldiamond (1961),

and the phenomenon of respondents answering what they believe the researcher, or in the case of the original study the Commander, want to hear is discussed further by Layng (1995). Behavioural responding may have provoked participants in my study to give answers that made them look supportive of the new technology, as opposed to highlighting their concerns or perceived failures. As such, the emphasis that can be placed on the discussions with team members, in the absence of a formal qualitative study, is limited. Nevertheless, the verbal feedback goes someway to explain the negative perspective that became evident from the results of the T3 questionnaire but had not been formally vocalised directly to me in my capacity as researcher and lead.

9.10.3 Conflicting practice

By the time of the follow-up questionnaire, approximately 350 patients, including the study 1, phase 1 and phase 2 cohorts had been examined on the microUS machine. Despite this growing experience, participants responding to section A of the ERUP NoMAD questionnaire reported that their experience of microUS had only marginally increased. Most likely, participants were only considering the scans performed for the ERUP trial rather than the overall workload when completing the questionnaire, but the response does not correlate with the actual use of the machine by the team of practitioners. As such, a further limitation that may have influenced the perception of microUS is its use outside of the ERUP trial.

The use of the machine for wider patient populations was supported by the consultant radiologist and consultant urologists given the results of published data (Klotz et al., 2021; Ghai et al., 2022; Basso Dias & Ghai, 2023), and in support of finding improvements in patient care. However, the biopsy technique required by this machine is different to routine clinical practice and, as I found whilst talking to my team, has been difficult to master with confidence. As discussed in Chapter 4, practitioners learning new knowledge and skills require time to develop and mature these before fully them embedding into practice (Culpan et al., 2019; Mitchell et al., 2019), and this was not possible within the time constraints of this research. Revisiting the NoMAD questionnaire once the biopsy technique becomes more familiar may elicit different responses and this should be considered for future research.

9.11 Conclusion

NPT has been a useful and successful tool in the evaluation of the implementation of microUS despite the perceived failure. The fifth measurable objective of the ERUP trial has been answered. The use of NPT, as an appropriate framework, has provided an understanding of the issues surrounding the implementation of new technology and techniques into clinical practice. The interrogation of the four constructs, supported by qualitative data from face-to-face discussions, has identified where the gaps in implementation have occurred, and where future support is required to ensure microUS, or indeed any new technology, can be successfully implemented. The main lessons learned are that appropriate training time is required for any new technique, and that a stepwise approach to supporting confidence in imaging, prior to utilising new technology in an unfamiliar procedural process, is advocated.

Evidence from this study suggests that microUS is not currently normalised into routine practice, and further is work needed to support practitioners for them to be able to see the reported value of this new technology in the prostate cancer pathway. Future study protocols must include a framework, such as NPT, PLA and BCT, to enable a continued advanced understanding of the success or failure of the implementation of microUS.

In this chapter, the methods used to evaluate how technology can be embedded into clinical practice, and how to assess if it has become normalised have been discussed. The lack of confidence in the use of microUS, supported by the poor sensitivity of this as a diagnostic test determined by phase 1, has negated the opportunity to progress to the planned third study phase. The next chapter discusses ERUP trial in its wider context and is followed with a reflective chapter on how this research has impacted on practice and patient care.

Chapter 10 Thesis discussion

A review of the completed thesis is provided in this chapter. The evidence addressing the study aims and measurable objectives is summarised, and the overall study design, its strengths, and its limitations are critiqued. The issues affecting the study are identified, and the wider impact of the research project is presented.

10.1 Study outcome review

This is the first study to evaluate the role of multi-parametric ultrasound, including the use of micro-ultrasound (microUS), in the active surveillance (AS) of prostate cancer within an imaging pathway delivered primarily by sonographers in the UK. Other studies are emerging where microUS is utilised to assess the prostate and identify high-risk areas of change within the gland prior to biopsy in patients on AS (Albers et al., 2022; Bhanji et al., 2022; Maffei et al., 2023). However, this is the first study which has investigated using the diagnostic properties alone to evaluate the likelihood of pathology and disease progression within the prostate in a similar study cohort to those published. This study is also distinct in its investigation of the process of embedding new technology within an imaging pathway. The outcomes provide a valuable contribution to the evidence for the use of ultrasound, and particularly the value of microUS, in this high-volume pathway. Despite the findings of my research indicating that the sensitivity of microUS is less than that found by other authors (Klotz et al., 2021; Maffei et al., 2023), I found no evidence to suggest microUS does not work within this AS pathway.

There are limitations to this research in terms of study design, discussed in section 10.5 below and, of equal relevance, in terms of the current local management of patients on AS and the NHS performance, which have affected the outcomes. However, this study is impactful in the wider context of prostate cancer care as it adds to the body of evidence regarding the best use of microUS in prostate cancer imaging and has identified the benefits of using a structured implementation process to support the introduction of new technologies in clinical practice. The primary and secondary aims of this study (Chapter 5.4) have been addressed and evidence produced to answer the measurable objectives.

10.2 Answering the aims and measurable objectives

In response to the background investigations of Chapters 1 to 4, two themes emerged that I have investigated in this thesis:

- Is there a role of emerging ultrasound technologies in the assessment and monitoring of localised prostate cancer in men on an active surveillance programme?
- How could new ultrasound technology and techniques be implemented and embedded into clinical practice within the multi-professional team?

The concurrent and consecutive study approach enabled a degree of pause and check between each phase, which, as O'Brien et al (2020) discuss, was important as "new normals" in delivering patient care pathways emerged during the research process.

Studies 1 and 2 were planned to answer the two key themes, with a third study initially planned to supplement and consolidate the findings of the ERUP trial into the context of the wider imaging community. The final study was planned to disseminate the findings through a prostate imaging and pathway learning event where the results of the investigations into microUS could be presented, shared, and options for wider utilisation discussed with the relevant health care providers. However, the findings of study 1 and study 2 indicated that sharing the results could hinder future development of microUS in other centres, particularly given that an influencing factor to the ERUP trial outcomes were the site-specific issues encountered. As such, study 3 did not proceed.

In the next section I discuss the outcomes of the two study aims and, in section 10.4, I discuss the evidence supporting the outcomes of the measurable objectives.

10.3 Outcomes of the study aims

10.3.1 Primary aim outcome

This proof-of-concept study aimed to evaluate if emerging ultrasound technologies could provide reproducible imaging that could be used to assess the prostate gland in men with known localised prostate cancer and who were being managed with active surveillance (AS) (Chapter 5.4). This aim was addressed in study 1, phases 1 and 2. Reproducible imaging using new ultrasound technology of microUS has not been

determined and a lack of confidence in this technique is evident from my study 2 results. In summary, this primary aim has has not been met.

There was poor agreement between practitioners following retrospective reviews of standard B-mode ultrasound, colour Doppler imaging, and microUS findings undertaken in study 1, phase 1 (Chapter 7.1.6). On analysis of agreement between imaging parameters and histology, the inter-reviewer reliability (IRR) was poor for all retrospective reviews, but improved results were found from the analysis of baseline consensus microUS scores and histology (7.1.8). However, even when a weighted kappa test was performed, to take into account the disagreements between the differing risk stratification categories, the IRR remained only fair with a result of κ = 0.39 (Table 7.20).

Study 1, phase 2 was designed to evaluate if there were features of microUS that could be exploited to monitor disease progression for patients on AS. No parameters were identified and, therefore, phase 2 was curtailed due to a lack of clinical and practitioner confidence in the use of the new technology.

My research has not confidently identified a role for microUS in the local clinical pathway. Given the absence of MRI in most of the study 1, phase 2 cohort, there was no reference standard available with which to compare the findings of the follow-up microUS image review. Whilst this issue may be related to the particulars of the local service, the results do indicate that without confirmatory MRI, microUS alone may not be able to adequately monitor patients and its role in the wider AS pathway remains uncertain. In the studies by Eure et al (2019), Albers et al (2022), and Maffei et al (2023), all patients had MRI prior to microUS assessment as part of their standard care, and all authors used this as a pre-biopsy reference standard. A limitation of the study by Albers et al (2022) was that the surgeon undertaking the microUS was not blinded to the MRI, and that MRI was used to target lesions for biopsy. Despite these studies indicating that microUS can supplement MRI in clinically significant prostate cancer (csPCa) detection during AS, it appears to remain standard practice to combine the use of MRI and ultrasound.

The multiparametric ultrasound versus multiparametric MRI to diagnose prostate cancer trial (CADMUS) (Grey et al., 2022) advocates the use of both imaging modalities

as it identified both missed csPCa if used in isolation. The CADMUS trial identified the use of both modalities would increase overall csPCa detection levels (ibid.). Therefore, any future trials should include the use of both imaging modalities to test the consistency of microUS in AS, particularly given the conflicting data from my ERUP trial and that of Sountoulides et al (2021). These authors (ibid.) identified that microUS provided an attractive alternative to MRI, particularly where MRI is unavailable or contraindicated. However, as discussed by Basso Dias and Ghai (2023), uncertainty remains as to whether microUS should be used on its own or in conjunction with mpMRI for enhancing prostate cancer detection, and there is discordance between published literature, which my study has attempted to address.

My results indicate that, within local practice, microUS cannot be confidently used to assess the prostate gland in men with known localised PCa and who are being managed by AS. However, other authors (Eure et al., 2019; Albers et al., 2022; Maffei et al., 2023) have found differing results. The most likely explanation for this disparity is the differences in study designs. In my study, only two of the patients in the AS cohort (study1, phase 2) had confirmatory biopsy which showed no progression. In the remaining eight participants, PSA results alone were used as a clinical indication of prostate change; again, there were no significant changes identified between the sequential blood tests of individual patients in those in whom these tests were completed.

My study is the first to use microUS in an attempt to identify lesions or prostate change without prior MRI to evaluate the prostate. The primary aim was to identify if microUS could identify pathology or disease progression so that it could be used in place of MRI. Despite this aim not being met, my study design, which excluded the need for MRI during AS, was a relevant method to test this theory.

10.3.2 Secondary aim outcome

The secondary aim (Chapter 5.4) was to investigate the impact of new technology, and additional role extension, on health care practitioners within diagnostic imaging, in the field of prostate cancer assessment and monitoring. The objective was to gain an understanding of how new technology is embedded or implemented into routine clinical practice. Novel interventions are only of benefit if they can be normalised (May

et al., 2016) into care pathways, and this has to be assessed within the real-life context. The context of where, and by whom, new interventions are being implemented is an important and practical problem for such studies (ibid.) and this was considered during my study. The findings of study 2 (Chapter 9.11) indicated that this secondary aim was met.

By using the normalisation process theory (NPT) (May & Finch, 2009), I was able to evaluate the impact of new technology on healthcare practitioners within my team, and within this clinical pathway. The use of NPT facilitated an appreciation of the difficulties encountered by practitioners in their attempt to use microUS as a diagnostic tool. The findings of study 2 indicated that microUS has not been embedded into routine clinical practice. This conclusion correlates with the findings of both clinical phases of study 1, and the results of study 2 underpin why there was a lack of clinical confidence in the use of microUS. The ERUP NoMAD questionnaire was supplemented with team engagement and discussions which, when combined with the survey data, indicated that practitioners did not value the use of microUS in this pathway, and they felt this technology brought added accountability and responsibility to their role. The secondary aim has been answered.

10.4 Measurable objective outcomes

Five measurable objectives were identified to support the primary and secondary aims, and these have been answered. The measurable objectives were:

- To evaluate the diagnostic parameters of diagnostic ultrasound that could be utilised to assess disease within the prostate gland.
- To evaluate the diagnostic parameters of diagnostic ultrasound that could be utilised to assess disease progression within the prostate gland.
- To evaluate if the intra and inter operator variability in the assessment of ultrasound imaging parameters of the prostate gland could be investigated.
- To determine if a suitable standardised imaging protocol and reporting tool or model could be utilised in the reporting of transrectal ultrasound imaging of the prostate.
- To gain a better understanding of how new ultrasound technology and techniques could be implemented and embedded into clinical practice.

A summary of the relationship of these with the study outcomes is outlined in Table 10.1 below.

Table 10.1 Comparison of measurable objective and study outcomes

Measurable Objective				
One	**Two**	**Three**	**Four**	**Five**
To evaluate the diagnostic parameters of diagnostic ultrasound that could be utilised to assess disease within the prostate gland.	To evaluate the diagnostic parameters of diagnostic ultrasound that could be utilised to assess disease progression within the prostate gland.	To evaluate if the intra and inter operator variability in the assessment of ultrasound imaging parameters of the prostate gland could be investigated.	To determine if a suitable standardised imaging protocol and reporting tool or model could be utilised in the reporting of transrectal ultrasound imaging of the prostate.	To gain a better understanding of how new ultrasound technology and techniques could be implemented and embedded into clinical practice.
Chapter 2, 5, 6 & 7	*Chapter 7 & 8*	*Chapter 7 & 8*	*Chapter 3, 5, 6, 7 & 8*	*Chapter 4, 5 & 9*
Study 1, phase 1 **Of the mpUS parameters used in this study, only microUS demonstrated utility. Moderate specificity indicated that this could be a useful tool to assess if no disease is present within the prostate**. MicroUS was found to have a higher specificity than MRI (53.8% vs 34.6%) in this patient cohort where there was real-time imaging and consensus between two observers.	**Study 1, phase 2** **Diagnostic parameters of mpUS / microUS which could indicate disease progression have not been identified.** No apparent disease progression was identified throughout the duration of the study, but appearances of the individual prostate were too varied to be confident in interpretation. A lack of consistency in patient management on AS was identified by this study.	**Study 1, phase 1 & 2** **Variability in the assessment of the prostate was identified with poor inter and intra reviewer agreement rates.** Inter-reviewer reliability was poor regardless of the ultrasound parameters used. The highest inter-reviewer reliability was found where there was real-time imaging and consensus between two observers, and with a weighted kappa of 0.38 calculated.	**Study 1, phase 1 & 2** **A three-point risk stratification scoring system improved reliability of image and histology assessment and its use is advocated as is aligned with clinical management.** An overall stratification of the risk of disease presence, rather than site specific reporting, yielded improved agreement between imaging and histology.	**Study 2** **Evidence from this study suggests that microUS is not currently normalised into routine practice.** The use of an implementation theory (NPT) provided an understanding of the issues surrounding of how new technology is embedded into clinical practice. A stepwise approach to supporting confidence in imaging, prior to utilising new technology in an unfamiliar procedural process, is advocated.

10.4.1.1 Measurable objective 1

- To evaluate the diagnostic parameters of diagnostic ultrasound that could be utilised to assess disease within the prostate gland.

Measurable objective 1 has been answered; of the mpUS parameters used in this study, only microUS demonstrated utility. I determined that standard B-mode imaging and colour Doppler imaging have insufficient agreement with histology to support assessment of disease within the prostate. Existing literature, as reviewed by Basso Dias and Ghai (2023), does indicate that microUS should replace standard ultrasound for prostate imaging. My findings concur with this conclusion due to the improved sensitivity and specificity of microUS compared to standard US that I identified (Chapter 7.1.13). Despite continued improvements in ultrasound technology of standard ultrasound technologies in recent years (Hoskins et al., 2019), my results are in keeping with the findings of Correas et al (2021), as well as the earlier study by Harvey et al (2012), which identified the limitations of standard B-mode imaging.

My research has identified that microUS demonstrated sufficient sensitivity and specificity to indicate this could be a reasonable test to assess for the presence of disease. However, the sensitivity, even of the initial baseline assessment, was only 73.3% compared to the MRI sensitivity in this cohort of 87%, and this may lead to a higher proportion of men being given falsely negative results if microUS was used in isolation. Nonetheless, its improved specificity compared to MRI in this cohort (53.8% compared to 34.6% respectively) (Chapter 7.1.11) indicates that there will be a higher proportion of true negative results if microUS was used to initially assess disease within the prostate. Whilst the findings of both clinical phases of study 1, and the outcomes of study 2, indicate that there are no parameters of microUS that could confidently identify disease progression within this local clinical context, the high specificity of microUS may lend itself to be used as a screening test for men at initial presentation into the outpatient department. Further research in this field is indicated.

10.4.1.2 Measurable objective 2

- To evaluate the diagnostic parameters of diagnostic ultrasound that could be utilised to assess disease progression within the prostate gland.

Measurable objective 2 could not be answered. The small cohort study 1, phase 2 was designed as a proof-of-concept study primarily to assess if there were any features of microUS that could identify disease progression and also to evaluate if adding

ultrasound into the local AS pathway was feasible. The cohort was too small to confidently identify imaging parameters that could be utilised. An inadvertent, and unexpected, finding of my study was the lack of consistent follow-up for men with pre-malignant benign conditions or low-grade prostate cancer. For this objective to have been met, there needed to be consistency of follow-up of all men being managed on an AS regime. The variability, or indeed absence of management plans, raises concerns that the addition of novel imaging, whose role in this pathway remains uncertain as discussed in section 10.3.1 above, could lead to further divergence from the NICE guidance for prostate cancer care (2021).

Had the primary aim of my study been met, there would be potential for microUS to replace the need for MRI in AS. Whilst designing the study, I was aware MRI was not employed within the local AS pathway, hence the rationale for the research, but there was a tacit understanding between the radiology and urology teams that regular PSA testing and monitoring was well established. As such, had microUS identified changes in the prostate, this could have been correlated with the tracked PSA levels and, following discussion at MDT, a confirmatory MRI, plus biopsy if indicated, could have been arranged. Whilst MRI is not employed in the local service, it is more widely utilised in other centres and, had there been a more positive outcome to study 1, phase 2, the impact across urology services could have been beneficial and the need for monitoring MRI scans could have been reduced. However, the unexpected finding of such disparity in the local monitoring pathways has limited the translatability of this research. Future studies into the role of microUS will require a clear and consistent AS regime to be employed and a multi-centre approach, including services with a more mature and established AS service in place, would provide the broader assessment of applicability that my study is missing.

10.4.1.3 Measurable objectives 3 and 4

- To evaluate if the intra and inter operator variability in the assessment of ultrasound imaging parameters of the prostate gland could be investigated.
- To determine if a suitable standardised imaging protocol and reporting tool or model could be utilised in the reporting of transrectal ultrasound imaging of the prostate.

Measurable objectives 3 and 4 have both been answered. The outcome of study 1, phase 1 indicated there is a high degree of inter- and intra-operator variability but this

is reduced with a risk stratification approach to reporting imaging that aligns closely with patient management (Table 6.2). Sufficient time for practitioners to gain experience using microUS system prior to the start of this research was a challenge and may account for the variability encountered. However, the findings of study 1, phase 1, indicated that this variability did not improve with greater experience. The findings contradict a study by Pavlovich et al (2021) that found the performance of microUS improved within increased training and experience. This contradiction can be understood in light of the study 2 results which found that practitioners disengaged with microUS. Study 2 participants found it difficult to use and interpret, and there was a sense that the practitioners were continuing to support its use due to sense of loyalty to me as department lead and team member rather than because they could see the value of its use.

Neither the steep and protracted learning curve, nor complexities of the use of microUS to guide biopsy, were anticipated as this was an ultrasound technology being used and interpreted by a team of experienced ultrasound and imaging practitioners. With such a high level of variability between reviewers in their interpretation of microUS images of the prostate, it was difficult to develop a suitable imaging protocol or reporting tool other than that of a pragmatic broad-based risk stratification system. Future study into intra and inter-operator variability will require a period of knowledge and skill development or consolidation prior to assessment of the interpretation of microUS findings. Research into the correlation between knowledge and skill development of practitioners and the applicability of the current PRI-MUS™ scoring system in real-life clinical settings is indicated.

10.4.2 Measurable objective 5

- To gain a better understanding of how new ultrasound technology and techniques could be implemented and embedded into clinical practice.

The use of NPT has provided an understanding of how new technology is, or in this instance, isn't embedded into clinical practice. Whilst there are other published studies using NPT as a means to assess implementation (Gillespie et al., 2018; McCrorie et al., 2019; Shaw et al., 2023), no studies have been found which relate to how imaging modalities and new technologies are introduced and normalised. There are frequent releases of new imaging parameters by manufacturers within the ultrasound modality

(Gandhi et al., 2018; Sidhu et al., 2018; Basso Dias & Ghai, 2023) but there is limited research into how these are adopted and embedded. The study by Pavlovich et al (2021) identifies that training for practitioners is essential, and found training led to improved outcomes of microUS. The authors did not investigate the learning curve of practitioners, nor how the relevant practitioners adapted to this new technology, which led to a gap in knowledge that my research has addressed.

My research adds to the body of evidence highlighting key individuals are commonly responsible for implementing changes (Nightingale et al., 2021; Wood, 2021). My research found that this can lead to a conflict between participants' experience of the new technology and the desires of the person leading the implementation to make it work. Many of the positive studies published related to microUS are from single centres with urologists as the lead author (Eure et al., 2019; Izzetti et al., 2021; Lughezzani et al., 2021); this may result in a conflict of interest and, not least, a different study design to the one I undertook. Indeed, the review by Harland and Stenzl (2021) identifies that microUS provides the potential to remove imaging in this pathway from radiology and to bring the diagnosis of prostate cancer

> "back into the hands of the urologist". (ibid. p.64)

This view is understandable in the differing health economies of Europe and North America, particularly for office-based speciality care where funding is at the point of delivery and directly to the care provider (European Observatory, 2024). However, in the UK, the centrally funded, free at the point of delivery, system (Delamothe, 2008) results in differing models of care using a wider skill mix approach and encouraging role extension as I discussed in Chapter 4.6. As such, investigating how microUS is embedded within the radiology component of the current 28-day faster diagnostic prostate cancer pathway (NHSE, 2022) was appropriate, but only translatable within the UK. Nonetheless, my research has addressed the gap in knowledge related to the delivery of microUS in this clinical setting. A multi-centre investigation into the compliance of urology services with the current AS guidance (Merriel et al., 2019; NICE, 2021), to gain an understanding of where the use of microUS may provide the greatest impact on pathway delivery is indicated.

10.5 Critique of thesis and impacts on study design

Following completion of both the systematic review of the role of ultrasound within AS (Chapter 2), and the scoping review evaluating the publications related to men's experience of AS (Chapter 3), in 2020 and 2021 respectively, two gaps in knowledge were identified that my thesis has addressed. The scoping review identified that men want reassurance throughout their AS pathway and appreciate the benefit of regular investigations, but this is coupled with the anxiety that tests bring due to the possibility of disease progression.

10.5.1 Impact of real-life capacity and performance issues

This anxiety is likely to be increased if there is no apparent planned care, often due to capacity issues within urology, despite guidance advising optimum AS regimes (Merriel et al., 2019; NICE, 2021). Data issued by NHS England in June 2023 identified that only 48.6% of people treated for urological cancers (excluding testicular cancer) received first definitive treatment within 62 days of being urgently referred for suspected cancer - the target is 85% (NHSE, 2024a).

Whilst I identified a gap in knowledge regarding the use of microUS, and identified a gap in the understanding of how this could be embedded within an AS pathway in the UK, at the time of designing my study there was a lack of appreciation of the real-life capacity issues faced in urology and the resultant lack of compliance to AS guidance that has become evident throughout this research. My study was designed to test the concept of introducing imaging into the pathway and it has become clear from the difficulties in recruiting to study 1, phase 2, that this is not feasible in the current health climate locally. There are evidenced capacity and performance issues across the NHS, (2020) and this is coupled with the need to deliver the 28-day faster diagnostic standard (NHSE, 2022). The impact of the Covid-19 pandemic remains with wider capacity issues being experienced as services attempt to bring waiting lists down and performance in line with government expected targets (NHSE&I, 2022). My initial study design did not take into account the lack of consistency in AS management, the performance difficulties now encountered, nor did it envisage the impact that the Covid-19 pandemic would have on health care delivery.

10.5.2 Patient selection limitations

In this proof-of-concept study, the study 1, phase 1 and 2 research cohorts were a representative sample of the wider population. However, a limitation of this wider population and, therefore, the research sample is the lack of ethnic diversity. The local population of Hull and East Yorkshire is limited in its diversity, and this is coupled with the socio-economic deprivation present in the area, which leads to known inequalities in outcomes following cancer diagnosis (Ingleby et al., 2022). Whilst there was little I could do to actively recruit participants from a more diverse ethnic or socio-economic background, the results from study 1, phases 1 and 2 may not be translatable to a wider clinical setting. However, this limitation has had no bearing on the blinded image review so will not have biased the intra- and inter-operator results, nor adversely impacted on the perceptions of practitioners attempting to use microUS in clinical practice.

10.5.3 Insight into the study design

The three components of the consecutive and concurrent study design employed in the ERUP trial facilitated a planned and measured approach. A further benefit I found of using a multi-phase sequential and concurrent study approach, which Bell et al (2014) also describe, was that it enabled the research to be conducted in a real-life clinical setting as it did not directly impact on direct care. As such, my research design has a high translation validity across other similar service sites (ibid.) and such an approach should be considered in future studies.

10.5.4 Qualitative data

As discussed previously, the use of NPT was appropriate but alternative implementation theories could have added richness to the data. In retrospect, qualitative data would have added value and aided interpretation of the NoMAD-inspired questionnaire. Face-to-face interviews with practitioners, such as those conducted by Gillespie et al (2018), could have improved the study. However, a more significant qualitative component with in-depth analysis would have been challenging within the restrictions of this PhD project. Nevertheless, this research has highlighted that the opinions of service providers afford context and meaning to quantitative data. In this study, the outcomes of the team engagement discussions provided insight into

the findings of study 2, and more emphasis should be placed on this source of data in future studies.

The value of qualitative data in research into the implementation of new interventions cannot be underestimated and should be included in future research to ensure the impact of new processes is fully understood (Palinkas et al., 2015). However, the pressures of referral demand, the need to reduce waiting times, and getting the procedure right first time (Halliday et al., 2020), as well as the time constraints of the PhD programme, prevented any extension to this proof-of-concept study. Investigations into the impact on practitioners of the changes to services required to meet 28-day faster diagnostic standards (NHSE, 2022) is advocated if the bottlenecks in the pathways are to be truly appreciated and resolved.

10.5.5 Pause and Check

As O'Brien et al (2020) discuss, there was an unanticipated "pause and check" between ethical approval and each of the studies commencing. Primarily, these pauses were directly attributable to the impact of the Covid-19 pandemic (Office for National Statistics, 2023). Whilst, to date, the pandemic was a unique event which imposed such hiatus, in retrospect, time for pause and check throughout the study period should have been planned into the research design. The enforced pauses I encountered allowed me to reflect on the provisional outcomes of each phase as they emerged and prevented a potentially detrimental third study being undertaken. As an insider researcher, and the driving force behind microUS implementation, I may have inadvertently exerted pressure and bias on participation due to a desire to ensure microUS succeeded. Given the results of the ERUP trial, it was sensible and pragmatic to cancel this final study.

There are many ways bias can be introduced into research but, as Krishna et al (2010) discuss, these often involve complexities of humans of which I am not immune. Whilst in retrospect, the human complexities of being an insider researcher, developing my own knowledge and skills of this challenging technology, and leading a team through the significant events of the Covid-19 were difficult to anticipate. However, supported discussions with my supervisory team did allow for periods of reflection and a review of approaches to the research to be explored. As such, despite the challenges a

successful research project has been completed. A learning point from my experience is to ensure that time for pause and check should be factored into future research designs to ensure reflection on the value of continued research occurs.

10.6 Impact of Covid-19

The biggest influence and impact on the undertaking and completion of this thesis was the Covid-19 pandemic. The shift from known, well navigated hospital-based health care delivery to one of telemedicine, on-line consultations, shielding, social-distancing, and an implicit understanding that diagnosis and treatment were to be deferred (Currie, 2020; Katims et al., 2020; NICE, 2020; Popert et al., 2020; Sikora, 2020) significantly impacted on how my designed study could be implemented. At the end of the financial year of 2019/20, immediately prior to the Covid-19 pandemic, the Humber and North Yorkshire Cancer Alliance provided funding for innovations in cancer pathways to support the embryonic 28-day faster diagnostic pathway for prostate cancer. This facilitated the purchase of the microUS machine within the Hull University Teaching Hospitals NHS Trust. This was, and remains, only the second machine purchased in the UK. However, the Covid-19 pandemic significantly impeded the installation of this system and delaying hands on experience with the system.

10.6.1 Installation and application delays

Due to the Covid-19 restrictions (Office for National Statistics, 2023), the installation was delayed until September 2020 with first on-site hands-on training not being delivered until April 2021. Further hands-on training was delivered in September 2021, with the final training visit completed in February 2022. Online training was available (Exact Imaging, 2023) and the basic virtual training was completed by all those practitioners recruited to review images of study 1, phase 1 and recruited into study 2. However, given the significant differences in detail, and the complexities of the PRI-MUS^{TM} scoring system (Ghai et al., 2016) (each PRI-MUS^{TM} score has a range of descriptors – Appendix 14 and 15, pages XXXVIII and XL) the on-line training was difficult to master, and the absence of face-to-face training with an expert was disadvantageous.

10.6.2 Network, bandwidth and DICOM challenges

I experienced critical issues related to the hospital network bandwidth and the DICOM coding of the data sent from the microUS system as discussed in Chapter 7.3.1. This delay prevented the team gaining adequate pre-research experience on the system. The steep learning curve of the new technology was not anticipated; it was falsely assumed that, as sonographers are expert in the field of ultrasound imaging, the new microUS parameter would be intuitive and the teams' innate scanning ability would mean it was easy to perform and interpret. Without the reassurance of the face-to-face training, this was found not to be the case.

10.6.3 Clinical supervision and mentorship

A further impact of the pandemic was the difficulty of being able to hold regular meetings with my clinical supervisor and wider clinical team. Many of the medics not delivering face-to-face patient care worked from home and the regular contact with the team was lost. My clinical supervisor, also Urology Clinical Director at the time, was understandably in demand as a clinical leader of the organisation. Time to discuss the nuances of my research design was justifiably not prioritised. Further to this, patients were comprehensibly anxious at having to attend a hospital during periods of lockdown in particular (Office for National Statistics, 2023). They had to attend on their own with no family support and be met with staff in personal protective equipment (PPE) through which they struggled to portray and communicate the compassion and empathy they all felt. Recruiting patients into a research study during this time was a challenge. However, I was able to recruit to target at a time when recruitment to non-Covid-19 trials were negatively impacted (Mirza et al., 2022) and funding postponed (Iacobucci, 2020).

10.6.4 Capacity, demand, and performance implications

Perhaps the greatest impact of the Covid-19 pandemic however has been the lost capacity and activity; the implications of which are still being felt and managed (NHSE&I, 2022). Whilst there are likely a range of issues related to adherence to published AS guidance (Merriel et al., 2019; NICE, 2021), the most significant is the pressure to meet targets for new cancer diagnosis over long term follow-up (Katims et al., 2020). The volume of patients requiring regular follow-up within the NHS continues to increase. This has safety implications as the demand is greater than traditional

systems and pathways can provide (Fenn, 2023). This proof of concept recruited 10 patients into the monitoring phase (phase 2) of study 1, yet I identified a further 15 eligible men who had no post-biopsy management plan in place. It is clear, a successful and safe AS pathway for patients needs more than the implementation of a new imaging intervention if it is to provide the care these men require.

10.7 Conclusion

The role of ultrasound in the active surveillance of prostate cancer has been evaluated by my research. Beyond the assessment of reliability, an assessment of whether the technology of limited mpUS, including that of microUS, can be normalised into routine clinical practice has been completed; evidence exists to demonstrate it has not been successfully embedded into the prostate cancer pathway. For this to have been successfully evaluated, my research had to be undertaken in the context in which the feasibility could be measured, and recruit participants specific to the clinical question posed. My study design was appropriate to achieve this and, therefore, the results have clinical validity. For mpUS and/or microUS to be clinically useful, it had to have provided some tangible benefits over the existing pathway. Ultimately, this new technology needed to support patient AS pathways that lead to improved outcomes. However, the inconsistencies of microUS encountered during my research identified no such benefit over the existing model of care.

The identified gaps in knowledge have been answered. In this clinical context there is no current identified role for the use of new ultrasound technologies in AS. However, given the small cohort, I cannot conclusively rule out it having a role in the future. Indeed, the specificity of microUS identified may lend itself to screening those men with low clinical risk in whom MRI is contraindicated or incompatible. Future technological developments of AI, in relation to ultrasound guided biopsy and prostate assessment, may yet provide an innovative role for multiparametric ultrasound in prostate cancer care pathways.

A conclusion has been drawn as to the role of ultrasound in the active surveillance of prostate cancer. In the next and final chapter, the impact and benefits of undertaking this research are discussed, and areas for future research proposed.

Chapter 11 Reflection, ripples and recommendations

In this final chapter, the wider impact of this research is discussed, the future developments in diagnosis and surveillance within the prostate pathway presented, and areas of future research proposed.

11.1 Reflection

It is February 2024 and I near completion of my thesis. I receive a call from a close friend with unexpected news. My friend had a PSA test believing it would be normal; after all, he is a fit man in his early sixties with no risk factors. His PSA level returned at 14 ng/mL which led to a transperineal (TP) US guided prostate biopsy and a diagnosis of clinically significant prostate cancer, Gleason 7 (4 + 3) in three cores. He has called for advice. It is at this point, the relevance and impact of my PhD on me personally is in stark relief. I have made a difference and can speak with authority and knowledge to my friend; for this small moment, it has been worth it. Yet the impact and value of this PhD is far wider than my ability to provide wise counsel to my friend.

11.1.1 Fusion guided prostate biopsy

Prior to embarking on my research journey, I was one of a team of sonographers performing fusion guided prostate biopsies. This procedure entailed a transrectal ultrasound scan which was aligned with the previously captured MRI of the prostate downloaded onto the ultrasound system (Parker, 2015). The MRI volume data was aligned and fused with the real-time ultrasound imaging so that an improved and targeted biopsy could be performed. The rationale for fusion guided MRI/ultrasound biopsy was to find the clinically significant prostate cancer (csPCa) and avoid the low-risk areas that do not require radical treatment. The study by Kasivisvanathan et al (2018) provided the findings of the PRECISION trial which demonstrated targeted biopsies significantly reduce the detection rate of insignificant prostate cancer and, as such, fusion biopsies became the standard of care. My early interest in the prostate pathway was driven by my attraction and fascination with new ultrasound technologies. The benefits of using fusion were soon realised and our own local service evaluation demonstrated results consistent with that of the published PRESICION trial (Parker et al., 2020). However, despite the diagnostic accuracy that our local service evaluation identified, the post-procedure complication rates of transrectal prostate

biopsies were becoming increasingly burdensome for patients with evidence of post biopsy significant infections leading to sepsis requiring intensive care recovery and, sadly, mortality being reported (Grummet et al., 2020). There was a desire to reduce the risks to patients and move towards delivering the safer TP prostate biopsy approach (Campbell et al., 2019). However, these biopsies were traditionally performed by urologists, in an operating theatre setting, and with a patient under general anaesthesia (GA).

11.2 Ripples

11.2.1 Transperineal prostate biopsy

With the advent of the Covid-19 pandemic, intensive care beds were being prioritised for patients with coronavirus complications. An almost complete cessation of non-emergency procedures requiring GA occurred, there became an urgent need for these diagnostic procedures to be performed under local anaesthesia and in a clinic environment. Reassuringly, evidence was emerging that fusion guided TP biopsies has a similar performance accuracy to those performed using the PRECISION trial transrectal route (Rai et al., 2021). My specialised research subject of prostate cancer diagnosis, and my avid interest in developing services and new technology, resulted in me leading this change alongside developing and undertaking my PhD. Using the known and installed Canon i700 ultrasound system (Canon Medical Systems, Crawley, UK) the new technique was developed, approved, and established in our institution in the summer of 2020.

11.2.2 TP biopsy service evaluation

Given the change in biopsy technique, and the challenges related to using the microUS system for these procedures reported during study 2 of the ERUP trial, I undertook a retrospective service evaluation to determine if this new procedure detected csPCa to a similar level to that of the previous fusion targeted transrectal biopsy (Parker et al., 2020). Whilst not a component of the ERUP trial, this review was aligned to my research. It was necessary to ensure the agreement rate results of study 1, phase 1 were related to the interpretation factors I identified rather than due to changes in diagnostic technique which may have resulted in misplaced biopsies being performed. I present this service evaluation as a ripple of the PhD to support the interpretation of my findings.

11.2.3 Evaluation method

All patients who had radical prostatectomy who had a previous diagnostic TP biopsy and MRI within the Hull University Teaching Hospitals Trust were included in the service evaluation. Retrospective data was collected from patients presenting between August 2020 and May 2023. The histology findings from the whole mount prostatectomy were compared with the histology findings following the TP targeted biopsy and MRI reports. Comparison of the site of the highest Gleason grade at prostatectomy was compared to the Gleason score of the target site biopsy. Agreement was recorded if csPCa was found in both histology reports.

11.2.4 Evaluation results

In total, 118 prostatectomies were performed, and all of these had at least one identified region of interest suitable for targeted biopsy at their pre-biopsy MRI. In 17 of those, two or more targets were identified at MRI, with each target biopsied and analysed separately. There were 135 lesions in total identified in the sample cohort.

csPCa was identified in both the target site biopsy cores and corresponding sites at prostatectomy in 95% (n = 128) of samples. Histology from seven targets (5%) at biopsy were negative for cancer despite being positive at prostatectomy. In all of these, csPCa was identified in the biopsy samples from none target sites. On review of the pre-biopsy MRI, there was a range of target sites in which the cancer had not been detected at biopsy. The negative biopsy results were distributed throughout the team of sonographers.

There was one recorded episode of urine retention reported post-biopsy in this cohort, but no reported complications of sepsis or frank haematuria requiring treatment identified.

11.2.5 Evaluation conclusion

The service evaluation identified that there was no significant difference in csPCa detection rates between the previous transrectal biopsy procedure and the new TP biopsy technique. No difference in practitioner performance was identified and this highlighted that practitioners could be trained to competently perform TP biopsy regardless of prior experience. Fusion guided TP biopsy was found to be a safe procedure and able to confidently identify csPCa. The Urology, getting it right first time

report (GIRFT) (Moore et al., 2024) now advocates TP biopsy as the diagnostic procedure of choice, and it is reassuring to demonstrate our service improvements safely and accurately deliver the pathway standard.

11.3 TP Biopsy service ripples

The findings of the evaluation demonstrated that the new TP service is in keeping with other published studies (Campbell et al., 2019; Kum et al., 2020) and comparable with the published study by Lopez et al (2021) who also identified that TP biopsy achieved an excellent csPCa detection rate with very low post procedure complications. As such, confidence in the histological outcomes of the study 1, phase 1 participants are maintained. Completing this PhD has facilitated my investment into the prostate pathway. This has consequently contributed to this service development which I led and had a positive impact on the diagnostic service for our patients.

11.4 Ripples to improve diagnostic confidence

The aim of the ERUP trial was to evaluate if there was a role for multiparametric ultrasound in AS. I have not found one to date, as discussed; nevertheless, the need for improved surveillance has not diminished. Although, despite evidence to suggest that the clinically safe TP biopsy results are as accurate as previous transrectal procedures (Lopez et al., 2021; Rai et al., 2021), there is still a proportion of patients who are found to have csPCa on repeat biopsy when on AS, and it is suggested this may be due to biopsy inaccuracy as much as related to disease progression (Dall'Era et al., 2012). One reflection on my research is how accurate are we at biopsy when we have no prostatectomy specimen to compare against? Diagnosis is currently reliant on MRI interpretation and biopsy needle guidance.

11.4.1 Hit or miss?

In my role as consultant sonographer, and due to my interest in technological developments in ultrasound, I have reviewed emerging pragmatic solutions, which may improve confidence in histological outcomes of TP biopsies. The service evaluation performed, and presented above, (11.2.5) reviewed biopsy outcomes with prostatectomy and found good results. However, in those patients with high-risk MRI and negative or low-risk histology post-biopsy, the clinical question asked is whether the biopsy was correctly targeted or has the MRI overcalled the region of interest, and

this takes time within an MDT to determine (Moore et al., 2024). Of the 341 biopsies performed between November 2023 and March 2024, a discrepancy between the histology outcome and MRI PI-RADS v2 score was found in 10% (n = 35) of patients. A system that could correlate the actual region of biopsy with the region of interest (ROI) on MRI may reduce the clinical uncertainty of hit or miss, and improve confidence of diagnosis.

11.4.2 Commercial collaboration

In June 2023, Canon Medical Systems (Crawley, UK) launched a new prostate software system on their Aplio i-series machines. This software attempts to do this required correlation by using segmentation software and computer assisted imaging (CAI) to reconstruct the ultrasound and fused MRI data set into a virtual 3D-prostate image. Prior to the advent of TP biopsy, I worked with the research and development of Canon Medical Systems as a clinical ultrasound advisor, and a ripple effect of my PhD was to continue this as the TP service develops. The benefits of using the software, in the real-life clinical setting of local anaesthetic TP biopsy, are emerging. However, as with all CAI (as discussed in Chapter 5.7), a large amount of data is required to train the system.

The Canon prostate system was trained with transrectal prostate datasets rather than TP imaging and, consequently, the software alignment is less that optimum but offers promise. Figure 11.1 and Figure 11.2 demonstrate the 3D reconstruction of the prostate, the ROI, and the sites of biopsy. The biopsy alignment is good for the ROI but has drifted for the non-targeted samples.

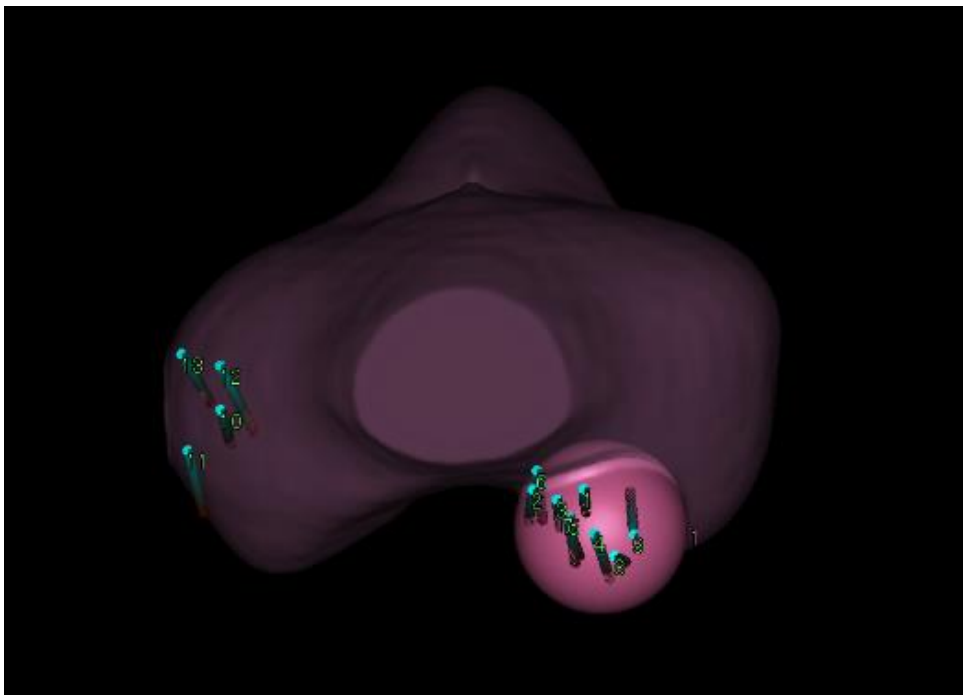

Figure 11.1 3D reconstructions of ultrasound volume dataset. Axial view.

The MRI ROI is depicted as the pink sphere; the individual biopsy sites in blue.

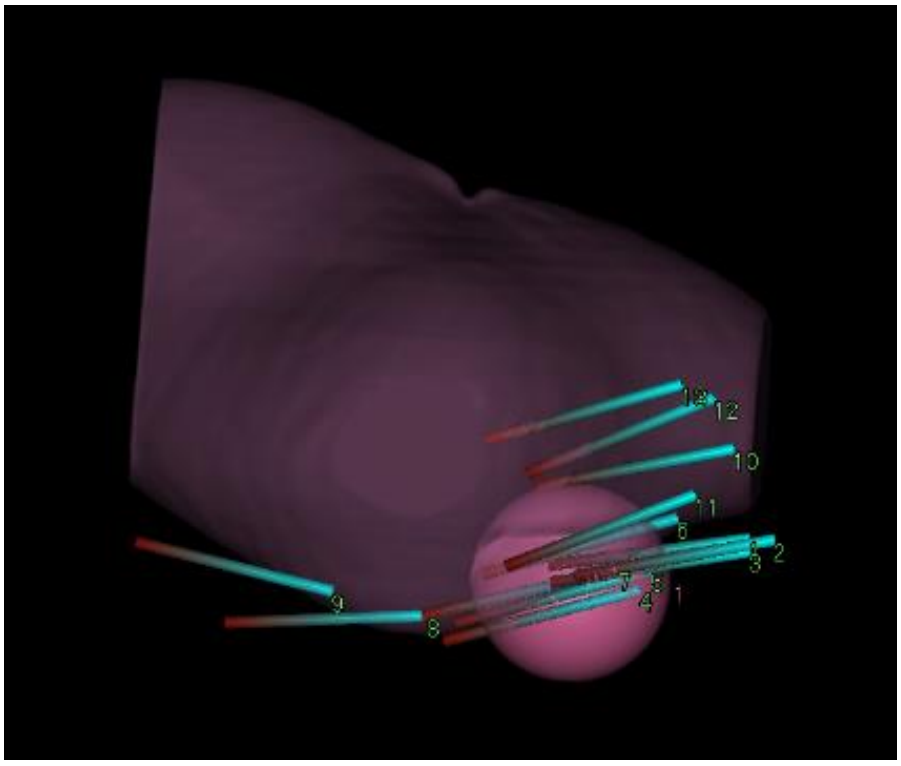

Figure 11.2 3D reconstructions of ultrasound volume dataset. Longitudinal view

There are issues with the 3D volume truncating and misrepresenting the prostate, as well as issues with alignment, but these early results demonstrate how biopsy sites and MRI could be correlated to improve confidence in the initial biopsy. Any patient

where there is doubt in needle placement could be referred for repeat biopsy prior to clinical plans being made; those with confident needle placement could be offered AS in the knowledge that reclassifying disease would be due to progression rather than an initial false negative biopsy. My involvement with this software development continues; I aim to further my research portfolio by investigating whether this technology can improve the confidence of prostate cancer diagnosis and reduce the need for confirmatory repeat investigations in the future.

11.5 Active surveillance management ripples

Whilst there may be exciting new imaging technologies such as prostate-specific membrane antigen positron emission tomography/computerised tomography (PSMA PET-CT) entering into the active surveillance of prostate cancer arena, microUS has not shown promise in the local context and alternative imaging is not available or indeed proven (Ahmadi et al., 2023; Bagguley et al., 2023). Locally, MRI capacity continues to be prioritised so that diagnostic targets can be met as discussed in Chapter 1.12. It is useful, therefore, to revisit what tests are readily available and how these could potentially be used in different ways. The core test in the prostate cancer pathway is the PSA blood test. Whilst this has its shortcomings as it highly sensitive (95%) but with a low specificity of only 18% (Roddam et al., 2005), it remains the bedrock for assessing risk of disease. Its low specificity is the reason that screening for prostate cancer is not advocated but PSA monitoring remains a valuable tool in the assessment of men suspected of, or being monitored for, csPCa (Pezaro et al., 2014).

As discussed in Chapter 3, men find regular testing reassuring (Ruane-McAteer, 2018), but with the clinical capacity for follow-up of patients being under extreme pressure (The King's Fund, 2024), there is a need to look for alternative solutions. NHS England (2020b) have published guidance for personalised care as they have identified that:

> "[personalised] stratified follow-up (PSFU) pathways tailored to individual needs offers huge benefits to patients and the NHS. . improves patient experience and … makes services more efficient and cost-effective." (ibid.)

This guidance suggests that a remote follow-up could be considered in men with stable PSA levels. This is supported by the NHS commitment to improving digital technology, as discussed in the published guidance for tackling the Covid-19 backlog (NHSE&I,

2022), and they identify that remote access frees outpatient capacity and, importantly, provides flexibility for patients. Remote monitoring is supported in the Urology GIRFT report (Moore et al., 2024), which advocates its use to minimise inconvenience to patients and avoid unnecessary visits to a hospital setting.

This flexibility is further explored by a Prostate Cancer UK funded project called the True North Model (Prostate Cancer UK, 2024a). This model includes an online portal for patients to access and view results, complete assessments, and message their clinical team. Crucially though, it includes a PSA tracking system that alerts clinical teams if a planned PSA test has not been performed and alerts them if planned PSA tests resulted fall outside of safe ranges personalised to individual patients. This system has been reviewed by the Royal College of Surgeon's Edinburgh's patient safety group (Fenn, 2023). They identified that the NHSE plan for PSFU lends itself to supported self-management by patients using remote digital platforms such as the True North PSA tracker. The findings from the Prostate Cancer UK project (2024) have shown this to be a safe and effective alternative to standard follow-up. Using the novel approaches that Fenn (2023) reviews may well place the patient in charge of their surveillance and lead to appropriate planned care for all those men eligible for, and desiring, a supported AS regime. However, this approach could also potentially increase health inequalities as those who are not computer literate or well-educated are going to be less likely to engage with these technologies (Nadarzynski et al., 2019). Where ultrasound and repeat biopsy sit within this new model of care requires careful further investigation.

11.6 Recommendations for future research

Many future research opportunities have emerged as a consequence of the potential pathway and service improvements discussed here, not least including evaluating the use of AI supported targeted biopsy and the evolution of personalised stratified active surveillance. However, further research into the role of microUS, and into the implementation of changes to the AS pathway, as a continuation of this thesis are indicated.

Whilst I may have not found a useful clinical role for ultrasound in AS, my findings suggest that microUS could be used for screening in patients in whom MRI is

contraindicated. Further research in this area is required to address the issue of confidence in the diagnostic capabilities of microUS, investigate the correlation between knowledge and skill development of practitioners is this field, and to understand the applicability of the current PRI-MUS^{TM} scoring system in real-life clinical settings.

One finding of my research that will make an immediate difference to patient care is the identification of weaknesses in the local AS pathway. Recognising and acknowledging inconsistencies in monitoring pathways is the first step to changing practice. Providing evidence of this inconsistency via my thesis has provided the foundation step towards locally reviewing and improving patient care. However, this needs to be placed into the wider context of NHS performance and pathway delivery and further investigation into the compliance of urology services with the current AS NHSE guidance (2024a) is indicated. This will facilitate an enhanced understanding of where microUS best fits within UK based prostate cancer care.

Completing this thesis has provided me with the opportunity for professional and personal growth and development. I believe my confidence in research methods has grown, and my understanding of the benefits of evaluating the implementation of new technologies has matured. Additionally, I have facilitated and supported development of the knowledge and skills of my sonographer team. This has led to greater professional involvement in the patient care pathway and the implementation of a TP biopsy service, which is just as accurate but safer for patients. Further qualitative research into the impact of the changing landscape of prostate cancer on practitioners will be invaluable to ensure continued service improvements and positive outcomes are sustained.

11.7 Conclusion

My investment into a prostate specific research project has given me profound insight into the real-life clinic pressures experienced both in imaging and by my urology colleagues. I started this PhD with the hope that I would find new ultrasound interventions, particularly the use of microUS, which would make a difference to patient care and outcomes for men diagnosed and living with prostate cancer. I have been unable to identify a role for ultrasound within the active surveillance of prostate

cancer, but, as I have discussed in this chapter, completing this thesis has resulted in improved patient care for those men on the diagnostic phase of the pathway.

The ERUP trial has facilitated an enhanced appreciation of microUS, and the challenges faced in the delivery of a prostate cancer service. However, I believe the greatest outcome from completing this thesis is the enriched understanding I now possess of the concerns and anxieties men present with as they start their diagnostic pathway. Ultrasound is just one part of this process; nonetheless, the service improvements that have occurred as a consequence of this research have smoothed the journey for patients to their all-important diagnosis.

"Wherever the art of medicine is loved, there is also a love of humanity."
Hippocrates, ancient Greek physician

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Word count (excluding references): 97,288

Appendix 1 Study 1, phase 1: Participant information leaflet

NHS
Hull University Teaching Hospitals
NHS Trust

Current Research in Ultrasound

Evaluating the Role of Ultrasound in Prostate Cancer Study (ERUP Study)

Participation Information sheet – Phase 1

Why is this research being done?

Prostate cancer can be difficult to detect but improvements in ultrasound technology may help us to identify disease more quickly than we can do now. Micro-ultrasound is a developing technology used in diagnostics to assess the prostate. With support from the local cancer alliance network, the radiology department has recently purchased a new ultrasound machine with this new technology. This machine will enable the team in radiology and urology to look at the prostate for evidence of cancer and determine if this new technology can detect disease at an earlier stage than is possible now.

Why have I been invited to take part?

You have been referred to urology for investigations of your prostate. The Consultant in charge of your care, or one of the doctors or nurses in your team, have asked us to do an MRI scan of your prostate. This looks at the prostate gland and can highlight areas of change that may indicate the need for biopsy. This research is being undertaken on men who have an MRI of the prostate that we can directly compare with the micro-ultrasound pictures, providing us with a valuable insight into the capabilities of this new technology. The data we collect will help improve diagnosis and biopsy planning for future patients. This is particularly important for men who cannot have MRI scans and to help the NHS cope with the demands for its services.

What are the benefits for me?

By taking part in this study, you will be helping patients of the future and will be helping Hull remain at the forefront of patient care. The data we collect may not be able to change your treatment but it will help men, like you, who are patients in the future. With your permission, will inform your consultant of anything incidental that we find on the scans as part of this research, and keep in close contact with you throughout.

How will my scan change if I choose to take part?

You will have a standard MRI scan as requested by your doctor or nurse. After that, we will arrange for you to have an ultrasound scan of your prostate. If you need a biopsy following your MRI, we will arrange to do this research scan at the same time. If you do not need a biopsy, we will arrange a convenient time for you to attend for an ultrasound scan that will be used in this study.

For this study, there will be two different ultrasound machines together in the room rather than one. Your prostate will be scanned using both machines, one after the other. After the scans have been completed we will then continue to undertake the prostate biopsy if needed or we will finish the examination and you will be free to go home.

The scans involve a narrow ultrasound probe being inserted a small way into the rectum. This will be similar to the digital rectal examination that you have had from your doctor or nurse. It will not be painful and we will stop the examination if you feel discomfort. The probe will be moved around a little and pictures of your prostate will be taken. The probe will be removed. A second probe will be inserted and the scan repeated using the new micro-ultrasound technology. Each scan will take no more than 5 minutes to complete.

The initial scan described above will be the same as if this research was not being done. The second examination is being done purely for this research study.

The pictures from the scans will be stored anonymously and will be compared to the MRI scan by independent reviewers, either a radiologist or a specialist sonographer. The outcomes of the reviews will be recorded on a secure, password protected database accessible only to the research team.

We will record the result of your latest prostate serum antigen (PSA) blood test which we access from the hospital electronic record system – this is something we do routinely as knowing your blood tests can be important to relate to the scan pictures we normally look at. We will also record the outcomes of any biopsies you have had taken. This extra information will let us see if there are any ultrasound features of the prostate that match the tissue sample readings the laboratories produce.

Is there any risk?

There are no known risks of having an ultrasound scan. Ultrasound is a very safe test.

Will this affect my treatment or care?

Being involved in this research will not affect how you are treated or cared for in any way.

Do I have to take part?

You do not have to take part in this research if you do not want to – it is completely your choice and we will not ask why you have or have not decided to be involved. Not being involved in this research will not affect how you are treated or cared for in any way.

Prior to your MRI you will be contacted by me, Pamela Parker, the lead researcher for this study. I will contact you by 'phone to explain more about our research and to seek your consent to join this study.

Travel and Parking

Travel and parking expenses related to your attendance for this research will be reimbursed by the ultrasound department. Please provide receipts where possible.

Will my Doctor know I have taken part?

We will let the Consultant in charge of your care know you have taken part as while this will not affect how you are looked after in any way, they are responsible for your care overall. We will also inform your own GP that you have been involved and send them a copy of this information sheet so that they are aware you have been involved.

What do I do now

Thank you for considering and taking part in this valuable study. I will contact you prior to your MRI and discuss the study with you. If you are happy to proceed I will make a mutually convenient appointment for the ultrasound scan. This is likely to be the same day and time as your planned prostate biopsy.

One the day of the appointment, there will be an opportunity before you are taken into the scan room to ask any questions you have. If you are happy to take part in the research we will ask you to sign a consent form before you go into the room.

Consent

You can change your mind and you can withdraw your consent at any time. If you withdraw from the study you will be asked if we can continue to use your data in accordance with the data protection details that follow in the next section.

Appendix 2 Study 1, phase 1: Participant consent form

Participant Consent Form – Phase 1

Evaluating the Role of Ultrasound in Prostate Cancer Study (ERUP Study)

Name of Chief Investigator: Pamela Parker	**Please confirm agreement to the statements by putting your initials in the boxes below**
I confirm that I have read and understand the information sheet dated **03/11/2021** (version **2**) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	
I understand that incidental findings may be detected during the scans. I give permission for these to be shared with my consultant	
I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
I agree to my consultant being informed of my participation in the study.	
I agree to take part in the above study.	
Participant Signature Date	
Name of Participant	
Researcher Signature Date	
Name of Researcher **Pamela Parker**	

Copy of ICF V2 given to participant, copy held in patient notes, copy retained by research team

Appendix 3 Ethics approval

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Mrs Pamela Parker
Consultant Sonographer
Hull University Teaching Hospitals NHS Trust
Ultrasound, Radiology
Castle Hill Hospital, Castle Road
Cottingham, East Yorkshire
HU16 5JQ

Email: approvals@hra.nhs.uk

23 November 2021

Dear Mrs Parker

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**A proof of concept study evaluating the role of emerging ultrasound technologies in the assessment and monitoring of localised prostate cancer in men on an active surveillance programme.**
IRAS project ID:	**301506**
Protocol number:	**N/A**
REC reference:	**21/SC/0326**
Sponsor	**Hull University Teaching Hospitals NHS Trust**

I am pleased to confirm that HRA Approval has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report

(including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The standard conditions document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **301506**. Please quote this on all correspondence.

Yours sincerely,
Benita Hallewell-Goodwin

Email: approvals@hra.nhs.uk

Copy to: *Mr James Illingworth, Hull University Teaching Hospitals NHS Trust*

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w: www.hull.ac.uk

PRIVATE AND CONFIDENTIAL
Pamela Parker
Faculty of Health Sciences
University of Hull
Via email

7th December 2021

Dear Pamela

REF FHS397 - A proof of concept study evaluating the role of emerging ultrasound technologies in the assessment and monitoring of localised prostate cancer in men on an active surveillance programme

Thank you for submitting your ethics application to the Faculty of Health Sciences Research Ethics Committee.

Given the information you have provided I confirm approval by Chair's action.

Please refer to the Research Ethics Committee web page for reporting requirements in the event of any amendments to your study.

Should an Adverse Event need to be reported, please complete the Adverse Event Form and send it to the Research Ethics Committee FHS-ethicssubmissions@hull.ac.uk within 15 days of the Chief Investigator becoming aware of the event.

I wish you every success with your study.

Yours sincerely

Professor Liz Walker
Chair, FHS Research Ethics Committee

UNIVERSITY OF HULL

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R2706 Micro Ultrasound Prostate study Confirmation of CC - Message (HTML)

File Message Tell me what you want to do...

HUNN, Louise (HULL UNIVERSITY TEACHING HOSPITALS NHS TRUST) PARKER, Pamela (HULL UNIVERSITY TEACHING HOSPITALS NHS TRUST)

R2706 Micro Ultrasound Prostate study Confirmation of CC

You replied to this message on 06/12/2021 11:59.

Dear Mrs Parker

Confirmation of Capacity and Capability at Hull University Hospitals Teaching NHS Trust

(Please retain a copy of this email as this confirms NHS permission for this site)

IRAS: 301506
LOCAL ref: R2706
EDGE ID: 144770
REC ref: 21/SC/0326

Full Study Title: A proof of concept study evaluating the role of emerging ultrasound technologies in the assessment and monitoring of localised prostate cancer in men on an active surveillance programme.
PI: Mrs P Parker

Sponsor: HUTH

This email confirms that Hull University Teaching Hospitals NHS Trust has the Capacity and Capability to deliver the above referenced study.

It is noted that all relevant Regulatory and Internal Approvals are in place. As the study Sponsor is also the same site (HUTH) where the research is to take place, there is no requirement for a site agreement or Organisation Information Document.

Given the current pandemic situation you must ensure you take the appropriate steps to protect yourself and all persons that may agree to participate in the study by adhering to the Government and Trust guidelines regarding Social Distancing and where appropriate the wearing of PPE

Please either update EDGE or inform me of the actual date the research activity commences

The study is on the EDGE database www.edge.nhs.uk and can be found using the R&D reference, IRAS number, EDGE ref or the study title all shown above

You will need to ensure the study is updated on EDGE with the following;

- All patient screening/recruitment data. Via the patient tab

If you need any further support from R&D please do not hesitate to contact me.

With best wishes for a successful study

Kind regards
Lou

Louise Hunn
Research Facilitator & RDU 1 Delivery Lead

Hull University Teaching Hospitals NHS Trust
Research & Development
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Castle Road, Cottingham
HU16 5JQ

NHS
Hull University Teaching Hospitals
NHS Trust

Appendix 4 Micro-ultrasound record sheet: baseline imaging

Hull University Teaching Hospitals NHS Trust

ExactVu lesion Detection Worksheet

EXACT IMAGING

Pt ID

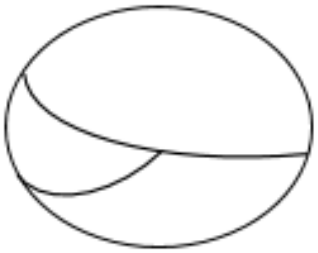
Date of Biopsy_____

Sonographer 1:_____Sonographer 2:_____

Shade site / area of highest PRIMUS Score

RIGHT

PRIMUS Score

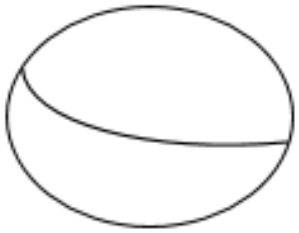


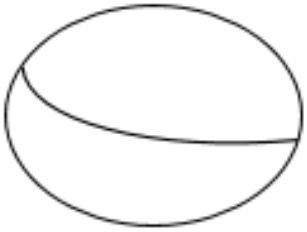
LEFT

PRIMUS Score

Para Sagittal

PRIMUS Score

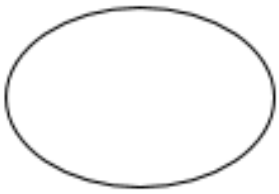


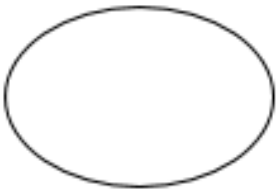


PRIMUS Score

Mid Medial

PRIMUS Score





PRIMUS Score

Lateral

Patient Information

PSA:____

DRE:____

Volume:_____

NHS
Hull University Teaching Hospitals
NHS Trust

Biopsy Worksheet

EXACT IMAGING

Patient Name:_____ D/O/B:_____

Date of Biopsy:_____ Hospital: Castle Hill Hull

Sonographer:_____

MRT Fusion Information

	Lesion 1	Lesion 2	Lesion 3
PIRADS Score			
Lesion position			
Cine Nos			
Target sampled with MicroUS			
Diameter of Lesion			

Appendix 5 Standard ultrasound review form

ERUP Study Data Collection Form

Lead Researcher only	Participant number:	
	Phase 1	Phase 2

Reviewer: Please circle 1 2 3 4 5 6

Date of Review:

Imaging Reviewed:

Standard US	Date of Scan

Cine Loop Images

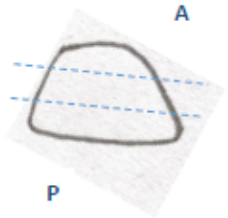
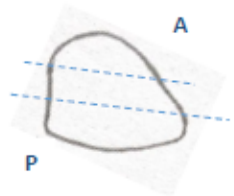
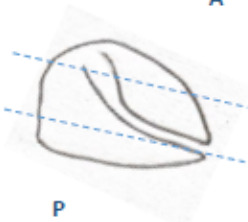
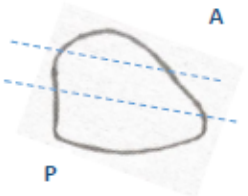
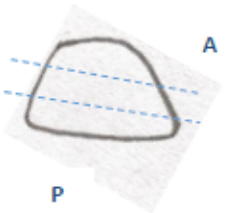
Please indicate findings of both longitudinal sweep and transverse sweep:

Longitudinal Sweep	Findings:	Transverse Sweep	Findings:
Opinion of prostate on review of cine loop	No apparent abnormality	Opinion of prostate on review of cine loop	No apparent abnormality
	Uncertain		Uncertain
	Normal BPH nodule (s)		Normal BPH nodule (s)
	Atypical focal area (s)		Atypical focal area (s)
If lesion identified, please indicate approximate site	Rt Lateral	If lesion identified, please indicate approximate site	Right Base
	Rt Mid		Left Base
	Central/midline		Right Mid
	Lt Mid		Left Mid
	Lt Lateral		Right Apex
			Left Apex

Approximate Prostate Volume:		
Length (cm)		
Height (cm)		
Width (cm)		
Volume:	x 0.53	

Unable to calculate? State reason:

Longitudinal Images: Please document all focal areas of abnormality identified on images

Please indicate approximate site of any lesion identified	Approximate size of any lesion (mm)	Please indicate your opinion of appearances of the prostate	Please indicate if colour flow is present
RIGHT Lateral Section 	1)	No apparent abnormality	Not present
	2)	Typical BPH	Yes - within whole colour box
	3)	Uncertain of appearances	Yes, confined to 50% of lesion only
	4)	Atypical & hypoechoic lesion	Yes - within whole lesion but not beyond
	5)	Atypical & hyperechoic lesion	Yes - diffuse perfusion throughout image
RIGHT Mid Section 	1)	No apparent abnormality	Not present
	2)	Typical BPH	Yes - within whole colour box
	3)	Uncertain of appearances	Yes, confined to 50% of lesion only
	4)	Atypical & hypoechoic lesion	Yes - within whole lesion but not beyond
	5)	Atypical & hyperechoic lesion	Yes - diffuse perfusion throughout image
Central / Midline Section 	1)	No apparent abnormality	Not present
	2)	Typical BPH	Yes - within whole colour box
	3)	Uncertain of appearances	Yes, confined to 50% of lesion only
	4)	Atypical & hypoechoic lesion	Yes - within whole lesion but not beyond
	5)	Atypical & hyperechoic lesion	Yes - diffuse perfusion throughout image
LEFT Mid Section 	1)	No apparent abnormality	Not present
	2)	Typical BPH	Yes - within whole colour box
	3)	Uncertain of appearances	Yes, confined to 50% of lesion only
	4)	Atypical & hypoechoic lesion	Yes - within whole lesion but not beyond
	5)	Atypical & hyperechoic lesion	Yes - diffuse perfusion throughout image
LEFT Lateral Section 	1)	No apparent abnormality	Not present
	2)	Typical BPH	Yes - within whole colour box
	3)	Uncertain of appearances	Yes, confined to 50% of lesion only
	4)	Atypical & hypoechoic lesion	Yes - within whole lesion but not beyond
	5)	Atypical & hyperechoic lesion	Yes - diffuse perfusion throughout image

Appendix 6 Micro-ultrasound review form

ERUP Study Data Collection Form

	Phase 1	Phase 2

Reviewer: Please circle 1 2 3 4 5 6

Date of Review:

Imaging Reviewed:

Micro US	Date of Scan

Cine Loop Images

Please indicate findings of both longitudinal sweep and transverse sweep:

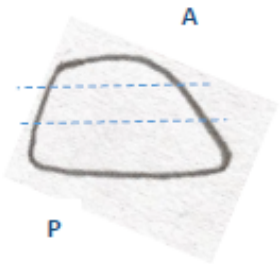
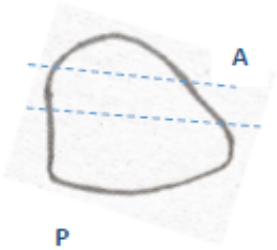
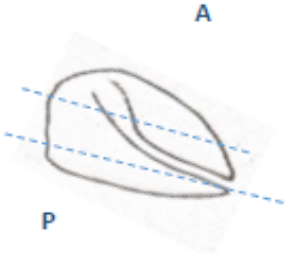
Longitudinal Sweep	Findings:		Comments:
Opinion of prostate on review of cine loop	No apparent abnormality		
	Uncertain		
	Normal BPH nodule (s)		
	Atypical focal area (s)		
If lesion identified, please indicate approximate site	Rt Lateral	If lesion identified, please indicate approximate site	Right Base
	Rt Mid		Left Base
	Central/midline		Right Mid
	Lt Mid		Left Mid
	Lt Lateral		Right Apex
			Left Apex

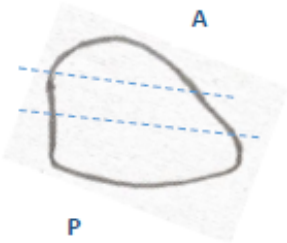
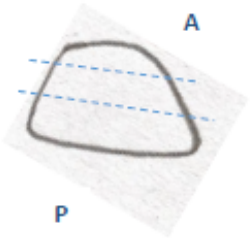
Approximate Prostate Volume:		
Length (cm)		
Height (cm)		
Width (cm)		
Volume:	x 0.53	

Unable to calculate? State reason:

Longitudinal Images: Please document all focal areas of abnormality identified on images

Image reporting as per the evidence based prostate risk identification using micro-ultrasound PRI-MUS™ protocol https://www.exactimaging.com/primus-protocol

Please indicate approximate site of any lesion identified	Approximate size of any lesion (mm)	Please indicate your opinion of appearances of the prostate		Please indicate PRI-MUS™ Score you would assign
RIGHT Lateral Section 	i)	Small regular ducts "Swiss Cheese"		1
	ii)	Hyperechoic with/without ductal patches		2
	iii)	Mild heterogeneity or Bright Echoes in hyperechoic tissue		3
	iv)	Heterogeneous "Cauliflower", "smudgy or mottled" or Bright Echoes ("Starry Sky")		4
	v)	Irregular Shadowing or Mixed-echo lesions or Irregular Prostate/border		5
		Uncertain		Uncertain
RIGHT Mid Section 	i)	Small regular ducts "Swiss Cheese"		1
	ii)	Hyperechoic with/without ductal patches		2
	iii)	Mild heterogeneity or Bright Echoes in hyperechoic tissue		3
	iv)	Heterogeneous "Cauliflower", "smudgy or mottled" or Bright Echoes ("Starry Sky")		4
	v)	Irregular Shadowing or Mixed-echo lesions or Irregular Prostate/border		5
		Uncertain		Uncertain
Central / Midline Section 	i)	Small regular ducts "Swiss Cheese"		1
	ii)	Hyperechoic with/without ductal patches		2
	iii)	Mild heterogeneity or Bright Echoes in hyperechoic tissue		3
	iv)	Heterogeneous "Cauliflower", "smudgy or mottled" or Bright Echoes ("Starry Sky")		4
	v)	Irregular Shadowing or Mixed-echo lesions or Irregular Prostate/border		5
		Uncertain		Uncertain

LEFT Mid Section 	i)	Small regular ducts "Swiss Cheese"		1
	ii)	Hyperechoic with/without ductal patches		2
	iii)	Mild heterogeneity or Bright Echoes in hyperechoic tissue		3
	iv)	Heterogeneous "Cauliflower", "smudgy or mottled" or Bright Echoes ("Starry Sky")		4
	v)	Irregular Shadowing or Mixed-echo lesions or Irregular Prostate/border		5
		Uncertain		Uncertain
LEFT Lateral Section 	i)	Small regular ducts "Swiss Cheese"		1
	ii)	Hyperechoic with/without ductal patches		2
	iii)	Mild heterogeneity or Bright Echoes in hyperechoic tissue		3
	iv)	Heterogeneous "Cauliflower", "smudgy or mottled" or Bright Echoes ("Starry Sky")		4
	v)	Irregular Shadowing or Mixed-echo lesions or Irregular Prostate/border		5
		Uncertain		Uncertain

Appendix 7 Study 1, phase 2: Participant information leaflet

NHS
Hull University Teaching Hospitals
NHS Trust

Current Research in Ultrasound

Evaluating the Role of Ultrasound in Prostate Cancer Study (ERUP Study)

Participation Information sheet – Phase 2

Why is this research being done?

Prostate cancer can be difficult to detect but improvements in ultrasound technology may help us to identify disease more quickly than we can do now. Micro-ultrasound is a developing technology used in diagnostics to assess the prostate. The aim of this study is to investigate if micro-ultrasound can be used to help monitor men who have regular review of their prostate and to see if it can detect any changes that may lead to earlier treatment if required.

Why have I been invited to take part?

You will have previously been investigated for suspected prostate cancer and have had an MRI scan. You may also have had a biopsy of your prostate although not all men do. Your consultant has diagnosed low grade prostate cancer and you are being monitored for any evidence of progression. This is known as active surveillance or watchful waiting. Whilst being monitored you will have regular blood tests and digital rectal examinations. Occasionally you may also be referred for an MRI scan. These routine tests can give us an indication of whether your prostate gland is stable or changing. However, published evidence suggests that micro-ultrasound will be able to add valuable information to the doctors looking after patients being monitored in the future that may lead to earlier treatment than they can currently provide.

What are the benefits of me joining this research?

This research is being undertaken on men who are being monitored so that we can increase our understanding of the benefits of using micro-ultrasound in the monitoring of prostate cancer. Being able to scan men who are currently being monitored will allow us to compare this new technology with the routine regular tests available. This will provide us with a valuable insight into the capabilities of this new technology. The data we collect will help improve the monitoring of men in the future. By taking part in this trial you will be helping patients of the future and will be helping Hull remain at the forefront of patient care.
The data we collect may not be able to change your treatment but it will help men, like you, who are patients in the future. With your permission, will inform

your consultant of anything incidental that we find on the scans as part of this research, and keep in close contact with you throughout.

How will my monitoring change if I choose to take part?

You will have routine blood tests and digital rectal examinations regularly as part of your prostate monitoring. For this research, you will be invited to have ultrasound scans in addition to the routine tests. The first ultrasound scan will be done in the next few weeks and then every 6-months for the duration of the study. You will be invited to a minimum of 1 and a maximum of 4 scans for this study. We will arrange a convenient time for you to attend for each of the ultrasound scans that will be used in this study.

When you attend for the ultrasound scans, there will be two different ultrasound machines together in the room rather than one. Your prostate will be scanned using both machines, one after the other. After the scans have been completed you will be free to go home.

The scans involve a narrow ultrasound probe being inserted a small way into the rectum. This will be similar to the digital rectal examination that you have had from your doctor or nurse. It will not be painful and we will stop the examination if you feel discomfort. The probe will be moved around a little and pictures of your prostate will be taken. The probe will be removed. A second probe will be inserted and the scan repeated using the new micro-ultrasound technology. Each scan will take no more than 5 minutes to complete.

Both of these scans are being done purely for this research study. They are in addition to your routine care.

The pictures from the scans will be compared to your previous MRI scan by independent reviewers, either a radiologist or a specialist sonographer. If you participated in phase 1 of this study, the pictures will also be compared to the previous ultrasound scans you had taken. The outcomes of the reviews will be recorded on a secure, password protected database accessible only to the research team.

We will record the result of your latest prostate serum antigen (PSA) blood test which we access from the hospital electronic record system – this is something we do routinely as knowing your blood tests can be important to relate to the scan pictures we normally look at. We will also record the outcomes of any biopsies you have previously had taken. This extra information will let us see if there are any ultrasound features of the prostate that match the tissue sample readings the laboratories produce.

Is there any risk?

There are no known risks of having an ultrasound scan. Ultrasound is a very safe test.

Will this affect my treatment or care?

Being involved in this research will not affect how you are treated or cared for in any way.

Do I have to take part?

You do not have to take part in this research if you do not want to – it is completely your choice and we will not ask why you have or have not decided to be involved. Not being involved in this research will not affect how you are treated or cared for in any way.

Once you have been given a diagnosis from the doctor looking after you and agreed a monitoring plan you will be contacted by me, Pamela Parker, the lead researcher for this study. I will contact you by 'phone to explain more about our research and to seek your consent to join this study. Thank you considering this invitation.

Travel and Parking

Travel and parking expenses related to your attendance for this research will be reimbursed by the ultrasound department. Please provide receipts where possible.

Will my Doctor know I have taken part?

We will let the Consultant in charge of your care know you have taken part as while this will not affect how you are looked after in any way, they are responsible for your care overall. We will also inform your own GP that you have been involved and send them a copy of this information sheet so that they are aware you have been involved.

What do I do now?

Thank you for considering and taking part in this valuable study. I will contact you in the next few weeks to discuss the study with you. If you are happy to proceed I will make a mutually convenient appointment for the ultrasound scan.

One the day of the appointment, there will be an opportunity before you are taken into the scan room to ask any questions you have. If you are happy to

take part in the research we will ask you to sign a consent form before you go into the room.

Consent

You can change your mind and you can withdraw your consent at any time. If you withdraw from the study you will be asked if we can continue to use your data in accordance with the data protection details that follow in the next section.

Information about me, Pamela Parker the lead researcher

I am receiving help from the research and development department within the Trust and the University of Hull as part of a PhD study. Hull University Teaching hospitals is sponsoring this research. All data I collect and store is in accordance with the Health Research Association and information can be found via the HRA link: www.hra.nhs.uk/patientdataandresearch

Your information and data protection

In this research study, we will use information from your MRI, ultrasound and biopsy investigations. We will only use information that we need for the research study. We will let very few people know your name or contact details, and only if they really need it for this study.

The data we collect will include your initials and a code number held on the secure hospital server. People will use this information to do the research or to check your records to make sure that the research is being done properly. People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead.

We will keep all information about you safe and secure. Everyone involved in this study will keep your data safe and secure. We will also follow all privacy rules.

Once we have finished the study, we will keep some of the data for a maximum of three years so we can check the results. The data will then be securely deleted. We will write our reports in a way that no-one can work out that you took part in the study.

What are your choices about how your information is used?

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.

Where can you find out more about how your information is used?
You can find out more about how we use your information

at www.hra.nhs.uk/information-about-patients/
our leaflet available from the urology nurse specialist or from ultrasound, at Castle Hill Hospital,
by asking one of the research team,
by sending an email to pamela.parker6@nhs.net or ResearchDevelopment@nhs.net ,
by ringing us on (01482) 623065

Our data protection officer can be contacted via email to HEYIG@nhs.net

Appendix 8 Participant consent form: study 1, phase 2

Hull University Teaching Hospitals NHS Trust

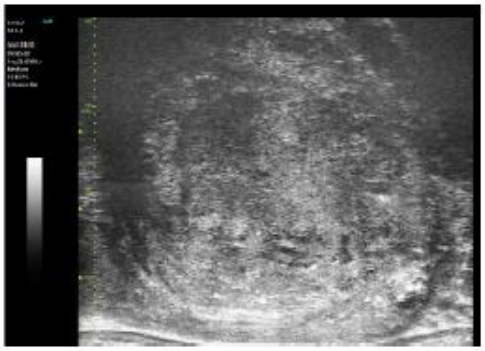
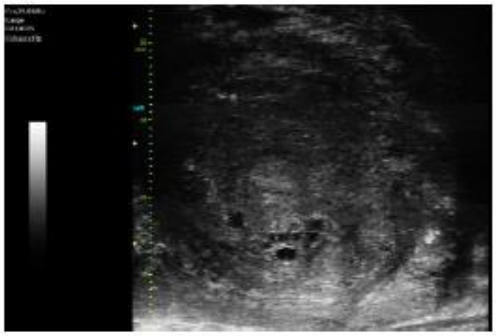
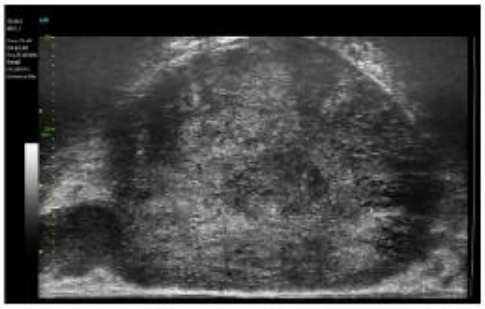
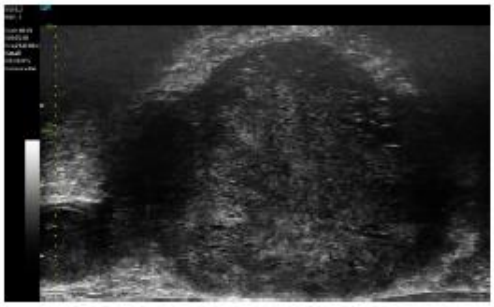
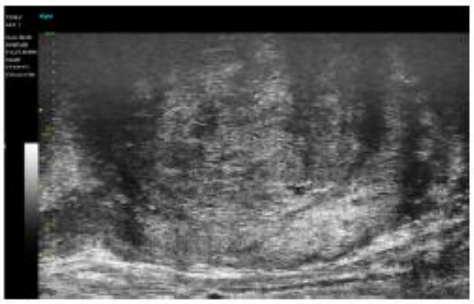
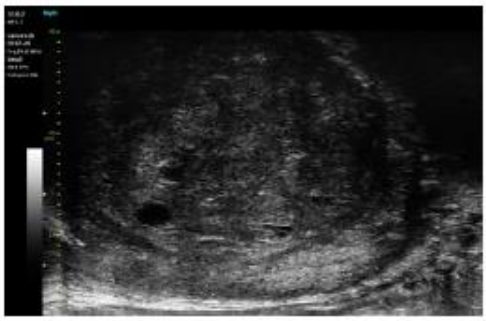
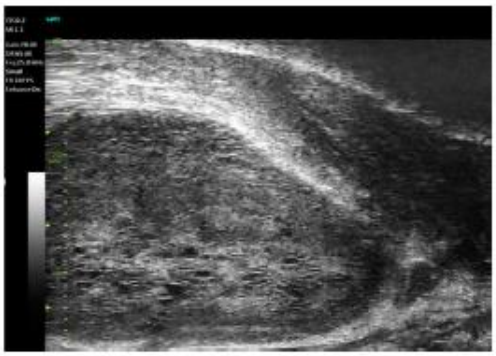
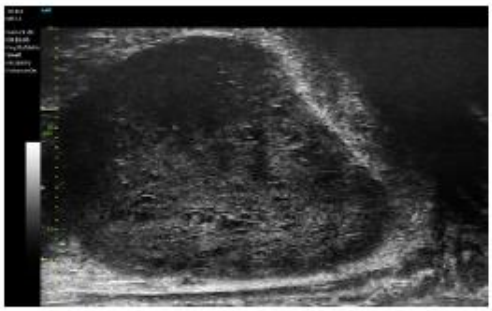
Participant Consent Form – Phase 2

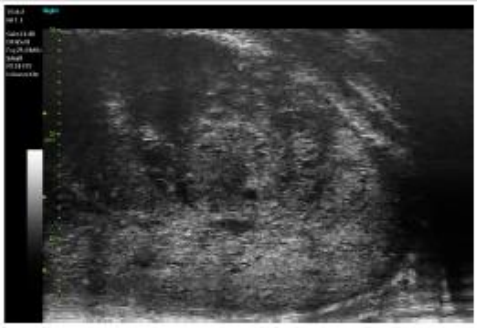
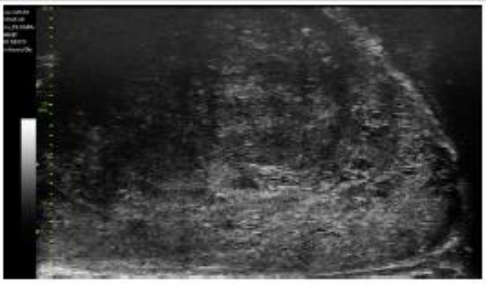
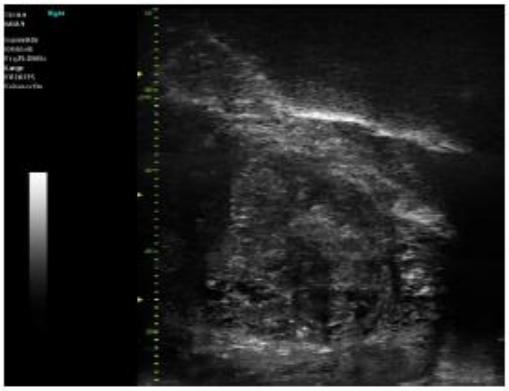
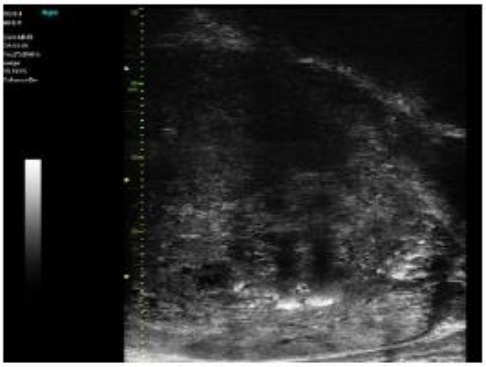
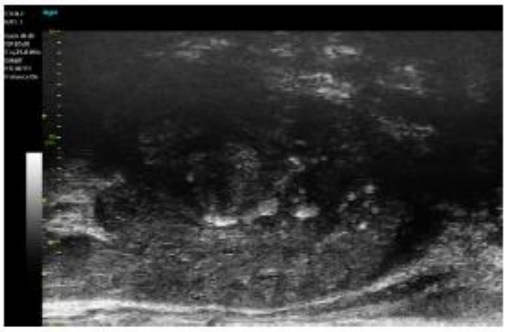
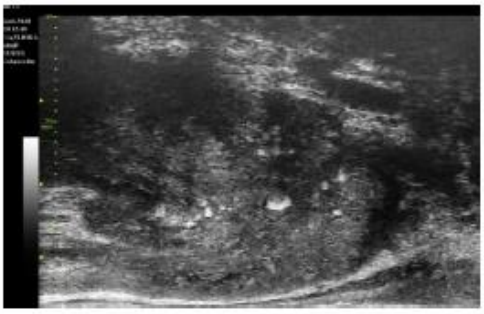
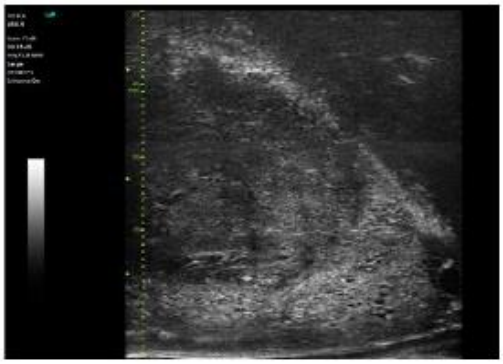
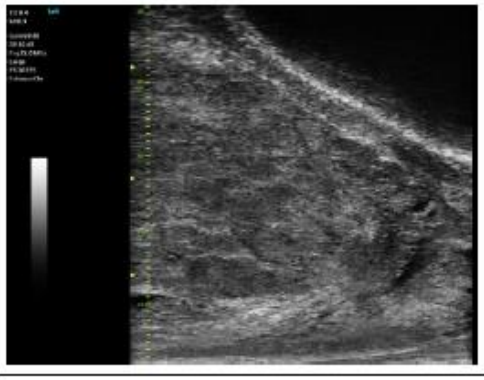
Evaluating the Role of Ultrasound in Prostate Cancer Study (ERUP Study)

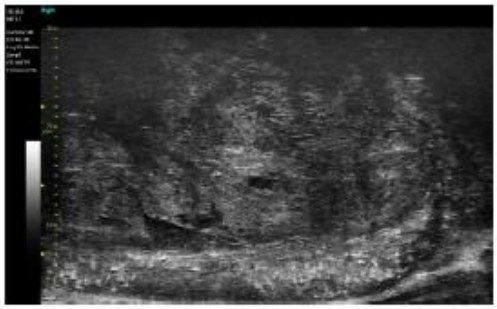
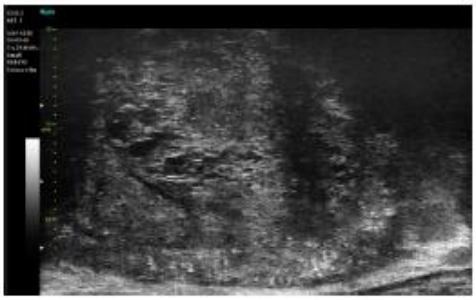
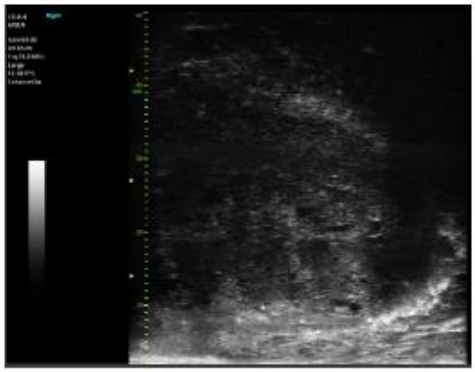
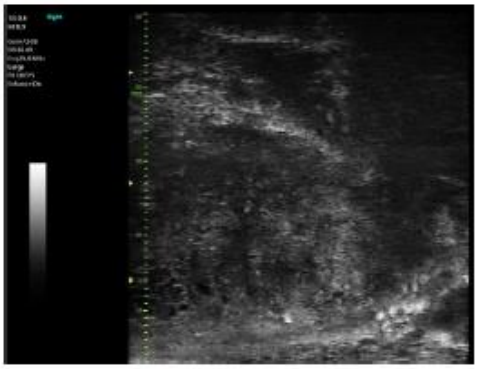
Name of Chief Investigator: Pamela Parker	**Please confirm agreement to the statements by putting your initials in the boxes below**
I confirm that I have read and understand the information sheet dated **03/11/2021** (ICF version 2) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	
I understand that incidental findings may be detected during the scans. I give permission for these to be shared with my consultant	
I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
I agree to my consultant being informed of my participation in the study.	
I agree to take part in the above study.	
Participant Signature Date	
Name of Participant	
Researcher Signature Date	
Name of Researcher **Pamela Parker**	

Copy of ICF V2 given to participant, copy held in patient notes, copy retained by research team

Appendix 9 Study 1, phase 2 participants representative images

UIN	Representative image of baseline microUS – image of highest score	Representative image of follow-up microUS – image of highest score
ERUP4 Equivocal score at baseline. Histology: Gleason 3+3 (0.5 mm core)		
ERUP22 Low risk score at baseline. Histology: ASAP		
ERUP26 Low risk score at baseline. Histology: benign		
ERUP27 Low risk score at baseline. Histology: benign		

ERUP44 Low risk score at baseline. Histology: benign		
ERUP50 Equivocal score at baseline. Histology: Gleason 3+3 (1 mm core)		
ERUP58 High risk score at baseline Histology : Gleason 3+3 (3 mm core)		
ERUP88 High risk score at baseline Histology : benign		

ERUP95 Low risk score at baseline. Histology: prostatitis		
ERUP104 Low risk score at baseline. Histology: 3+4 (2mm core)		

Appendix 10 ERUP NoMAD questionnaire

Evaluating the Role of Ultrasound in Prostate Cancer Study (ERUP Study)

Implementation of new technology into clinical practice survey

This survey is designed to help get a better understanding of how to apply and integrate new technologies and complex interventions in health care.
This survey asks questions about the implementation of **micro-ultrasound in prostate imaging**. We understand that people involved with **prostate imaging** have different roles, and that people may have more than one role.

From the statements below please choose an option that best describes ***your main role*** in relation to **micro-ultrasound in prostate cancer assessment**:

I am, or will be, involved in managing micro-US in prostate assessment ☐
I am, or will be, involved in performing micro-US and prostate imaging ☐
I am, or will be, involved in the interpretation of micro-US as radiologist or at MDT ☐

For this survey, please answer all the statements from the perspective of the role you specify. Depending on your role or responsibilities in relation to micro-ultrasound, some statements may be more relevant than others.

The survey is in 3 parts. Part A asks some brief questions about yourself and your role. Part B includes three general questions about **micro-ultrasound and prostate imaging**; Part C contains a set of more detailed questions about **micro-ultrasound and prostate cancer assessment**. For each statement in Part C, there is the option to agree or disagree with what is being asked **(OPTION A)**. However, if you feel that the statement is not relevant to you, there are also options to tell us why **(OPTION B)**.

Please take the time to decide which answer **best suits your experience for each statement and tick the appropriate box**

Part A: About Yourself

Question 1:
Please provide your professional background:

Sonographer	
Consultant Radiologist	
Radiology Registrar	
Consultant Urologist	
Urology Registrar	
Would rather not say	

Question 2:

Approximately how many years' experience of performing or interpreting / reviewing prostate imaging do you have?

0 – 1 years	
1 – 3 years	
3 – 5 years	
5 – 10 years	
10 + years	
Would rather not say	

Question 3:

Do you currently perform any transrectal ultrasound to provide any diagnostic information in your clinical practice? Please select the answer that best reflects your practice.

Yes – I provide a diagnostic interpretation of the prostate in my reports	
Yes – I identify target lesions suitable for biopsy but do not provide comment on this in my report	
No – I only use ultrasound to identify the prostate to guide biopsy either with or without MRI fusion imaging	
No – I currently do not perform any transrectal ultrasound in my clinical practice	

Question 4:

Have you any experience of performing and / or interpreting micro-ultrasound imaging of the prostate? Please select the answer that best reflects your experience.

Yes – I am regularly using this technology in my everyday practice and am confident in its use and interpretation of the images produced	
Yes – I am using it on a trial basis and am learning to interpret images produced	
Yes – I have undertaken the online core training modules and hands on training but have limited experience in clinical practice	
Yes – I have undertaken the online core training modules only	
Yes – I have seen some images but have not undertaken any specific training or procedures	
None - I have very limited or no experience of micro-ultrasound to date	

Part B: General questions about micro-ultrasound in prostate cancer assessment

Please indicate on the arrow with a X, or circle the number on the scale that best fits how you feel today

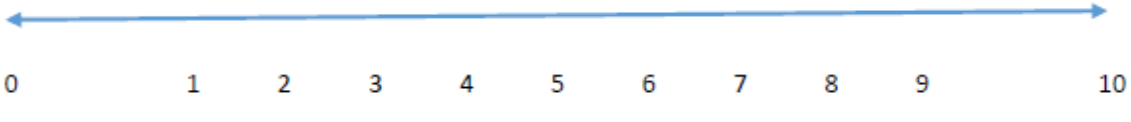
When you use or interpret micro-ultrasound **how familiar** does it feel?

Still feels very new — Feels completely familiar

0 1 2 3 4 5 6 7 8 9 10

Do you feel the use or interpretation of micro-ultrasound **is currently** a normal part of your work?

Not at all — Somewhat — Completely



0 1 2 3 4 5 6 7 8 9 10

Do you feel the use or interpretation of micro-ultrasound **will become** a normal part of your work?

Not at all — Somewhat — Completely

0 1 2 3 4 5 6 7 8 9 10

Part C: Detailed questions about micro-ultrasound in prostate cancer assessment

For each statement please select an answer that best suits your experience using Option A. If the statement is not relevant to you, please select an answer from Option B.

Section C1		OPTION A					OPTION B		
		Strongly Agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree	Not relevant to my role	Not relevant at this stage	Not relevant to micro-US
1	I can see how micro-US differs from usual ways of working								
2	Staff in this team have a shared understanding of the purpose of micro-US								
3	I understand how micro-US affects the nature of my own work								
4	I can see the potential value of micro-US for my work / role								

Section C2		OPTION A					OPTION B		
		Strongly Agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree	Not relevant to my role	Not relevant at this stage	Not relevant to micro-US
1	There are key people who drive micro-US forward and get others involved								
2	I believe that participating in micro-US is a legitimate part of my role								
3	I'm open to working with colleagues in new ways to use micro-US								
4	I will continue to support micro-US								

For each statement please select an answer that best suits your experience using Option A. If the statement is not relevant to you, please select an answer from Option B.

Section C3		OPTION A						OPTION B		
		Strongly Agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree		Not relevant to my role	Not relevant at this stage	Not relevant to micro-US
1	I can easily integrate micro-US into my existing work									
2	Micro-US disrupts working relationships									
3	I have confidence in other people's ability to use micro-US									
4	Work is assigned to those with skills appropriate to perform or interpret micro-US									
5	Sufficient training is provided to enable staff to implement micro-US into practice									
6	Sufficient resources are available to support the use and/or interpretation of micro-US									
7	Management adequately supports the use and / or interpretation of micro-US in clinical practice									

For each statement please select an answer that best suits your experience using Option A. If the statement is not relevant to you, please select an answer from Option B.

Section C4		OPTION A						OPTION B		
		Strongly Agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree		Not relevant to my role	Not relevant at this stage	Not relevant to micro-US
1	I am aware of published reports about the effects of micro-US in prostate cancer assessment									
2	The staff in my team agree that micro-US in prostate cancer assessment is worthwhile									
3	I value the effects that micro-US has had on my role and responsibilities									
4	Feedback about micro-US is encouraged and can be used to improve it in the future									
5	I can modify how I work with micro-US in prostate cancer assessment									

Appendix 11 Study 2: Participant information leaflet

Hull University Teaching Hospitals NHS Trust

Current Research in Ultrasound

Evaluating the Role of Ultrasound in Prostate Cancer Study (ERUP Study)

Participation Information sheet – Study 2

Why is this research being done?

Micro-ultrasound is a developing technology used in diagnostics to assess the prostate.. With support from the local cancer alliance network, the radiology department has recently purchased a new ultrasound machine with micro-ultrasound functions. This machine will enable the team in radiology and urology to look at the prostate for early evidence of cancer development. The aim of this study is to investigate if this technology can be used to help monitor men who have regular review of their prostate and to see if it can detect any changes that may lead to earlier treatment if required. This third phase of the study is evaluating the implementation of, and confidence in using, new technology in everyday clinical practice.

Why have I been invited to take part?

This research is being undertaken on men who are being investigate for suspected prostate cancer, or who are being monitored for signs of prostate cancer progression. We are doing this so that we can increase our understanding of the benefits of using micro-ultrasound in the diagnosis and active surveillance or watchful waiting pathway of prostate cancer.

You have been invited to participate as you currently have an active role within the prostate cancer pathway. You either currently perform transrectal ultrasound imaging of the prostate, interpret MRI prostate imaging or review imaging results as part of the MDT, or a combination of all. The opinions of all health care professionals is invaluable if we are to successfully implement this new technology within the local pathway and help inform the evidence base around prostate imaging.

Being able to scan men who are currently being monitored will allow us to compare this new technology with the routine regular tests available. This will provide us with a valuable insight into the capabilities of this new technology. The data we collect may help improve the diagnosis and monitoring of men in the within the prostate cancer pathway. By taking part in this trial you will be

helping patients of the future and will be helping Hull remain at the forefront of patient care.

What does phase 3 of the research look like and will my role change?

Patients locally, with suspected prostate cancer or those opting for active surveillance or watchful waiting, are being invited into phase 1 or phase 2 of this study. Both phases involve participants having both a standard transrectal ultrasound scan and a second transrectal ultrasound examination with the new micro-ultrasound examination. In your role you will asked to either, perform, interpret or make decisions based on the findings of the new micro-ultrasound. This will be additional work over and above your current routine practice.

To gain an insight and better understanding of how new technology is implemented into everyday clinical practice, your views about the use of micro-ultrasound will be sought and captured using a survey. This survey will be undertaken at the start of the study and repeated between 6 – 12 months later. We are using a survey adapted from the normalisation process theory toolkit. It is important to understand the opportunities and challenges that implementing new technology present so that these can be address as this becomes embedded into patient care. You can find out more about NPT and its aims being following this link http://www.normalizationprocess.org/what-is-npt/

The survey will be sent electronically. All responses will be stored on a password protected data base and only accessible to the lead researcher. The responses will be anonymised by the online survey tool prior to being uploaded onto the database by the lead researcher.

Do I have to take part?

You do not have to take part in this research if you do not want to – it is completely your choice and we will not ask why you have or have not decided to be involved. Not being involved in this research will not affect your current role or clinical practice.

What do I do now?

Thank you for considering and taking part in this valuable study. I will contact you in the next few weeks to discuss the study with you. If you are happy to proceed I will ensure that you are sent a secure and individual link to the survey. The survey will be sent again in 6 – 12 months so that any changes in your opinion of this new technology can be captured. A maximum of two surveys will be sent.

Consent

You can change your mind and you can withdraw your consent at any time. If you withdraw from the study you will be asked if we can continue to use your data in accordance with the data protection details that follow in the next section.

Information about me, Pamela Parker the lead researcher

I am receiving help from the research and development department within the Trust and the University of Hull as part of a PhD study. Hull University Teaching hospitals is sponsoring this research. All data I collect and store is in accordance with the Health Research Association and information can be found via the HRA link: www.hra.nhs.uk/patientdataandresearch

Your information and data protection

In this research study we will use information from your survey results to inform how new technology can be implemented in practice. We will only use information that we need for the research study. We will let very few people know your name or contact details, and only if they really need it for this study.

The data we collect will include your initials and a code number held on the secure hospital server. People will use this information to do the research or to check your records to make sure that the research is being done properly. People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead.

We will keep all information about you safe and secure. Everyone involved in this study will keep your data safe and secure. We will also follow all privacy rules.

Once we have finished the study, we will keep some of the data for a maximum of three years so we can check the results. The data will then be securely deleted. We will write our reports in a way that no-one can work out that you took part in the study.

What are your choices about how your information is used?

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.

Where can you find out more about how your information is used?

You can find out more about how we use your information

at www.hra.nhs.uk/information-about-patients/

our leaflet available from the urology nurse specialist or from ultrasound, at Castle Hill Hospital,
by asking one of the research team,
by sending an email to pamela.parker6@nhs.net or ResearchDevelopment@nhs.net ,
by ringing us on (01482) 623065

Our data protection officer can be contacted via email to HEYIG@nhs.net

Appendix 12 Study 2: Participant consent form

Hull University Teaching Hospitals NHS Trust

Participant Consent Form – Study 2

Evaluating the Role of Ultrasound in Prostate Cancer Study (ERUP Study)

Name of Chief Investigator: Pamela Parker	Please confirm agreement to the statements by putting your initials in the boxes below
I confirm that I have read and understand the information sheet dated **03/11/2021** (ICF version **2**) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my role or legal rights being affected.	
I agree to take part in the above study.	
Participant Signature	Date
Name of Participant	
Researcher Signature	Date
Name of Researcher **Pamela Parker**	

Copy of ICF V2 given to participant, copy retained by research team

Appendix 13 Study 2 Interim ERUP NoMAD questionnaire

Evaluating the Role of Ultrasound in Prostate Cancer Study (ERUP Study)

Implementation of new technology into clinical practice survey

Interim questionnaire – April 2023

Dear prostate team member,

Thank you for your help and support in reviewing the prostate ultrasound cases that have been collected as part of the ERUP trial. I am in the process of analysing the scores and hope to have some initial results ready to share soon. I appreciate you are all busy but please could I ask you three simple questions before I issue the results. As previously, there is no right or wrong answer; the questions are building up data as to how best to implement new technology in practice.

Thanks again for your help

For the following questions, please indicate your responses on a scale of 1 – 5.
1 being not at all and 5 being completely

Coherence: NoMAD 4

Question 1:	Response	Score	Please tick
I feel that I easily grasp the potential value, benefits and importance of using micro-ultrasound within the prostate cancer pathway.	Not at all	1	
	Very little	2	
	Somewhat	3	
	To a large extent	4	
	Completely	5	

Cognitive Participation: NoMAD 8

Question 2:	Response	Score	Please tick
I am willing and able to be involved in this new imaging practice, either directly performing the examinations or by interpreting images produced or both.	Not at all	1	
	Very little	2	
	Somewhat	3	
	To a large extent	4	
	Completely	5	

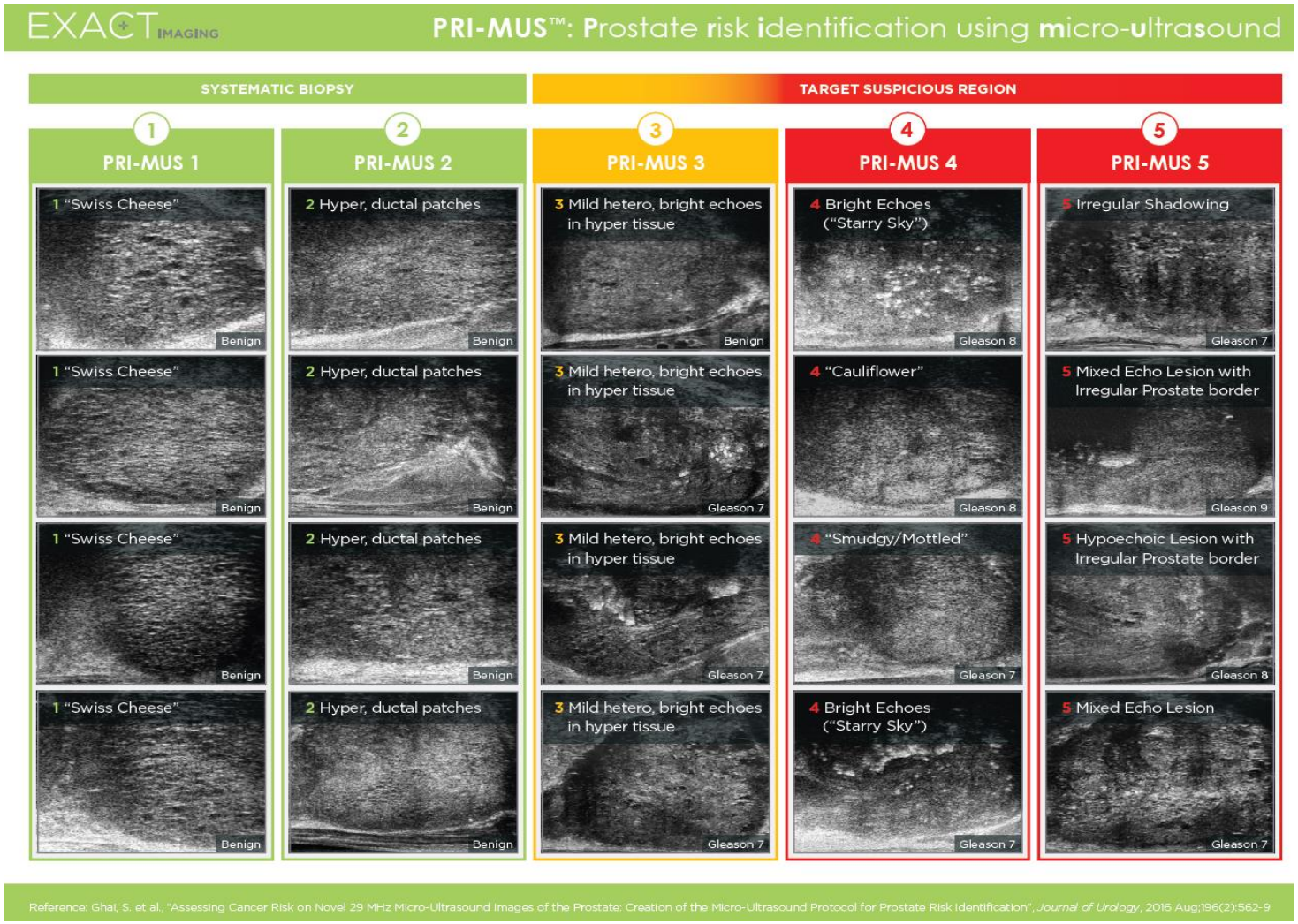
Collective Action: NoMAD 11

Question 3:	Response	Score	Please tick
I feel I have the right knowledge, skills and training to be able to confidently perform and / or interpret micro-ultrasound imaging of the prostate in clinical practice.	Not at all	1	
	Very little	2	
	Somewhat	3	
	To a large extent	4	
	Completely	5	

Reflexive Monitoring: NoMAD 14

Question 4:	Response	Score	Please tick
I feel I am able to trust my colleagues within the team to competently perform and / or interpret micro-ultrasound imaging.	Not at all	1	
	Very little	2	
	Somewhat	3	
	To a large extent	4	
	Completely	5	

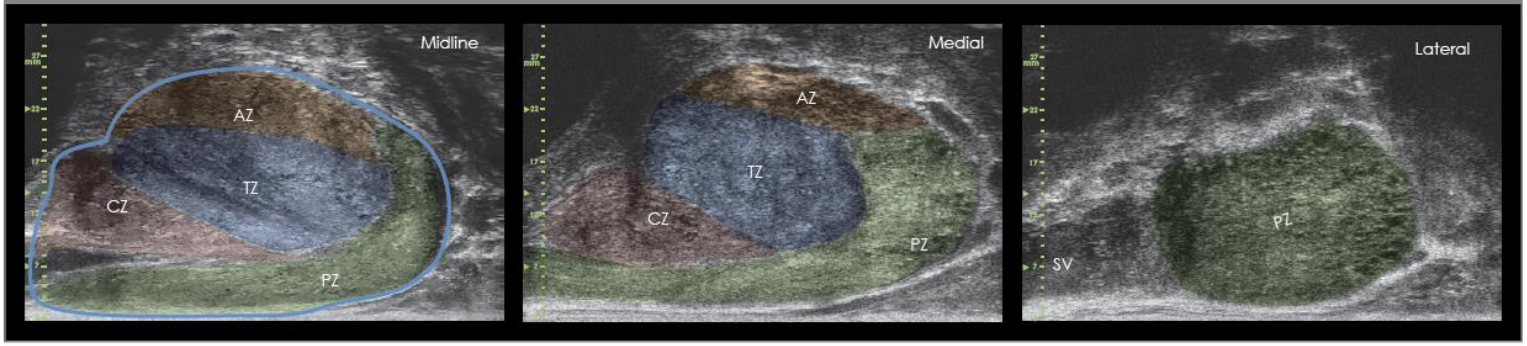
Appendix 14 PRI-MUS™ : Peripheral zone identification



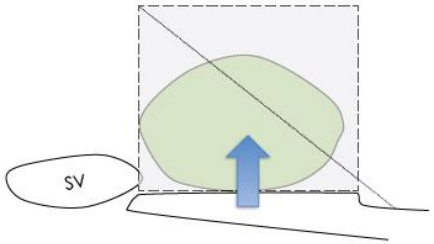
EXACT IMAGING

Micro-ultrasound Sidefire Biopsy Techniques

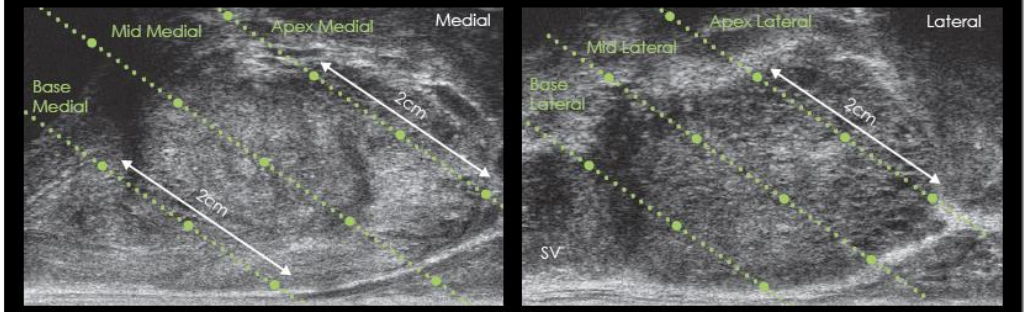
Prostate Anatomy (using high-resolution micro-ultrasound)



Core Length



Core Spacing and Needle Guide Scale



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PN 6641 Rev 2.2

Appendix 15 PRI-MUS™ : Anterior zone identification