Developing an evidence-based system to facilitate the predictive assessment and optimisation of older adults with cancer

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Abstract

Introduction: Older adults with cancer have worse outcomes than their younger counterparts, including higher postoperative complications, chemotherapy toxicity and treatment allocation to best supportive care. Oncogeriatric assessment (OGA) can provide predictive information and optimisation targets to improve these outcomes. OGA has multiple implementation barriers, including uncertainty in delivery, health economic concerns and siloed data. The aim of this thesis was therefore to develop an evidence-based system to facilitate the predictive assessment and optimisation of older adults with cancer.

Methods: Multiple methods were used, including i) a systematic realist review to understand implementation factors; ii) a decision-analytic health economic evaluation; iii) the design, implementation and delivery of a digital-first OGA service; iv) quantitative survey evaluation of a digitalised, patient reported OGA; v) the development and analysis of a complex model of an oncogeriatric population using machine learning.

Results: A whole system approach is required to improve the implementation of OGA in cancer settings, including utilisation of technology, leveraging non-specialist staff skills and cancer MDT, insurer, payer and regulator consensus. OGA has additional costs over standard care alone of between £390 and £576, dependent upon implementation configuration. However, when major assumptions about the effectiveness of OGA were modelled or OGA is used before chemotherapy, with minimal healthcare staffing inputs and technological assistance, it was cost-effective. A new digital-first OGA service was implemented successfully, and patient-reporting was feasible for older adults with suspected or confirmed cancer. A complex model of an oncogeriatric population using synthetic individual patient data showed high fidelity to real world data and generated a sandbox environment for predictive algorithms for OGA selection and treatment outcome risk profiling.

Conclusion: A digital-first OGA system is feasible and usable and may be cost-effective with careful implementation context considerations. The use of artificially intelligent systems may enhance patient selection and risk prediction but requires future validation.

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List of Abbreviations

ADL	Activities of daily living
AI	Artificial Intelligence
AOC	Assessment of Older adults with Cancer
AOI	Assessment of Older adults under Investigation
ARISCAT	Assess Respiratory Risk in Surgical Patients in Catalonia
ASCO	American Society of Clinical Oncology
AUDIT-C	Alcohol Use Disorders Identification Test-C
BADL	Basic Activities of Daily Living
BGS	British Geriatric Society
BMI	Body Mass Index
BN	Bayesian network
CARG	Cancer and Aging Research Group
CAS	Complex adapting system
CESD-R	Center for Epidemiologic Studies of Depression-Revised
CFS	Clinical Frailty Scale
CGA	Comprehensive Geriatric Assessment
CI	Confidence interval
CPCAS	Cancer Pathway Comorbidity Assessment System
CRASH	Chemotherapy Risk Assessment Scale for High-Age Patients
ECOG	Eastern Cooperative Oncology Group
EHR	Electronic Health Record
FL	Fuzzy logic
GDS	Geriatric Depression Scale
HRQoL	Health-related quality of life
HUTH	Hull University Teaching Hospitals NHS Trust
IADL	Instrumental activities of daily living
IPD	Individual patient data
MCI	Mild cognitive impairment
MDT	Multidisciplinary Team
MET	Metabolic equivalent
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment

MSAS	Memorial Symptom Assessment Scale
NHS	National Health Service
NPT	Normalisation Process Theory
OGA	Oncogeriatric Assessment
OR	Odds ratio
OT	Occupational Therapy
PERS	Personal emergency response system
PGM	Probabilistic graphical modelling
POPS	Proactive care of Older Patients undergoing Surgery
PSA	Probabilistic sensitivity analysis
PQIP	Perioperative Quality Improvement Project
PROM	Patient reported outcome measure
QALY	Quality adjusted life year
RR	Relative risk
RWD	Real world data
SIOG	International Society of Geriatric Oncology
SMR	Standardised mortality ratio
SORT	Surgical Outcomes Risk Tool
TUG	Timed-up and Go-test
UI	User interface
USA	United States of America
UX	User experience
VES-13	Vulnerable Elders Scale-13

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Declarations

I confirm that this work is original and that if any passage(s) or diagrams(s) have been copied from academic papers, books, the internet or any other sources these are clearly identified by the use of quotation marks and the references(s) is fully cited. I certify that other than where indicated, this is my own work and does not breach the regulations of HYMS, the University of Hull or the University of York regarding plagiarism or academic conduct in examinations. I have read the HYMS Code of Practice on Academic Misconduct, and state that this piece of work is my own and does not contain any unacknowledged work from any other sources.

Chapter 1 – Introduction

1.1 Ageing and cancer

When all cancers are combined, the incidence rates are strongly associated with older age and rise steeply from around 55-59 years of age. Statistics from Cancer Research UK in 2013-2015, showed that 36% of new cases of cancer were diagnosed in people aged ≥75 years each year on average (1). For both men and women, the highest age-specific incidence rates were in the 85-89 age group (1). Mortality rates for cancer are also higher in older people. In the UK during 2014-2016, 53% of all yearly cancer deaths occurred in people aged ≥75 years, and were highest in people aged ≥90 years (2).

Data from the Office of National Statistics in the UK clearly shows that the population is both growing and ageing, with 18.2% of people aged ≥ 65 years (3). The growing population is driven by a combination of increased natural change (the difference between births and deaths), reduced emigration and increased immigration. The ageing population is attributed to reduced mortality, improved health provision, technological advances and healthier lifestyles (3). The old age dependency ratio (OADR) – the ratio of people aged >65 years for every 1,000 working-age (16-64 years) people – is increasing as a direct result of these population changes (3). The OADR differs across the UK and by 2036 some regional OADRs are projected to reach close to 1,000 (i.e., the dependent population will nearly match the working population) (3). The combination of cancer epidemiology and population statistics will mean that more older people will likely be diagnosed with cancer in the future, and healthcare services will need to adapt accordingly (4).

1.2 The problem

Aside from increased cancer mortality, older adults have generally worse outcomes than their younger counterparts, including higher rates of postoperative complications, longer length of hospital stay, increased chemotherapy toxicity and post-discharge institutionalisation (5-7). Older adults may be more likely to receive best supportive care only and receive under-treatment by surgical modalities (8). Medical complexity has a tendency to increase with age through accruing co-morbidities, medications and functional deficits over time, leading to multimorbidity (two or more chronic medical conditions), polypharmacy (concurrent use of ≥5 medications) and functional decline (reduced ability to undertake self-care activities of daily living due to decrements in physical or cognitive functioning) respectively (9-11). Cognitive issues associated with ageing require additional considerations (e.g., advanced dementia

leading to loss of mental capacity). This makes shared decision-making difficult, and the cancer multi-disciplinary team (MDT) may have to paternalistically decide on treatment, whilst considering the views of the family and/or carers.

Evidence-based decision-making concerning the treatment of older adults with cancer has further difficulty because they are underrepresented in clinical trials (12). This can lead to two recognised extremes of clinical decision-making. Firstly, 'overtreatment' – where the profile of likely benefits versus risks is unfavourable and the patient is treated anyway. Secondly, 'undertreatment' – where the benefit versus risk profile is favourable, but the patient is not offered maximum possible treatment (13). Older patients exhibit various degrees of frailty. Frailty is defined as decreased physiological reserve and function across a range of organ systems, leading to vulnerability to withstand stressors, and requires objective measurement using any number of available and validated instruments (14). However, frailty may be incorrectly assumed, leading to undertreatment, or not identified, leading to overtreatment (15-17). A recent systematic review and meta-analysis of prospective studies demonstrated that frailty can have a profound effect on the odds of surgical complications (

Table 1), therefore its objective detection can generate significant data for decision-making (18).

Outcome	**Odds ratio (95% confidence interval)**
All complications	2.53 (2.07-3.10)
30-day mortality	3.49 (2.4-5.09)
Higher 1-year mortality	2.9 (1.99-4.24)
Length of stay > 5 days	2.78 (1.45-5.30)
Length of stay > 14 days	2.40 (1.08-5.36)
Acute kidney injury	5.03 (1.74-14.54)
Neurological complications	3.41 (1.08-10.73)
Respiratory complications	9.21 (2.35-36.02)
Wound infection	2.85 (1.65-4.94)
Sepsis	3.84 (1.37-10.71)

Table 1 – Frailty and postoperative surgical complications.
Frailty has significant predictive power for the odds of postoperative complications and this data may be useful for decision-making (18).

Older adults can tolerate and benefit from treatment when selected appropriately (19). The consideration of life expectancy from non-cancer mortality (i.e., determined from pre-existing co-morbidities) appears to be important when deciding on adjuvant chemotherapy, which can

improve overall survival in older adults (20). However, the therapeutic landscape is developing from traditional surgical and chemotherapeutic approaches, towards immunotherapy and targeted cancer therapies. For example, immunotherapy for genitourinary malignancies appears to offer benefits independently of age in clinical trials (21) and checkpoint inhibitors do not appear to be associated with high-grade toxicity in older adults (22).

1.3 The significance

The increasing number of older adults with cancer presents numerous challenges to the patient, members of the cancer MDT, healthcare and social services and government. Patient-centeredness is being increasingly recognised in global healthcare with attempts to improve quality of life (QoL) and care (23). However, the higher negative outcomes observed in older adults with cancer may create unfavourable patient reported outcomes and experience. For example, Silveira *et al*., (24) studied 289 head and neck cancer patients and found that patients aged ≥65 years had significantly worse health-related QoL (HRQoL) scores versus their younger counterparts. In the UK, the National Health Service (NHS) does not yet offer universal geriatrician-led services for older adults undergoing cancer treatment and regional variation is evident (25). This can lead to the so-called 'post-code lottery' – creating ethical and moral dilemmas at the patient level, which then extend to political and legal structures. Centralisation of tertiary services may improve outcomes for some, although older adults with cancer may be subject to increased travel burdens, which can influence rejection of cancer treatment and limit access to care (26-28).

A systematic review has shown that a significant factor in older adults accepting treatment is the clinician's recommendation (28). This finding imparts additional emphasis on the decision-making process of the MDT, necessitating thorough patient assessment and the collection and utilisation of all available holistically gathered information. The important influence of the family on care preferences was demonstrated by a systematic review with thematic analysis (29). Etkind *et al*. (29) recommended that clinicians should consider an older adult with advanced illness and the family as a unit when making decisions.

A scoping review of the role of ageism on clinical decision-making demonstrated that chronological age is deeply integrated into clinical decision making (30). Furthermore, a Department of Health report found an over reliance on chronological age to proxy conditions such as frailty, which are associated with *adverse* ageing, rather than chronological age *per se* (31). Whist chronological age does have some relevance in clinical decision-making (e.g., dose

modification), it is just one factor to consider and cannot guide treatment tolerance alone. Ageism has been considered to be one factor underlying increased mortality for patients with lung cancer (32) and transparency around the use of age is likely to improve clinical decision making (30).

The increased negative outcomes of older adults with cancer are likely to be associated with elevated healthcare and social costs. Data in support of this pragmatic assertion is largely drawn from the Unites States of America (USA). For example, Deshmukh *et al*., (33) studied 2,227 patients ≥66 years with anal cancer and estimated the cancer-related lifetime economic burden of Medicare patients to be US$112 million. Clinical coding of frailty and complexity are poor in the UK (34), which creates difficulty in gathering the necessary intelligence to analyse the true cost of adverse ageing on cancer care. This lack of data is therefore unsupportive towards the generation of business models, political or legal frameworks for improved services.

1.4 The solution

To assess and optimise older adults with cancer, international guidelines from authoritative bodies, including the American Society of Clinical Oncologists (ASCO) and International Society of Geriatric Oncology (SIOG) recommend undertaking a pre-treatment comprehensive geriatric assessment (CGA) (13, 35). A recent umbrella review provided a widely used definition of CGA for all settings: "*a multidimensional, multidisciplinary process which identifies medical, social and functional needs, and the development of an integrated/co-ordinated care plan to meet those needs*" (36). The domains assessed by CGA cover physical and mental health conditions, functional, social and environmental factors (**Table 2**) (37). CGA has been accepted as the gold standard of inpatient care for frail older adults and new models are evolving for other patient groups (36). For example, CGA has been employed for surgical patients across specialties and Eamer *et al.* (38) found CGA offered improved outcomes for patients recovering from hip fracture in a systematic review. These findings promoted systemic service provision changes towards a new model of care called orthogeriatrics, which involves joint, MDT-based care between orthopaedic surgical teams, geriatric services and allied health professionals. The orthogeriatric model was shown to reduce mortality in a meta-analysis (39) and reduce discharge to an increased level of care, with a probable small reduction in length of stay and cost (38). However, insufficient studies were available to determine the effectiveness for elective surgical oncology patients. The use of CGA in cancer care can be justified at multiple levels: patient priorities, identifying vulnerabilities for optimisation, predicting outcomes, aiding decision-making and has medicolegal relevance.

Physical medical conditions	Comorbid conditions and disease severity Medication review and polypharmacy management Nutritional status Alcohol and smoking Problem list
Mental health conditions	Cognition Mood and anxiety Fears Substance misuse and addiction
Functional status	Core physical functions such as mobility and balance Falls risk Basic and instrumental activities of daily living Life roles that are important to the patient
Social circumstances	Social networks: informal support available from family, the wider network of friends and contacts, third sector and statutory care Financial needs and poverty
Environment	Housing: comfort, facilities and safety Use or potential use of 'telehealth' technology Transport facilities Accessibility to local resources

Table 2 – The domains of CGA.
There are five broad domains of CGA physical and mental health conditions, functional status, social and environmental circumstances. Modified from Welsh *et al*. (37).

1.4.1 Patient priorities

Assessment whilst living with cancer is a significant priority for patients, as identified by the James Lind Alliance priority setting partnership and feature in the 'Living With and Beyond Cancer Top 10' (**Figure 1**). Themes emerging from these priorities include better prognostication of outcomes, including treatment side effects and the impact on clinical decision-making, therefore the benefits of CGA discussed in the following sections appear to map well with current patient priorities.

1) *"What are **the best models for delivering** long-term cancer care including screening, diagnosing and managing long-term side effects and late-effects of cancer and its **treatment** (e.g., primary and secondary care, voluntary organisations, self-management, carer involvement, use of **digital technology**, etc)?"*

2) *"How can patients and carers be **appropriately informed of cancer diagnosis, treatment, prognosis, long-term side-effects and late effects of treatments, and how does this affect their treatment choices?"***

3) *"How can care be better **co-ordinated** for people living with and beyond cancer who have **complex needs** (with more than one health problem or receiving care from more than one specialty)?"*

Figure 1 – Four questions extracted from the 'Living With and Beyond Cancer Top 10' of the James Lind Alliance priority setting partnerships.
Many patient priorities can be met by including CGA in cancer care. Key aspects are in bolded text.

1.4.2 Identifying vulnerabilities for optimisation

An urgent surgical consultation for suspected cancer or an outpatient oncology encounter offers a limited timeframe to conduct a CGA. However, CGA can uncover wider health issues that may be uncovered during a routine history and physical examination, including functional deficits requiring assistance, untreated malnutrition or unoptimised comorbidities (40). A study by Kenis *et al*. (41) of 1,967 older adults (≥70 years old) with cancer found that unknown geriatric problems were detected in 51.2% of patients, representing a significant undetected and therefore unaddressed need. Correspondingly, in the context of advanced cancer, opportunities to address age-related concerns have been found to be missed. Lowenstein *et al*., (42) undertook a study of outpatient oncology encounters of 37 patients ≥60 years of age with advanced cancer, and found that around 50% of the time further intervention for patient's age-related concerns were not implemented (i.e., patients mentioned issues, but they were not acted upon).

The Eastern Cooperative Oncology Group Performance Status (

Figure 2) was developed in 1982 for standardisation of the quantification of participants' vitality in clinical trials (43). Perfomance status is also used in clinical practice, although it is no longer recommended for use on its own (44).

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry out all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light house work, office work)
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry out any selfcare; totally confined to bed or chair
5	Dead

Figure 2 – Eastern Cooperative Oncology Group Performance Status.
The Eastern Cooperative Oncology Group Performance Status is used for quantification of patient's vitality. Adapted from (43).

A systematic review of CGA in older adults with haematological malignancies revealed that multiple health issues were detected, despite those patients having a good performance status or favourable physician's clinical judgement (45). For example, in those patients with a performance status of 0 or 1, between 6-50% had at least one geriatric domain impairment.

In the context of surgical manangement of cancer, optimisation of vulnerabilities fits well within the newer model of perioperative medicine. The perioperative period is now thought to begin from the intial contemplation of surgery, through to full recovery and patient-centred, multidisciplinary and integrated models of perioperative medical care are now recommended (46). However, peri-operative pathways may need to be re-engineered in the context of cancer pathways (47). Surgery is often the only curative option for solid malignacies and its comtemplation from the outset should be assumed, regardless of a suspected or confirmed cancer status, so that early oppurtunities for optimisation can be realised. Co-morbidity screening within CGA can identify patients with undiagnosed/undertreated diabetes or anaemia of which there is growing evidence that optimisation pre-operatively can improve post-operative outcomes (48, 49). CGA can also identify co-morbid conditions that require wider preoperative MDT coordination with specialties such as cardiology, to prevent avoidable delays to surgery from uncontrolled/undiagnosed hypertension and heart failure (50). CGA can also include lifestyle factor screening including alcohol and smoking, which could be overlooked as a risk factor for cancer rather than an opportunity for early intervention to improve outcomes. The preoperative period in the context of cancer could be seen as a 'teachable moment', in terms of lifestyle change whereby immediate benefits are salient (51, 52).

The concepts of preoperative optimisation and vulnerability identification during CGA extends into prehabilitation, whereby impairments are identified prior to major surgery and intervened, including physical fitness training, nutritional optimisation and psychological therapy (53). However, the impact of these interventions on postoperative outcomes is still not clear, due to significant heterogeneity and the lack of methodologically robust prospective trials (54-56). Interest in prehabilitation has extended to chemotherapy. For example, a trial of exercise prehabilitation on baseline cardiopulmonary exercise function during neoadjuvant chemotherapy, prior to oesophagogastric cancer surgery is currently underway (57).

1.4.3 Complex intervention

CGA prior to cancer treatment can also be viewed as a complex intervention. Several trials have recently been reported concerning the use of geriatric interventions, either isolated or selected based on CGA findings and their effect on cancer outcomes. Results are variable but often neutral. Gilbert *et al*. (58) undertook a stepped-wedge cluster-randomised trial of a combined geriatrician and dietitian outreach team intervening on 147 patients (≥ 70 years old) undergoing major surgery for colorectal cancer across five hospitals. Whilst guideline adherence and prescription of oral nutritional supplements improved there was no effect on perioperative outcomes. The recently published geriatric assessment-driven intervention (GAIN) RCT analysed 605 patients (≥65 years old) with solid cancer starting chemotherapy (59). The intervention arm completed a GA and interventions, whereas those in standard care completed a GA but the results were sent to the treating oncologist without intervention by the team completing GA. The incidence of grade ≥3 chemotoxicity was reduced by 10.1% with an increase in advance directive completion in the GAIN arm, but no difference in emergency department visits, unscheduled hospital (re-)admission, mean length of stay, chemotherapy changes or survival. The recently reported GAP70+ cluster RCT of geriatric assessment and management as an intervention, compared to standard care, recruited 718 patients (≥70 years) with advanced cancer with a geriatric domain impairment and commencing chemotherapy (60). Mohile *et al*. (60) found that the intervention group had reduced chemotherapy toxicity (relative risk [RR] 0.74) and falls (RR 0.58) and increased medication discontinuation. This was particularly encouraging considering the CGA-processes were delivered by oncologists rather than geriatricians.

CGA models of care have been found to reduce perioperative complications in arterial surgery and meet cost-effectiveness criteria within the NHS (61). However, meta-analysis including other international RCTs did not demonstrate favourable effects on postoperative delirium, length of stay, 30-day readmission and mortality (62). Secondary outcomes from a two-group, parallel single blind phase II RCT with GA as the intervention did not demonstrate any difference in HRQoL or healthcare use (63). There are several other neutral trials published and more protocolised (e.g., Røyset *et al.* (64)) so the evidence for CGA as complex intervention is still evolving.

1.4.4 Predicting outcomes

Versteeg *et al*. (65), undertook a systematic review of CGA in patients with solid malignancies receiving chemotherapy. The authors found that nutritional status, functionality and co-

morbidity associate frequently with worse outcomes, however, they were unable to conclude definite value in predicting toxicity and mortality. Since then, two key tools have been developed and recommended in the ASCO guidelines, CARG (Cancer and Aging Research Group) or CRASH (Chemotherapy Risk Assessment Scale for High-Age Patients) (13). A recent systematic review by van Abbema *et al*. (66) of predictors of chemotherapy intolerance in older adults with cancer found increased risk with ≥1 fall in the last six months, mobility problems, poor performance status and comorbidity with odd ratios for the latter two factors ranging between 3-6 and most lower confidence limits above 1.5. CRASH and CARG include many of the identified predictors, although they would benefit from evaluation in different populations.

Multiple recent systematic reviews have demonstrated that CGA domains can predict mortality in older adults with cancer (67-69). CGA can also predict adverse postoperative outcomes, although extracting clinically useful statistics is very difficult, even from an umbrella review (70). Furthermore, there are more specific, validated and briefer mortality scoring indices than CGA that can be used for predicting non-cancer mortality in oncology patients (71). The current consensus from authoritative guidelines (13) and systematic review findings (67-69) is that components of CGA appear to have a significant influence within predictive models. However, the main value of CGA now appears to be in identifying vulnerabilities, and future models that combine demographic, physical, pathological, genetic or physiological data are likely to be developed.

1.4.5 Clinical and shared decision-making

The cancer MDT decision-making process is considered the gold-standard for cancer treatment decision-making, based on evidence of improved patient, research and institution outcomes *versus* single clinician decision-making (72). A recent systematic review of the effect of CGA on clinical decision-making was undertaken by Hamaker *et al*. (73), which showed that CGA altered the oncological treatment plan in 28% of patients, mainly to a lower intensity, and generally appeared to improve treatment completion and reduce treatment complications. This is consistent with a meta-analysis by Puts *et al*. (74), which showed that decision making was modified by CGA in 23.2% of cases. However, none of the studies included were randomised. The comprehensive perspectives of older adults with cancer have been found to be missing in cancer MDTs (75). Furthermore, a lack of true person-centredness in MDT meetings and treatment decision-making was found in an ethnographic study of UK head and neck cancer MDTs (76). The authors also highlighted the ability of the MDT member who presents the

patient's case to frame the information around their own treatment ideal (76). The inclusion of information from a CGA (including early patient preferences) may help to increase person-centredness.

Qualitative and mixed methods studies of decision-making in older adults with cancer have identified that a common theme is 'trust in my oncologist'. Most patients accepted or strongly valued the recommended treatment, although they felt that this was their own and final choice (77, 78). Shared decision-making combines both the patient's values and preferences with clinical expertise to develop an individualised care plan (79). Shared decision-making has been noted in the literature for three decades and is thought to be a significant component of person-centered care. This formulates part of a wider movement to biopsychosocial models of health that focus on patient-defined outcomes (80). The national Perioperative Quality Improvement Programme (PQIP) in the UK recommends shared decision-making, risk calculators and functional capacity assessment (e.g., CGA) as part of individualised risk assessment (81). Patient advocacy groups, healthcare policy changes, resource distribution inequalities and medicolegal cases have all supported this drive (80). The medical risks of surgery (e.g., postoperative delirium), which are more likely in older adults, are frequently missed from shared decision-making. All data needs to be open and transparent about risks to enable shared decision-making to function correctly, and this has medicolegal relevance.

1.4.6 Medicolegal relevance

With an increasingly data-driven movement in healthcare, CGA affords greater insight into the predicted outcomes following cancer treatment (13). Given the international recommendation to use CGA by authoritative bodies (13, 44) and the recent Montgomery ruling in 2015, medicolegal relevance has emerged (80). The Montgomery ruling found that patients must be warned of material risks – those that "*a reasonable person in the patient's position would be likely to attach significance to*…" or that "*the doctor is or should reasonable be aware that the particular patient would be likely to attach significance to it*. (81)"

Although this has not yet been tested in the UK, it is theoretically possible a claimant could make a negligence case against an NHS Trust for not using CGA where harm was suffered, or risks that could have been detected using CGA were not conveyed during the informed consent process. The utilisation of CGA serves as decision support technology, promotes good medical record keeping, shared decision-making and the adherence to established guidelines, which

may help to avoid medicolegal cases from breaching a duty of care or inadequate conveyance of risks during informed consent (82).

1.5 The problems with the solution

1.5.1 Introduction

Overall, there is clear evidence of the value of undertaking CGA in oncology practice, however, evidence from surveys of NHS Trusts reveal that implementation is minimal. McCue *et al*., (83) undertook a survey of 41 NHS trusts and found that 93% do not undertake CGA within oncology departments. A survey undertaken of 127 NHS Trusts, which represents nearly 84% of all 152 NHS Trusts showed that only 42% offered geriatric outpatient medicine services for older surgical patients, regardless of underlying pathology (25). Even within the privatised healthcare system of the USA, CGA implementation is minimal with only 23% of 305 community oncologists undertaking a multisite geriatric oncology trial, reporting the use of CGA in their clinics (84). There are several challenges with introducing CGA prior to oncological treatment: i) identifying the optimal CGA; ii) implementation of CGA; and iii) the best utilisation of its results for predicting outcomes and optimisation.

1.5.2 The optimal CGA

A recent umbrella review of preoperative CGA domains exploring different domains of CGA concluded that the optimal CGA does not exist, although the authors asserted that finding a 'one-size' CGA should not be the sole aim (70). Study of CGA in cancer populations is universally difficult due to the heterogeneity of the populations studied, methodological differences, CGA tools utilised, the outcomes measured and their statistical reporting. Instead, the authors reiterate its core objectives: uncovering issues and prehabilitation, generating more or better data for shared decision-making and allowing the patients and clinicians to understand the postoperative course. Specific domains of CGA were found to be predictive for specific negative outcomes (e.g., the degree of co-morbidities and increased mortality). The authors also recommended that domains of the CGA that can be modified prior to treatment (e.g., mood and nutrition) should be the focus (70). Bruijnen *et al*. (68) offered support to these findings in their systematic review of the predictive value of CGA domains. They found that physical function and nutritional status were the most predictive domains for mortality and chemotherapy-related outcomes and physical function was the most predictive for postoperative complications. Physical function is most commonly assessed by the Timed-up and Go (TUG) test, a newer version of the Get-up and Go test, the four-meter gait speed or hand grip strength (68). Since CGA was originally designed and validated for frail medical

inpatients, when it is used outside of its context several issues arise. In most studies, patients are selected for treatment, therefore some instruments such as activities of daily living (ADL) scales may reach a ceiling, especially in purely surgical cohorts. Given the lack of agreeance on domains or tools required, this further supports the theory that the optimal CGA in cancer settings should enable the maximum number of vulnerabilities to be detected for optimisation instead of designing CGA to predict outcomes.

1.5.3 Implementation of CGA in oncology settings

1.5.3.1 Implementation barriers

One of the main arguments used to explain why CGA is not universally implemented, is the time taken to undertake the assessment and therefore the associated costs. One group argued that the cost of a trained healthcare worker undertaking a CGA seemingly represents much less than the cost of toxicity and its complications (85). However, when the implementation science is considered, this simple health economic argument breaks down. Gladman *et al*., (34) categorised the implementation issues creating the 'know-do gap' in the implementation of CGA. When applied to the geriatric oncology setting there are several systemic issues apparent of which only one is related to health economics (**Figure 3**).

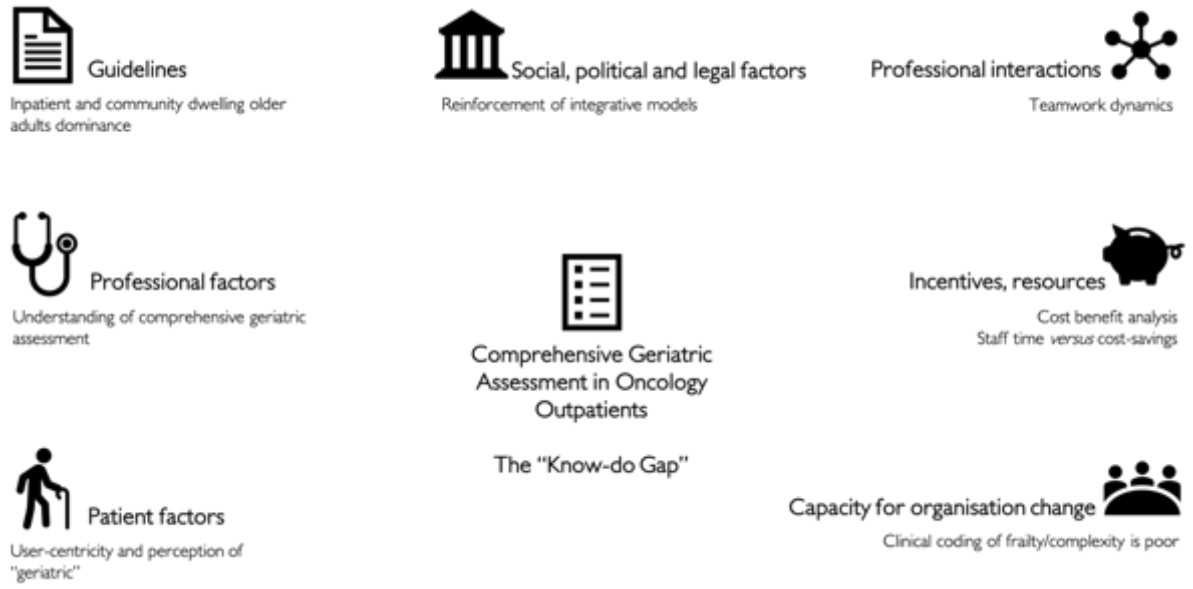


Figure 3 – The 'know-do gap' of introducing comprehensive geriatric assessment into oncology outpatient care.
There are seven major factors involved: i) UK guidelines focus on CGA for inpatients and community-dwelling older adults; ii) understanding of CGA by professionals within the cancer MDT tends to be poor; iii) CGA has never been subject to user-centric design and the use of 'geriatric' may be unfavourable; iv) there is no sociopolitical reinforcement of CGA models in cancer care; v) CGA relies heavily on inter-disciplinary working

and care co-ordination; vi) the health economics of CGA in oncology are unclear; and vii) change is required within an organisation to embed CGA and the underlying data to generate a business case is often lacking.

Although there have been more publications in recent years regarding the use of CGA in other patient groups including oncology outpatients, much of the evidence is drawn from inpatient groups (38, 86). Despite evolving and new models of care, including orthogeriatrics and oncogeriatrics, there is likely to be a residual knowledge mobilisation deficit amongst specialists who are not solely focussed on the care of older adults (34). Surveys have revealed that perceived barriers to implementing geriatric medicine services for older surgical patients, which would include oncology patients, include workforce issues, funding and inadequate training and education (25). Robust cost-benefit analyses are difficult for CGA, due to the aforementioned issues regarding poor coding, although there is evidence of funding being increasingly split between medical and surgical directorates (25). This finding exemplifies that overriding social, political and legal factors can have a significant effect on implementation. For example, in the intervening years between 2013 and 2017, there were several high-level influencing factors. These include the NHS England and the King's Fund publications regarding a movement towards more integrated models of care, the Association of Anaesthetists of Great Britain and Ireland 'whole pathway' recommendation, National Emergency Laparotomy Audit recommendations regarding older adults and British Geriatrics Society (BGS) curriculum changes to include perioperative medicine. An increase of the number of trusts providing geriatric medicine service for older surgical patients was found from 29.2% to 53.3% in 2013 and 2017 respectively (25, 87).

Williamson *et al*. (88) proposed multi-component assessment of community-dwelling adults in the UK during 1964 to identify unreported needs. The term CGA was subsequently popularised through research undertaken in the 1980s, however, its user-centricity has never been fully evaluated and it frequently takes the form of a bundle of questionnaires selected by clinicians (34, 89). The term 'geriatric' in CGA and its design is probably undesirable to older adults compared to the term 'older person' (90). When CGA is used in a different context (e.g., oncology), it appears desirable to redefine terminology. The term oncogeriatric assessment (OGA) has appeared in the literature (91) and use of a new cancer-specific definition may help to encourage its reengineering. Modifying the definition of CGA from a recent umbrella review (36), OGA could be defined as a multidimensional, multidisciplinary process which identifies medical, social and functional needs, and the development of an integrated care plan to meet those needs for older adults with cancer. The term *integrated* in this context refers to integration

of the care plan into the cancer MDT. The MDT is also much larger in OGA than a traditional CGA because it includes the cancer MDT and the members from allied health professions (e.g., dietetics, occupational therapy [OT] and physiotherapy) and elderly medicine. OGA may also include pharmacy, mental health and social services. Communication and co-ordination between such a large and separated group of professionals therefore becomes essential for implementation success (34).

A patient-friendly service name for OGA correspondence is also useful, such as Assessment of Older adults with Cancer (AOC). However, the timing of an OGA within a cancer pathway is likely to be crucial. Kocman *et al.* (92), undertook a formative evaluation using normalisation process theory (NPT) and implemented CGA into the perioperative/surgical cancer care pathway at the point of pre-operative assessment. Implementation was not successful at the end of a 12-month trial where time-limited targets and preferences appeared to outcompete the efforts of implementing CGA (92). Some participants interviewed raised the question of the need for geriatrician-led services (92), although this is unlikely to be currently sustainable given the number of nationally unfilled vacancies for consultant geriatricians, and a lack of subspecialists in oncogeriatrics or perioperative medicine (92, 93). Moreover, undertaking a CGA at the stage of preoperative assessment is very late in the cancer pathway (**Figure 4**).

The cancer pathway can be activated through three major routes: i) the breast, bowel, cervical targeted lung health check national screening programme; ii) primary care referral via the 2 Week Wait pathway, where patients should be seen within two weeks of a referral from primary care; or iii) a referral generated internally within secondary or tertiary care, including emergency admissions. Following specialist review, patients with suspected or confirmed cancer are added to an MDT discussion. Patients can also be directly added to an MDT discussion without a specialist review; this usually occurs via radiology departments. From the patient's perspective there is a period where they are *under investigation*. Following an MDT discussion and clinical decision-making process regarding their treatment options, their diagnosis will be communicated to them. It may therefore be necessary to undertake OGA at the point within a cancer pathway where a patient exhibits cancer symptoms or has other concerning clinical or investigative evidence of suspected cancer but has not been confirmed and/or informed of a cancer diagnosis. Under the new Faster Diagnosis Standard (effective from April 2019), patients should expect to be informed if they have cancer within 28 days. For this reason, it may be necessary to rename OGA to Assessment of Older adults under Investigation (AOI) to avoid prematurely or incorrectly conveying a cancer diagnosis to a

patient. OGA results must be available for clinical and shared decision-making to realise their benefit. In some MDTs, clinical decisions are made, diagnoses conveyed to patients and treatment options are explained, all on the same day. This activates the treatment period of the cancer pathway, and the use of the name AOC would be reasonable. A decision to undertake surgery affords a further opportunity to undertake OGA at the preoperative assessment window. However, as noted by Kocman *et al.* (92) opportunities for optimisation compete with national targets at this late stage. National targets have a degree of devolution between UK countries. Targets for NHS England for all cancer treatments including best supportive care are 31 days from the point of a shared decision between the responsible consultant and the patient. From the point of 2 Week Wait referral or screening programme activation, patients should receive their first treatment within 62 days. Cancer targets competing against hospital-wide CGA were also found in a large mixed methods study which including embedding CGA toolkits in acute NHS hospital trusts (94). Detailed consideration of the cancer pathway provides early support for the need to completely redesign CGA for older adults with suspected or confirmed cancer and integrate this into the perioperative pathway as early as possible.

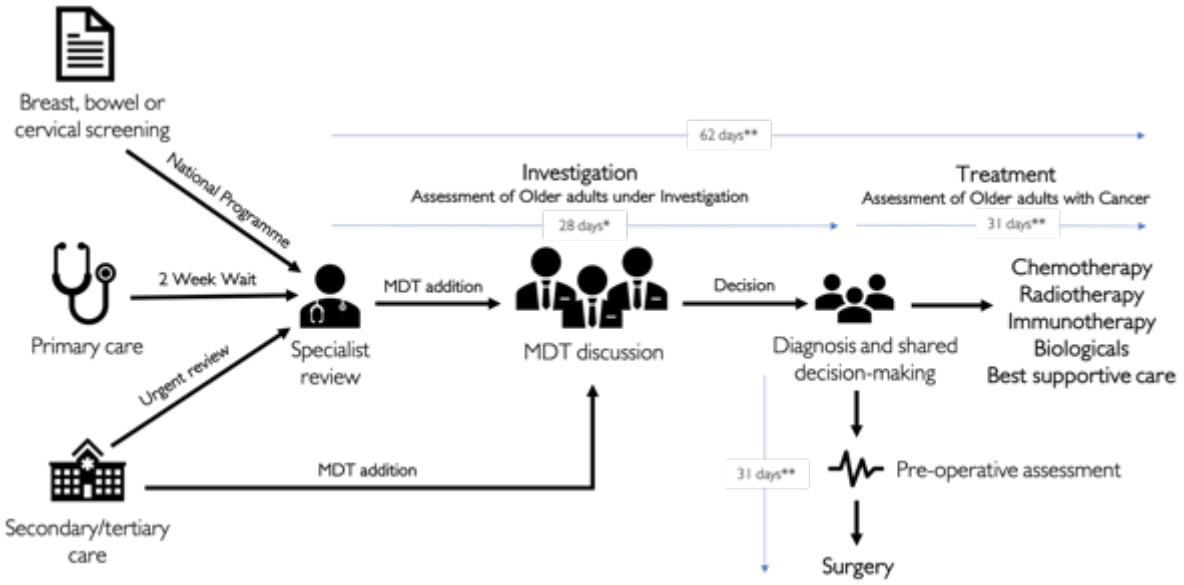


Figure 4 – A typical cancer pathway and the interaction with national targets.
A patient can enter a cancer pathway through three major routes: i) national screening programme; ii) 2 Week Wait referral from primary care; or iii) an internal referral within secondary care or externally to tertiary care. Following specialist review, patients with suspected or confirmed cancer can be added to an MDT discussion. Patients can also be directly added to an MDT discussion without a specialist review (e.g., by radiology). From the patient's perspective there will be a period where they are under investigation. When cancer is confirmed at an MDT discussion a clinical decision is made and a cancer diagnosis will be communicated to a patient, and then treatment options explained. Before surgery, a pre-operative assessment is undertaken. National targets for NHS England compete with the potential to undertake OGA throughout the pathway. *Under the Faster Diagnosis Standard, patients should receive a cancer diagnosis within 28 days. **Current targets for NHS England state that patients should receive their first treatment within 31 days of a shared decision and 62 days of an urgent referral from primary care or screening pathway activation.

1.5.3.2 Implementation enablers

CGA is frequently referred to as the 'core technology' of geriatric medicine (89), however, there are few papers on the use of technological innovation to improve its assessment (95). The small studies that exist do show feasibility and improved efficiency of patient-led electronic data capture for OGA in older adults with cancer. However, further research employing traditional technological methodology regarding user-centered design and user experience (UX) for electronic OGA interfaces is required (95). Digitising the questionnaire assessment component of OGA towards patient-led reporting may be an implementation enabler by reducing clinician time and therefore implementation cost. There will almost always be a need for a dedicated staff member to have oversight of the OGA service and some components, such as cognition screening, cannot (currently) be patient reported. In the absence of precise electronic health record (EHR) capture of co-morbidities, which is difficult, this still requires careful review by an experienced clinician.

The gold-standard interpretation and intervention of CGA findings is geriatrician-led within a MDT, however, this creates the need for dedicated staff, funding and excellent teamwork dynamics. Successful models of CGA implementation, exemplified by the Proactive care of Older Surgical Patients (POPS) team at Guy's and St Thomas' NHS Foundation Trust, possess these characteristics and they have been shown to demonstrate improved outcomes (96). Partridge *et al*. (96), undertook a randomised controlled trial (RCT) of preoperative CGA in vascular surgery patients and demonstrated a reduction in the length of stay, postoperative morbidity and level of care on discharge compared to usual care. However, vertically scaling this service to cover oncogeriatrics as well would be difficult. National inequalities of care persist whereby patients are served by the many NHS Trusts that simply cannot implement this model of care due to high-level funding, workforce, sociological and logistical issues. Whilst models such as POPS deserve praise for their outcomes, they are not reproducible across NHS Trusts in the current funding or post-pandemic climate. If effective and lower cost models could be developed and validated, large consultant-led, human resource heavy CGA teams may be viewed as cost-inefficient. The role of geriatricians as an enabler towards OGA is still unclear, with competing definitions evident in implementation studies (92, 94).

Prescreening of older patients with cancer with an abbreviated tool can help identify those who require full OGA, thereby reducing OGA service workload and focussing resources according to suspected need. There are various frailty screening tools for this purpose, including the Groningen Frailty Index (GFI), Fried's frailty phenotype, Vulnerable Elderly Survey (VES-13), Triage Risk Screening Tool (TRST) and the Geriatric 8 (G8) (70). Huisman *et al*. (70) undertook an umbrella review of CGA for older surgical patients with cancer and found that multiple domain impairments (CGA based frailty measurements) were predictive of mortality with hazard ratios as high as 8.88 (95% confidence interval [CI] 1.09-72.29). The authors noted that screening tools covering multiple domains may not be sensitive enough to detect impairments in those domains. The G8 screening tool has been systematically reviewed in older adults with cancer with 85% sensitivity and 64% specificity for predicting OGA impairments. A systematic review of OGA domains and screening tools examined five trials using either VES-13 or G8 and was only able to suggest their feasibility to select patients undergoing radiotherapy for OGA (69). A systematic review of frailty screening tools in older adults with cancer, including G8, VES-13, TRST, GFI, Fried's frailty phenotype and abbreviated CGA, found that G8 and TRST had the highest sensitivity, 87% and 92% respectively (97). However, G8 had specificity of 61% and TRST of 47% and each had negative predictive value of around

60%. The authors concluded that due to the low discriminative power if may be better for patients to proceed to full OGA. Following this review, a prospective cohort study of 106 patients found similar discriminative power of VES-13 (sensitivity 60% and specificity 78%) for detecting frailty and concluded that VES-13 screening may be useful in busy departments where full CGA is not possible (98). This view was further supported by a SIOG task group update who undertook a systematic review and consensus panel and found that the G8 generally appeared to offer the best sensitivity (99). Regression modelling offered further support for the G8 test in a prospective cohort study of older adults with cancer (100). G8 tended towards higher detection of patients requiring CGA, although with consequent misclassification of normal patients. However, over-detection may be preferred versus under-detection of patients with vulnerabilities who do not subsequently benefit from a full OGA (100). In summary, G8 appears to be the best instrument to detect patients requiring OGA, although it cannot be administered remotely like VES-13. It may be preferable to targ*et al*l older cancer patients with full OGA wherever possible, unless prescreening is all the institution can offer, due to logistical and workload issues.

In Belgium, a World Health Organisation inspired Cancer Plan was developed in 2008, which included OGA implementation (101). This was formally studied and the implementation of OGA was left to local hospitals to manage. A trained healthcare worked (e.g., junior doctor) undertook screening using the G8 screening tool, which identified 63.6% of patients for full OGA. A OGA was then undertaken and local protocol-driven recommendations (all of which were referrals to other specialties or departments) were made for 76.3% of the patients undergoing full OGA, including to a dietician (60.4%), social worker (40.3%) and psychologist (28.9%). Interestingly only 7.3% of recommendations were to a geriatrician, highlighting that much of the OGA process can be managed using prescreening and protocol driven recommendations without significantly increasing the workload of elderly medicine departments. However, only one third of these recommendations were performed in 50% of patients, demonstrating that even with enforced implementation, in a research environment, the fidelity of the process can be suboptimal (101, 102).

1.5.4 Utilisation and interpretation of OGA in oncology settings

Cancer MDTs are the core unit of cancer care but have been described as "*frenetic business meetings that often run beyond their allocated timeslots*" (103). The results of OGA are only useful if they are used in clinical decision-making. If OGA can be successfully implemented into oncology practice, a consequent barrier will be the utilisation of OGA results within a

cancer MDT. OGA data in its raw form may represent a list of problems, which would be difficult to integrate into a fast-paced meeting with up to 30-40 patients to discuss. The actioning of these problems may add to an already saturated workflow consisting of arranging further investigations, breaking bad news, shared decision-making and informed consent, with diffusion of responsibility within the group. Verduzco-Aguirre *et al*. (104) undertook a retrospective review of 173 patients who underwent OGA. They found that agreement between OGA recommendations and final treatment decisions were high, especially when those recommendations were formally acknowledged by the treating oncologist (83%). Direct incorporation into the MDT discussion would likely be more effective and summarisation into a universally understood format would be important. This summary could contain key outcome predictions as recommended by ASCO (13), including a chemotherapy toxicity score (e.g., CARG) and estimation of all cause non-cancer mortality using validated predictive tools (e.g., the Suemoto Index – discussed fully in Section **5.3.18.2**). Given the potential for referral (and optimisation) opportunities to be missed following OGA recommendation, as found in the Belgian study (102), referrals could be generated by an OGA service, or automatic e-referrals generated within EHRs. However, the former may increase implementation cost through administrative time and the later may elevate opportunity cost through technological innovation.

1.6 Chapter summary

With an ageing and growing population, health services must adapt to the increasing numbers of older adults requiring comprehensive cancer care. An OGA is recommended as a solution to improving outcomes for older adults with cancer. OGA is proven to offer benefits by enabling the identification of vulnerabilities suitable for optimisation prior to cancer treatment and can help predict outcomes to aid shared decision-making. However, given the strains on the health service and its current funding priorities, OGA becomes an implementation problem for the NHS, which also derive from classic CGA being used outside of its original context. OGA has a notorious number of barriers, which are system-wide and not simple health economic arguments. There are also several enablers including the potential to reengineer the role of OGA and push forward the timing of its use in the cancer pathway. Prescreening can reduce the number of patients requiring full OGA, although is perhaps best reserved for centres where it is the only implementation of OGA possible. OGA can be patient reported and digitalised and the interpretation and recommendations from OGA can be protocolised and summarised. The burden of excess work generated by OGA implementation can be abstracted

from the cancer MDT. OGA could serve as an opportunity to capture the patient's view regarding their treatment early in decision-making. This demonstrates the potential to redesign the OGA system using digital technology and principles from systems thinking, data science and engineering. The appetite for doing this has recently been expressed and could have significant impact on workforce requirements, implementation issues and patient outcomes (95). A cost-effective OGA system could be vertically and horizontally scaled within an organisation, reproduced across the NHS or principles could be applied to other challenging healthcare systems.

1.7 Thesis aim

The aim of this thesis was to develop an evidence-based system to facilitate the predictive assessment and optimisation of older adults with cancer. Several aspects of this aim are worthy of early emphasis and clarification: i) *develop* – this may include ideas, innovation, existing or original research; ii) *evidence-based* – the highest level of evidence should be sought where available, only defaulting to expert opinion where necessary; iii) *system* – this may be at the data, service, technological or organisational level; iv) *facilitate* – this refers to facilitating implementation, one of the most significant areas highlighted in this chapter; v) *predictive assessment* – this refers to the role of OGA in prediction of outcomes using existing or novel models; and vi) *optimisation* – referring to highlighting opportunities for health optimisation and arranging their management but not prehabilitation, which is beyond the scope of this thesis.

1.8 Thesis objectives

Considering the key issues raised in this chapter and to meet the aim of this thesis, the following objectives were planned. It should be noted that these have been modified iteratively to circumvent the disruption associated with the COVID-19 pandemic.

1. Explore the implementation factors of OGA
2. Evaluate the health economics of undertaking OGA before cancer treatment
3. Design, operationalise and evaluate a digital-first and patient reported local OGA service
4. Develop a complex model of an oncogeriatric population

1.9 Research questions

These aim and objectives of this thesis could be further refined into several specific research questions as follows: -

1. How should OGA be implemented?
2. Is undertaking OGA prior to cancer treatment cost-effective?
3. Is a digital-first, patient reported OGA acceptable, usable and feasible?
4. Can additional insights be gained from modelling an oncogeriatric population?

Chapter 2 addresses the first research question through a qualitative method, whilst the remainder of the thesis takes a quantitative methodological approach. **Chapter 3** discusses the methodology in more detail.

Chapter 2 – Implementation of geriatric assessment in oncology settings: A systematic realist review

2.1 Chapter introduction

This chapter presents the text of a research paper published in the *Journal of Geriatric Oncology* in January 2021 (105). The text is identical to the original publication, except that headings, subheadings, tables, figures and references have been renumbered in keeping with this thesis. Some spelling and grammatical changes have been made from North American to British English. Supplementary tables in the original publication have been appended to the thesis **Appendix** accordingly.

2.2 Abstract

Older adults with cancer are more likely to have worse clinical outcomes than their younger counterparts, and shared decision-making can be difficult, due to both complexity from adverse ageing and under-representation in clinical trials. Geriatric assessment (GA) has been increasingly recognised as a predictive and prehabilitative tool for older adults with cancer. However, GA has been notoriously difficult to implement in oncological settings due to workforce, economic, logistical, and practical barriers. We aimed to review the heterogenous literature on implementation of GA in oncology settings to understand the different implementation context configurations of GA and the mechanisms they trigger to enable successful implementation. A systematic realist review was undertaken in two stages: i) systematic searches with structured data extraction combined with iterative key stakeholder consultations to develop programme theories for implementing GA in oncology settings; ii) synthesis to refine programme theories. Medline, Embase, PsycInfo, Cochrane Library, CINAHL, Web of Science, Scopus, ASSIA, Epistemonikos, JBI Database of Systematic Reviews and Implementation Reports, DARE and Health Technology Assessment were searched. Four programme theories were developed from 53 included articles and 20 key stakeholder consultations addressing the major barriers of GA implementation in oncology practice: time (leveraging non-specialists), funding (creating favourable health economics), practicalities (establishing the use of GA in cancer care) and managing limited resources. We demonstrate that a whole system approach is required to improve the implementation of GA in cancer settings. This review will help inform policy decisions regarding implementation of GA and provide a basis for further implementation research.

2.3 Keywords

Geriatric assessment, neoplasms, implementation science

2.4 Author contributions

I conceived the idea of undertaking a systematic realist review for this research supported by my supervisors Dr Mark Pearson, Professor Mike Lind and Professor Miriam Johnson. Mrs Sarah Greenley provided expert guidance on the search strategy and Miss Alex Bullock provided a second review of the papers selected for inclusion. All authors read and approved the final manuscript.

2.5 Introduction

Older adults with cancer generally experience worse outcomes compared to younger adults, including increased post-operative complications, length of hospital stay, chemotherapy toxicity and discharge to dependent care settings (5-7). Age-related cognitive issues and the accrual of co-morbidities, medications and functional deficits, creates complexity (9-11). This makes shared decision-making between the patient and cancer multi-disciplinary team (MDT) more difficult, compounded by underrepresentation of older adults in clinical trials (12). Undertreatment (e.g., inappropriate best supportive care) or overtreatment (e.g., avoidable post-treatment morbidity and mortality) is possible, although older adults can tolerate and benefit from cancer treatments when appropriately selected (19). The clinician's recommendation is a significant factor in treatment acceptance (28) and the use of chronological age as a proxy for health status is associated with worse patient outcomes (30-32).

To enhance decision-making, international guidelines from authoritative bodies, including the American Society of Clinical Oncologists (ASCO) and International Society of Geriatric Oncology, recommend pre-treatment geriatric assessment (GA) for older adults (13, 35). GA has evolved in oncology from comprehensive principles employed by inpatient geriatric medicine (36), to a more focussed cancer-specific GA (CSGA) and/or the use of short screening tools (e.g., G8) (69, 106). Traditional comprehensive GA (CGA) is a complex intervention most commonly defined as "*a multidimensional, multidisciplinary process which identifies medical, social and functional needs, and the development of an integrated/co-ordinated care plan to meet those needs*" (36). Systematic reviews have demonstrated that CGA improves mortality and function for older medical patients and orthopaedic patients admitted with hip fracture (38, 107). Evidence that CSGA models improve outcomes are

lacking. One randomised controlled trial (RCT) demonstrated feasibility (108). Another RCT was negative for improved morbidity or mortality (109), although other protocols have been published (110). The current view of GA in oncology therefore focuses on its role in prognostication, rather than its therapeutic effectiveness as a complex intervention (13, 35). Even so, first principles suggest that identifying and acting on unknown vulnerabilities identified through CSGA will improve outcomes. Moreover, implementation issues within RCTs may limit their effectiveness (109).

GA is notoriously difficult to implement in oncology with numerous barriers frequently cited, including workforce limitations (94), time, health economics, logistics, training, and practical concerns (34). International guidelines inadequately cover implementation details, which tend to focus on reducing time required to undertake GA by using brief instruments. Insufficient detail is provided on practical, technological, and logistical enablers and a more detailed analysis of implementation science in this setting is required (13, 35). We aimed to review the heterogenous literature on implementation of GA in oncology settings to understand the different implementation context configurations of GA and the mechanisms they trigger to enable successful implementation. A review of the implementation of GA in oncology settings is presented, focussing on the strategies that can be employed to overcome the major implementation barriers.

2.6 Methods

Realist review is a theory-driven approach designed to understand the contextual basis of success for complex interventions and their mechanisms (105, 112, 113). Given the heterogeneity of implementation literature regarding GA in oncology, realist review was selected to explore the contexts, mechanisms and outcomes of GA implementation in this setting. The study protocol for this review was registered with PROSPERO (CRD42019156058) (115). The review meets the Realist And Meta-narrative Evidence Syntheses: Evolving Standards (RAMESES) quality standards for realist review (116) (as documented in **Appendix**

Table 15) and is reported consistent with the RAMESES reporting guidelines (see **Appendix**

Table 14). A two-stage approach was employed as we sought to focus on undertaking a robust systematic review, rather than an initial scoping review (116).

2.6.1 Stage 1 – identifying the evidence relevant to GA and testing and refining the programme theories

The primary ideas used to develop an intervention are termed the programme theories (112), which herein explain how to implement GA and achieve predictive and prehabilitative outcomes. The systematic review search strategy is outlined in

Figure 5 and inclusion and exclusion criteria are outlined in

Figure 6. We undertook a single comprehensive search strategy, as opposed to an iterative search strategy, to ensure we fully understood the heterogenous research base and capture its diversity (117). Backward citation searching involved screening reference lists of relevant papers. Forward citation searching utilised Web of Science from the included studies after full text screening.

Timescale

Electronic databases were searched using their relevant control language from inception to July 2019

Databases

MEDLINE®, Embase, and PsycInfo via OVID; The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials within the Cochrane Library; CINAHL via EBSCOhost, Web of Science Core Collection, Scopus, Applied Social Sciences Index and Abstracts (ASSIA) via ProQuest, Epistemonikos, JBI Database of Systematic Reviews and Implementation Reports, Database of Abstracts of Reviews of Effects, and Health Technology Assessment

Search terms

For cancer: "cancer*", "neoplas*", "tumor*", "tumour*", "malignan*", "carcinoma*", "metasta*", "oncolog*", "leukemi*", "leukaemi*", "lymphoma*", "myeloma*", and "sarcoma*". The Medical Subject Heading (MeSH) term "Neoplasms" was also used where possible, depending on the database.

For geriatric assessment: MeSH terms "Geriatric Assessment" and "Health Services for the Aged". The MeSH terms "Needs Assessment", "Risk Assessment", "Diagnostic Services", "Health Services Needs and Demand", "Health Services", "Delivery of Health Care", "Outcome and Process Assessment (Health Care)" were also combined with "geriatrics". MeSH terms were 'exploded' (using the Ovid® interface where appropriate). See **Supplementary Data File 1** for full search strategies.

Limits

Limits were applied for adult humans in MEDLINE® and to remove conference abstracts from Embase. Where >2,000 results were returned from a database using the above search strategy, attempt was made to filter the results using an implementation research filtering strategy devised by an Information Specialist (SG) based on similar systematic reviews. This was applied to the combined results from the MEDLINE®, Embase, and PsycInfo via OVID and Scopus. This included the MeSH terms "Implementation Science", "Organizational Innovation", "Quality Improvement" and "Diffusion of Innovation", combined with the keywords "barrier*", "constraint*", "facilitator*", "enabler*", "sustainability", "feasibility", "maintenance", "acceptab*", "appropriat*", "uptake", "embed*", "adher*", "usage", "engagement", "fidelity", "Institutionalis*", "institutionaliz*", "implement*", "dissemin*", "adopt*", "practice*", "organi?ational change*", "diffus*", "quality improvement*", "transform*", "translat*", "transfer*", "sustainab*", and "capacity". Searches across all fields were also made for the terms (system* ADJ2 change*) in combination with MeSH terms and other keywords. Where databases returned <2,000 results using the GA and cancer terms, implementation filters were not used.

Software

EndNote X9 (Clarivate, USA) was used for search results management and abstract screening.

Figure 5 – Systematic review search strategy.
Search strategy for systematic review. Abbreviations: GA = geriatric assessment.

Inclusion criteria for research studies

- Reported data from participants aged 65 and over
- Participants had a diagnosis of cancer
- Article focused on the implementation or use of GA

Exclusion criteria for research studies

- Reported data on implementation or use of GA in community, care of the elderly, orthogeriatric, and acute settings
- Absent detail of the implementation strategies employed, barriers of implementation, facilitators of implementation, amount of infrastructure and human resources required or the satisfaction of patients undergoing the assessment process
- Studies reporting the diagnostic accuracy of screening tools, unless screening was part of a relevant implementation strategy
- Studies focussing solely on healthcare education
- Review articles, case report, editorial, opinion piece or commentary

Figure 6 – Inclusion and exclusion criteria for systematic review.
Inclusion and exclusion criteria for studies retrieved using systematic review strategy. Abbreviations: GA = geriatric assessment.

Title and abstract screening were initially undertaken, followed by full text retrieval and review by GM. 'If then' statements were developed to document the various proposed situations towards successful GA implementation, which was supported by evidence drawn from the literature and our research group discussions (118). These statements generated programme theories linked to their respective proposed context, mechanism and outcomes for presentation and critique of plausibility and relevance by our research and steering groups. The quality of the evidence was determined by its ability to build or test the relevance of a programme theory, based on established methodology for realist reviews (116, 119-121). Data extraction followed for articles meeting this test of relevance and were primarily extracted by one team member (GM), with a random 25% independently checked by a second team member (AB). The data extraction process was form-based and included the programme theory that the article intended to support, the explicit or implicit conclusions made relevant to that theory and how the relevant evidence was organised (112). Data extraction included the study type, research methodologies and evidence to enable testing of programme theories. Following data extraction, relationships between context (e.g., organisational conditions), mechanisms (e.g., processes) and outcomes (e.g., all consequences and overall impact) were synthesised. Extracted information was organised into evidence tables with respect to different bodies of literature (e.g., implementation strategy, barriers and facilitators). Patterns related to context-mechanism-outcome configurations were themed across the evidence table. Finally, patterns were linked to form hypotheses.

Key stakeholders were identified by peer recommendations from the professional network of the steering group, and then informal consultations were conducted to test and refine programme theories. Experts consulted from oncology MDTs included medical and clinical oncologists, surgeons, nurses, allied health professionals, MDT coordinators and a cancer business manager. Meetings with geriatricians, information technology (IT) staff and a clinical coding manager responsible for oncology services were also arranged. We presented stakeholders with proposed solutions to successfully implement GA and invited them to express how the contextual elements of GA may impact on the behaviours of those involved in its implementation. These consultations were documented by GM and used in combination with literature synthesis to support or refute programme theories. Data synthesis was further supported from a combination of individual reflection and group discussion in order to challenge the integrity of each theory, judge competing theories and compare the stated theory with actual practice. Data from the studies or stakeholder consultations were used to confirm, refute or refine the candidate theories. Alternative theories were sought where theories could not explain the data.

2.6.1.1 Patient and public involvement

Early findings were discussed with five patients in the context of their lived experience of cancer. Three of these patients were consulted on the configuration of a new GA service for oncology patients developed and operated by the lead author (GM).

2.6.1.2 Ethical approval

This realist review was part of a larger study which gained ethical approval by the Yorkshire and Humber – South Yorkshire Research Ethics Committee (19/YH/0382) (see **Appendix Figure 52**). Consultations with key stakeholders were not deemed to be research. Hull York Medical School ethical approval was gained prior to the start of the study.

2.6.2 Stage 2 – analysing and synthesising evidence to test the proposed programme theories

Following the completion of preliminary mapping of evidence into tables, the steering group was consulted. This group consisted of trans-disciplinary experts including oncologists, palliative care physicians, mixed-methodology researchers, statisticians, sociologists and systems thinking academics. The findings were discussed, and the resultant hypotheses were confirmed or rejected. Confirmed hypotheses were used as synthesised statements of context, mechanism, outcome narratives along with their supporting evidence. The process of analysis,

synthesis and discussion was iterative in order to reach sufficient refinement of programme theories towards developing a new system for optimisation and predictive assessment of older adults with cancer.

2.7 Results

After deduplication of articles, 5,458 describing GA were screened and 214 were included in the review (**Figure 7**). Backward citation searching identified a further two articles and forward citation searching three articles. Twenty key stakeholder consultations were undertaken. Fifty-three articles were selected that provided sufficient detail on implementation of GA. Twenty-seven programme theories were initially developed from the 53 articles, which were consequently expressed as four programme theories addressing the major barriers in GA implementation in oncology practice: i) workload (*leveraging non-specialists*); ii) funding (creating favourable health economics); iii) practicalities (establishing the use of geriatric assessment in cancer care); and iv) resources (managing limited resources). **Appendix Supplementary Table 3** summarises the 53 included studies, their study designs and major findings.

Table 3 summarises the four programme theories linked to relevant studies and includes citations to the studies that helped generate them, in order to make the following text more readable, which also integrates insights from key stakeholder consultations and reflection. **Figure 8** presents a conceptual framework for implementing GA in oncology.

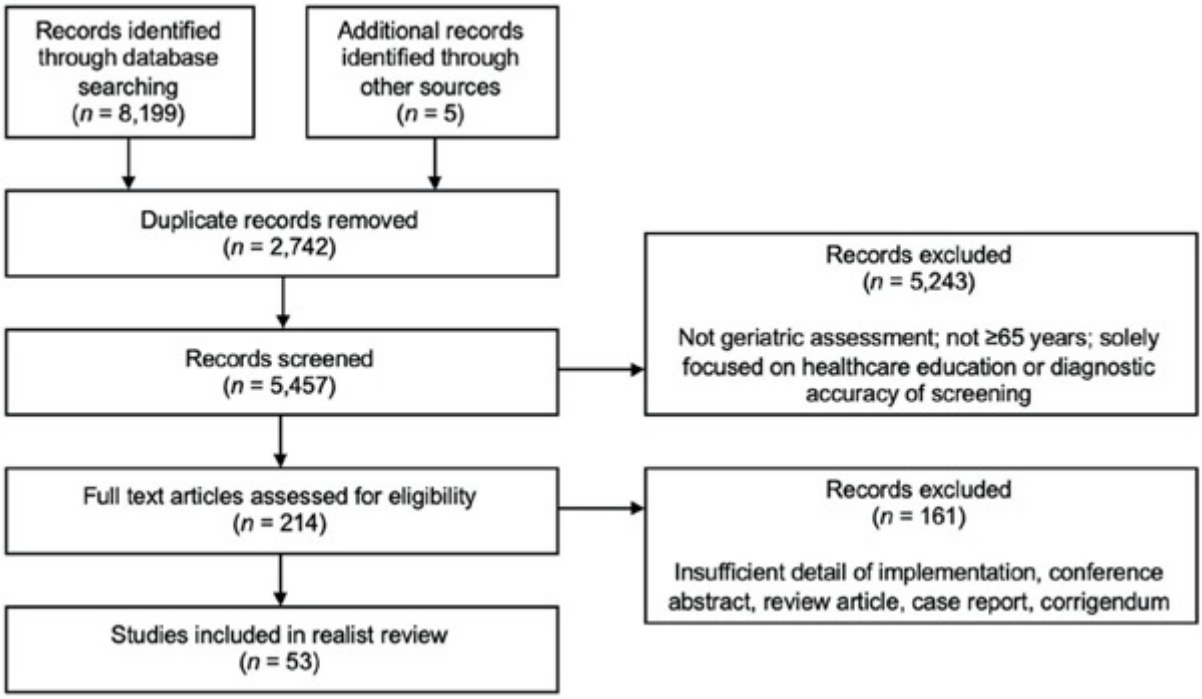


Figure 7 - Literature search preferred reporting items for systematic review and meta-analyses.
Literature search preferred reporting items for systematic review and meta-analyses diagram for the systematic review of eligible studies.

Theme	Context-mechanism-outcome	References
Programme theory 1 – leveraging non-specialists time		
Time is frequently cited as a major barrier to implementing GA in oncology care, although certain implementation configurations can help to leverage non-specialists time. These include: -		
Protocolised organisational structure	The process of undertaking GA can be delegated away from cancer specialists within a protocolised organisational structure. This can help to establish the *indications*, *benefits,* and *alternatives* of GA within the cancer multi-disciplinary team.	(122-140)
Role of the geriatrician	Processes and structures can be instituted (e.g., IT systems, protocolisation, and pathways) to enable non-geriatricians to undertake GA. This can help to generate efficient referrals to geriatricians to maximise their input as a scarce resource.	(94, 124, 126, 127, 129, 132-148)
Patient self-report	If patients can self-report (where able) as much of a GA as possible, either remotely or otherwise independently from the clinician, by using the best available psychometrically validated instruments for this method of administration, then the clinician time to complete the GA process can be reduced. *However*, where IT is utilised to offer patient-led geriatric assessments within a digital-first strategy (e.g., using mobile or tablet devices), processes must be instituted to fall back to clinician-led or paper-based alternatives to enable data capture from groups unable or unwilling to self-administer the assessment digitally	(126, 140, 142, 149-162)
Workforce	The protocolisation and systemisation of the healthcare provider components of a GA can be outsourced to trained staff other than physicians where time is a scarce resource. This can reduce the implementation time and cost, whilst also creating new roles and opportunities for an evolving workforce (e.g., physician associates, advanced nurse practitioners, and allied healthcare professionals)	(132, 133, 135, 137-140, 142, 143, 146, 148, 160, 163)
Assessment-guided care processes	Geriatric assessment-guided processes can be developed according to local service configurations and availability. This means that many of the recommendations of GA can be fulfilled by referring to allied health professionals and other specialist services creating a network effect and emergence of a complex adapting system	(137, 139, 146, 164-166)
Autonomisation	Processes (e.g., agreements, protocolisation, and pathways) can be established to autonomise the professional(s) undertaking a GA before cancer treatment. This means that the same professional(s) making the recommendations can take responsibility for their implementation and follow-up.	(124, 125, 132-134, 139, 141, 143, 153, 165)
Programme theory 2 – creating favourable health economics		
Cost is another frequently cited barrier to implementing GA in oncology care, although certain implementation configurations and system-wide factors may help to create favourable health economics to sustain implementation, including: -		
Geriatric oncology programmes	There may be cases where organisations have sufficient resources (e.g., time, funding, and workforce) to establish a formal Geriatric Oncology Programme. In these cases, attempts should be made to embed local/regional networks to enable the programme to have full clinical governance, create training opportunities (e.g., fellowships), leverage inter-disciplinary skills, and recruit into research studies. This can ensure long-term incentives are created to maintain long-term funding.	(137, 139, 140, 147, 148, 160, 162, 163, 167)

Insurers and payers	If insurers and payers can be convinced of the wider value of multidimensional predictive assessment and prognostication from the perspective of economics, including pricing of insurance premiums, hospital tariffs, and population health planning, then new top-down opportunities can be recognised for key stakeholders to encourage the use of GA.	(133, 137, 139, 140)
Business intelligence	GA-based services can be subjected to data-driven continuous quality improvement and health economic analysis. Service-level improvements can be made to improve clinical- and cost-effectiveness and build business cases for longer term, mainstream funding and therefore sustained implementation. IT systems can be established to build real-time, searchable databases of structured local/regional data with high granularity relevant to geriatric oncology. This data can drive predictive analytics, institutional case series and business intelligence towards clinical treatment, research, and quality improvement.	(130, 137, 139, 164, 168, 169)
Information technology	If GA-guided interventions can be delivered using IT (e.g., mobile/web applications, Internet of Things devices), then some interventions can be delivered and monitored at home, saving the travel burden, costs, and environmental impacts of visits to local services and encouraging independence	(160, 166)
Programme theory 3 – establishing the use of geriatric assessment in cancer care		
Geriatric assessment can take different configurations in cancer care and can be driven by both internal and external factors, including: -		
Cancer-specific geriatric assessment	Lack of evidence and/or an international consensus often precludes the homogeneity of GA in oncology settings. *However*, CSGA can be undertaken utilising a synthesis of the best available psychometrically validated instruments appropriate to the patient population, the method of administration, and the potential unmet needs (e.g., pain and fatigue) of patients with cancer. The outputs of GA can therefore be aligned to prediction of outcomes or optimisation before cancer intervention.	(126, 137, 143, 149, 150, 152-155, 158, 170)
Cancer multi-disciplinary team policy	If models of reactive (e.g., by referral) and proactive selection (e.g., screening of suspected cancer outpatient lists) for GA can be agreed within individual cancer multi-disciplinary teams, then GA can be used for patients most likely to benefit from its predictive and optimisation capabilities.	(133, 135, 143, 160, 161, 168, 171)
Screening	If cancer centres have limited resources to undertake GAs, then population-relevant screening tools with high diagnostic accuracy (e.g., G8) can be utilised either to identify patients potentially more in need of GA or as an independent decision-support tool.	(94, 126, 128, 129, 132, 133, 137, 141, 143, 146, 148, 156, 160, 167, 168, 171, 172)
Clinician accessibility	Geriatricians cannot often be integrated within cancer multi-disciplinary team meetings to convey results of GA. However, summarised GA findings which are suitable for non-geriatricians can be integrated into MDT processes to facilitate utilisation of results in clinical decision-making.	(125, 127, 129, 131-133, 137-141, 143-145, 148, 163, 168, 171)
Local champion	If medical and surgical oncologists can be aligned by consensus and championed by a local opinion leader towards utilising GA at the level of the MDT, then the benefits of GA can be made available to all cancer patients.	(94, 128-133, 139, 140, 160, 173)

Clinical staff education	Brief educational interventions can encourage GA to be considered as both a shared-decision support tool (e.g., predictive assessment) and a complex intervention (e.g., through generating referrals). This can enable members of the cancer MDT to better understand its role in cancer care and promote embedding of GA into routine practice. Furthermore, ancillary motivators can be conveyed to front-line clinicians including reduction of potential medico-legal burden, continuous professional development, and research opportunities. This can help establish new bottom-up incentives that can drive local adoption of GA in cancer multi-disciplinary teams.	(125, 128, 129, 131, 133, 137-140, 160, 162, 167)
Patient education	Patients can undergo brief educational interventions (e.g., scripted face-to-face summarisation or audio-visual introduction) concerning the indications and benefits of GA in oncology settings. They may therefore be more likely to engage fully in the process and become active participants.	(128, 137, 142, 151)
Whole system approach	A whole system approach can be considered, including local implementation champions, regional policies, quasi-autonomous non-governmental organisation guidance (e.g., National Institute of Health and Care Excellence) and governmental lobbying by specialist interest groups/medical organisations. This could help refocus the care agenda for older adult with cancer and powerful facilitators could be established to encourage national implementation	(133, 137, 139, 140, 160, 167)

Programme theory 4 – managing limited resources

Resources can be limited to undertake geriatric assessment in cancer care, although there are ways of managing this scarcity including: -

Timing of assessment	GA can occur early in the cancer pathway, immediately after the index clinical review. This enables the results of GA to be available to the cancer MDT for shared decision-making and more time will become available within existing cancer pathway targets to enable prehabilitation	(94, 130, 131, 133, 136, 173)
Primary care integration	Integration with primary care and community services can be improved, in terms of GA timing, health data utilisation, aftercare agreements and referral guidelines. The process of GA can therefore be streamlined and the challenges of the longitudinal care for the most frail and older adults can be improved	(148, 160)
Policy	Locally or nationally set cancer pathway targets can be relaxed or an exception agreed for older adults to be allowed time to undergo GA before decision-making. This eliminates one-size-fits-all pathway configurations, which can be more accommodating for older adults with cancer, and the pressure to meet targets in the context of complexity can be relieved	(137, 143, 174)
Information technology	If systems can be developed (e.g., cybernetics, automation, and algorithms) so that implementation cost (e.g., time, training, human resources, procurement) can be minimised, then GA can be embedded into routine oncology practice without the need for a separate geriatric oncology team.	(94, 126, 129, 132-134, 136-140, 142-144, 146, 148, 151, 158, 160, 162, 163, 165-167, 172)
Outpatient space	If outpatient space is limited for inter-professional teams, then increased use of phone, video, instant messaging and automated conversational agent consultations can be considered (e.g., pharmacy, nutrition, and social work interventions), which can also reduce travel burden, costs and environmental effects	(160)

Existing resources	If referrals to geriatrician-led services are required based on GA results and these are integrated into existing structures (e.g., internal liaison, geriatric day clinic), then this reduces the initial barriers of establishing a dedicated geriatric oncology service and promotes inter-speciality cross-fertilisation	(133, 137, 139, 140, 144, 145, 147, 148, 160, 163)

Table 3 – Programme theories tested in the review.
The four programme theories with their sub-theories are presented. Abbreviations: GA = geriatric assessment; MDT = multi-disciplinary team; IT = information technology.

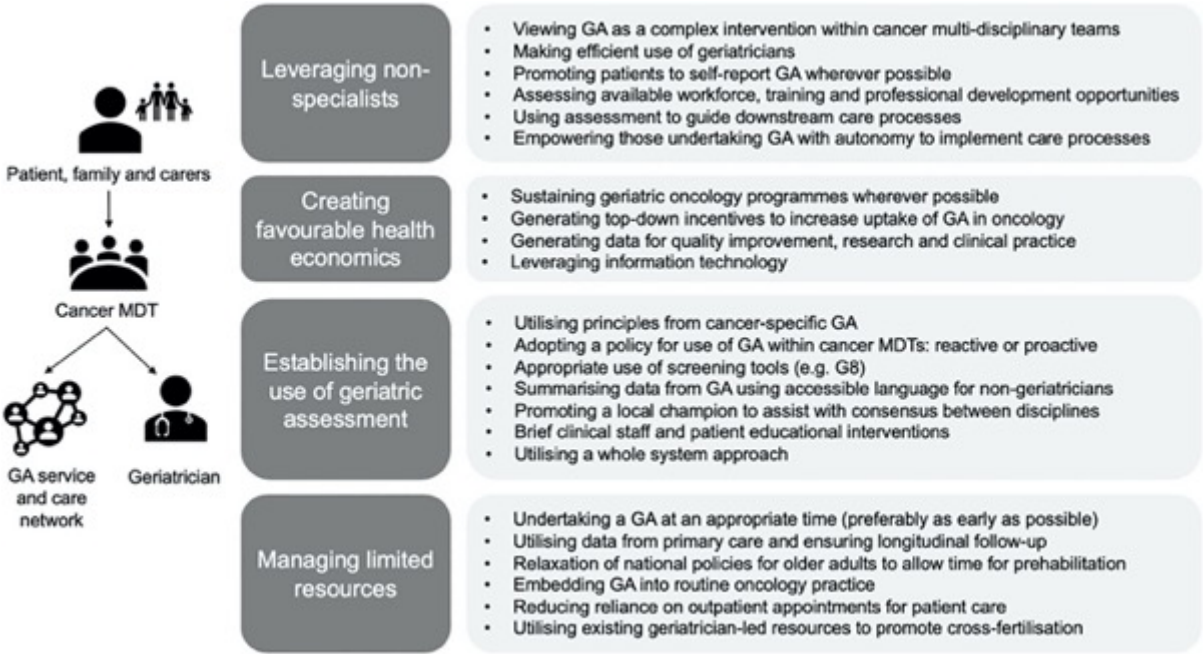


Figure 8 – Conceptual framework for implementing geriatric assessment in oncology practice.
Summary of the key concepts for implementation of geriatric assessment in oncology practice. Abbreviations: GA = geriatric assessment; G8 = geriatric 8; MDT = multi-disciplinary team.

2.7.1 Programme theory 1: leveraging non-specialists

2.7.1.1 Protocolised organisational structure

GA is a complex intervention with indications, benefits, and alternatives, although it is frequently viewed as an assessment undertaken solely by geriatricians. Protocols for the use of GA within the cancer MDT can be constructed, which can help GA to be viewed as a complex intervention that can benefit oncological care. This view can help cancer specialists better

appreciate the holistic value of GA, so that they can focus on cancer diagnosis and treatment, knowing that geriatric issues will be covered at some point, and vulnerabilities identified.

2.7.1.2 Role of the geriatrician

The role of the geriatrician is frequently identified by two extremes: i) reliance on geriatrician-led oncology services or Geriatric Oncology Programmes (GOPs); or ii) patient-led, CSGA with referrals to other services, including geriatric medicine. A GA can be undertaken by non-geriatricians, with careful protocolisation and systematisation within the host organisation. Geriatricians should be considered a scarce resource, as national workforce shortages to meet current and emerging healthcare demands are evident (92, 93). Implementation configurations which consider this real barrier therefore seem favourable and progressive. GA results can drive protocolised referrals to other healthcare professionals including allied health professionals (e.g., dieticians), geriatric medicine, and external services (e.g., social services). This implementation strategy reduces the number of consultations geriatricians have to undertake within cancer services, whilst enabling them to focus on the most complex patients.

2.7.1.3 Patient self-report

Patient self-report of GA either remotely or otherwise independently from the clinician has demonstrated feasibility. Not all patients will be capable of self-reporting, therefore systems must be in place to fall back to clinician-led reporting. This also requires psychometrically validated instruments, which are suitable for patient self-report wherever possible. Remote self-reporting can occur through paper-based methods (e.g., post) or digitally (e.g., mobile devices). An outpatient area can also be used, with the advantage of assistance being available if necessary. This can reduce the clinical time required to administer the assessment. Digital methods also offer more efficient capture of information and the potential to automate the processing of data. Digitalised remote completion may involve modern communication channels, including email, short message service, and push notifications, which save paper and offer environmental advantages. The process of self-reporting is widely acceptable to older patients and assistance is not required in the majority; therefore, it removes an additional time burden from all clinical staff.

2.7.1.4 Workforce

Time is a scarce resource and a frequently cited barrier for cancer specialists. A substantive GA has healthcare provider components, including cognitive screening, co-morbidities assessment, medication review, and physical examination. However, this can be protocolised,

systematised, and rationalised for outsourcing to trained staff other than physicians. Clinicians are often competing against overbooked clinics, frenetic MDT meetings, inpatient reviews, operating lists, and other service-critical activities. Leveraging an alternative workforce therefore reduces implementation time and subsequently cost. Opportunities exist to capitalise on emerging roles (e.g., physician associates) to undertake GA. Identifying the training opportunities, continuing professional development and support structures to create, develop, and sustain these positions is key.

2.7.1.5 Assessment-guided care processes

GA can guide subsequent care processes by identifying opportunities to refer to other healthcare professionals (e.g., dietetics), according to local service configurations and availability. Where referrals cannot be fulfilled (e.g., they are unavailable or have no capacity), there is an opportunity to collect important data on unmet needs. This can be used to drive business cases for service improvement, so could be viewed as a facilitator. Establishing assessment-guided care processes may create favourable networks, which can sustain conditions for implementation of GA. The concept of networks and their feedback loops is derived from complex adapting systems (CAS) theory, which has been applied to implementation science (175). CAS theory considers individual agents (e.g., cancer MDT, GA service, general practitioner) as a collection of dynamic, self-similar entities which are adaptive (175). Over time a degree of mutual dependency upon referrals can be anticipated, leading to the emergence of normalised co-operation between services and the individuals operating them.

2.7.1.6 Autonomisation

Recommendations made to cancer specialists from a GA team are not always implemented. There may be legitimate reasons, although some cases may be from lack of insight into their benefits. Where GA-guided referrals are made by clinical staff other than the cancer specialist, protocolisation can be established to autonomise the professional(s) undertaking a GA. The same professional(s) making the recommendations can take personal responsibility for their implementation and follow-up, which may improve adherence to GA-guided recommendations. This autonomisation also reassures the cancer MDT that these referrals will be handled and helps to leverage the expertise of non-specialists.

2.7.2 Programme theory 2: creating favourable health economics

2.7.2.1 Geriatric oncology programmes

The ideal model of GA in cancer care is frequently cited as a formal Geriatric Oncology Programme (GOP). A GOP is geriatrician-led and generally well-integrated into cancer pathways with mature referral criteria and strategy. Other members of the geriatric medicine team (e.g., clinical nurse specialists and allied health professionals) have key positions and may co-lead aspects of the service. However, this model exhibits significant workforce and economic resources making implementation challenging. If organisations can operate a GOP, maximisation of sustainability should take precedence to fully embed the GOP within cancer care. This includes developing local/regional networks to enable full clinical governance of the GOP within cancer services, creating training opportunities (e.g., fellowships), leveraging inter-disciplinary skills and developing research studies. Generating high quality health economic data to demonstrate favourable outcomes helps build the case necessary to secure long-term funding. Cancer clinicians would likely become dependent upon GOP services, leading to ongoing demand and therefore sustainability.

2.7.2.2 Insurers and payers

Insurers generally do not cover GA within oncology and often institutions underwrite this themselves. There are no national financial incentives within the UK to undertake GA as part of cancer care. Dialogue is therefore required with insurers and payers to convince them of the wider value of multidimensional predictive assessment and prognostication. This includes health economic impacts (e.g., reducing chemotherapy toxicity admissions), the pricing of insurance premiums (e.g., risk mitigation), hospital tariffs (e.g., improved clinical coding) and population health planning. New top-down opportunities can be recognised by key stakeholders to encourage the use of GA at a national level.

2.7.2.3 Data and quality improvement

The use of data can support the understanding of the positive effects that implementing GA can have on cancer services. For example, reduced chemotherapy toxicity rates following GA service introduction. Data-driven continuous quality improvement can be undertaken and used for health economic analyses, particularly cost consequence analysis. Service-level improvements can further improve clinical- and cost-effectiveness and generate the data needed to support sustainability. IT systems can be established to build real-time, searchable databases of structured local/regional data, with high granularity relevant to geriatric oncology.

This also drives advanced predictive analytics, institutional case series and provides further data towards clinical treatment, research, and service evaluation.

2.7.2.4 Information technology

GA-guided interventions can also be delivered using IT. Smartphone and web applications and Internet of Things devices have demonstrated feasibility for the delivery and monitoring of GA-guided interventions at home. This can save the travel burden, costs, and environmental impacts of visits to local services and encourages patient independence. Clinicians can gain reassurance from community monitoring of vulnerable patients and acquire new insight into the biopsychosocial effects of cancer and its treatment.

2.7.3 Programme theory 3: establishing the use of geriatric assessment in cancer care

2.7.3.1 Cancer-specific geriatric assessment

There is a lack of evidence regarding which tools to use within a CSGA. Whilst attempts have been made to reach international consensus, heterogeneous instruments are often recommended. This largely depends on the rationalisation for their selection (e.g., short time taken to complete) versus their underlying psychometric properties. Cancer-specific geriatric assessment was popularised by Hurria *et al*. (106) in 2005. Building on this principle and taking advantage of the numerous systematic reviews of psychometric instruments that have been published since, CSGA can be developed further. The outputs of the GA can be aligned to the prediction of outcomes or optimisation before cancer intervention. A synthesis of the best available psychometrically validated instruments appropriate to the patient population, the method of administration and the potential unmet needs (e.g., pain) of patients with cancer can be designed at national levels. Homogeneity of the CSGA process at the national level may facilitate meta-analysis of CSGA outcomes, something which has not yet been undertaken. Positive findings at this level may help convince some clinicians who are doubtful of the evidence behind GA in cancer care.

2.7.3.2 Cancer multi-disciplinary team policy

Cancer MDTs may have initial uncertainty about how best to use GA in their care pathways. There are two main strategies: reactive (i.e., the index clinician makes a referral to a GA service) and proactive (i.e., the GA service proactively screens cancer pathway outpatient lists). Even within a single cancer site MDT, two different strategies may be employed and the conversion rate to cancer from outpatient lists should be explored. This insight can be used to

strategise selection of patients who will most likely benefit from the predictive and optimisation capabilities of GA.

2.7.3.3 Screening

Some cancer centres have such limited resources to undertake GA that a screening strategy should be considered. Screening can either help select which patients would benefit most from a GA or can be used as an independent decision-support tool. Where screening is undertaken, population-relevant screening tools with high diagnostic accuracy (e.g., G8) can be utilised.

2.7.3.4 Clinician accessibility

The integration of a geriatrician within a cancer MDT is often favoured, although current workforce limitations make this an unscalable solution. The strategy of dual cancer-site and geriatric oncology MDTs has demonstrated feasibility in some studies but was thought to be logistically too difficult in our stakeholder consultations. In NHS cancer services, MDTs frequently run over lunchtime hours and back on to outpatient clinics. There is little scope within specialist's timetables to attend another MDT and this also depends on geriatrician–leadership and a formal GOP being established. These dependencies make this proposition unscalable in many healthcare systems. However, GA findings can be summarised in ways that are suitable for non-geriatricians, either using proformas or well-designed software. Summarised GA findings using accessible terminology can be integrated into MDT processes to facilitate utilisation of results in clinical decision-making, in the absence of a geriatrician.

2.7.3.5 Local champion

There is lack of consensus between medical and surgical research groups regarding the use of GA in cancer care. A cohesive view of the cancer pathway and where GA fits is distinctly missing. At the local level, this consensus is vitally important so that GA can be used centrally by the MDT and made available to all patients who will likely benefit. The championing of GA by a local opinion leader can help to establish this consensus.

2.7.3.6 Clinical staff education

Rather than trying to train cancer specialists (e.g., surgeons and oncologists) in geriatric principles, brief educational interventions appear better suited. Alternatives include a geriatric rotation in higher specialist oncology training. These should encourage GA to be considered as both a shared-decision support tool (e.g., predictive assessment) and a complex intervention (e.g., through generating referrals). This is in keeping with national work in the NHS such as the UKs national Perioperative Quality Improvement Programme (176). The aim should be for

members of the cancer MDT to better understand the role of GA in cancer care and promote embedding into routine practice at the level of the MDT. Furthermore, ancillary motivators can be conveyed to front-line clinicians, which include: i) reduction of potential medico-legal action; ii) continuous professional development; and iii) research opportunities, particularly in collaboration with geriatric specialists to promote inter-departmental cross-fertilisation. This can help establish new bottom-up incentives that can drive local adoption of GA in cancer MDTs.

2.7.3.7 Patient education

Patients may be unwilling to complete a GA when they have not been adequately briefed about its indications and benefits. There may be a role for brief educational interventions for patients (e.g., scripted face-to-face summarisation or audio-visual introduction). This may help to fully engage patients in the process and help them to become active participants, by realising the value in GA at the point in their care.

2.7.3.8 Whole system approach

The issues of GA in oncology practice are a whole system implementation problem and a higher-level approach is required (175). This may include quasi-autonomous non-governmental organisation guidance (e.g., National Institute of Health and Care Excellence) and governmental lobbying by specialist interest groups (e.g., British Geriatrics Society, Geriatric Oncology Special Interest Group) and charitable organisations (e.g., Macmillan Cancer Support). This could help refocus the national care agenda for older adults with cancer and establish powerful facilitators to encourage national implementation.

2.7.4 Programme theory 4: managing limited resources

2.7.4.1 Timing of assessment

Undertaken too late in the cancer pathway and the results of a GA are unlikely to be used in shared decision-making and opportunities for optimisation and prehabilitation are missed. Undertaken too early and there is a chance that older adults who have a symptomatic benign condition or a false positive on screening undergo a GA, which is not ultimately required for decision-making. The latter situation may be preferred as it affords the opportunity to identify general health vulnerabilities that can be addressed. In a reactive model, the ideal time to undertake GA is immediately after the index specialist review when cancer is suspected, and investigation continues. In a proactive model, screening of 2 Week Wait lists is possible, including inviting patients for GA before the index specialist review. However, this generates

a risk of overloading the GA service and not targeting those most in need, who may enter the cancer pathway through other routes.

2.7.4.2 Primary care integration

A significant number of new patients enter a cancer pathway through referrals from primary care. This opens the possibility of undertaking GA at the point of referral. A deterioration in health of an older adult is an opportunity to undertake GA, even if cancer is eventually excluded. However, increasing the workload of general practitioners or straining primary care services is discouraged. To avoid unnecessary duplication of data collection or intervention during GA, there is scope for improved health data utilisation from primary care. Primary care electronic health records are rich in data and mining this information using new technologies is possible. For example, natural language processing can extract and summarise health care data in structured (e.g., height and weight) or unstructured (e.g., free text) forms. Cancer specialists are unlikely to have sufficient resources to provide robust aftercare agreements for frail older adults returning to the community. Primary care plays a role here, but robust longitudinal care coordination will be required to manage complex patients, ideally with a community geriatrician. Evolving services such as Integrated Care Centres may be important in this space.

2.7.4.3 Policy

Locally or nationally set cancer pathway targets were identified as a significant competing barrier. However, these could be relaxed, or an exception agreed for older adults to undergo GA before decision-making. If the pressure to meet targets in the context of complexity can be relieved, this could create time in the pathway for GA and prehabilitation.

2.7.4.4 Information technology

There is still an opportunity cost for IT infrastructure and mechanisms to accommodate patients who cannot use technology must be implemented. For a digital patent reported CSGA, the remainder of the clinical components could be integrated into routine oncology appointments, without the need for a formal GA service. There is some evidence that even a Timed Up and Go test can be predicted using a three-question decision tree, although this remains to be prospectively validated (177). This movement appears to have driven the reductionism of CSGA and emphasis on using short instruments easily used in outpatient settings by non-specialist staff (13).

2.7.4.5 Outpatient space

Physical space and logistics have also been cited as an implementation barrier. If outpatient space is limited for inter-professional teams, technology can also offer solutions. Professionals undertaking CSGA can consider the use of telephone, video, instant messaging and automated conversational agent consultations. These are particularly suited towards advice-based interventions undertaken by allied health professionals (e.g., pharmacists, dieticians, and social workers). The decreased reliance on face-to-face consultations, where appropriate, can also reduce perceived or actual travel burden for patients, healthcare costs and consequent environmental effects.

2.7.4.6 Existing resources

Where referrals to geriatrician-led services are required based on GA results, these can be integrated into existing structures (e.g., geriatric day clinic). This can reduce the initial barriers of establishing a dedicated GOP and promotes inter-speciality cross-fertilisation. Exploration of the individual capacity of specialties and services is important. Geriatricians may be able to accommodate referrals from cancer services within a few weeks. If early GA through a proactive model and/or the relaxation of cancer pathway targets for older adults can be negotiated, then existing geriatric services can be utilised.

2.8 Discussion

We have systematically reviewed and synthesised evidence from 53 research articles and 20 key stakeholder consultations using realist methodology regarding the implementation of GA in oncology settings. We have developed four major programme theories based on the most cited implementation barriers, namely limited workload capacity, absence of funding, uncertain practicalities and limited resources. For each of these programme theories we have attempted to outline enablers around themes that map to these barriers. Enablers include protocolisation of GA towards the generation of GA-guided interventions formulated as referrals to other services by clinically autonomous non-specialists. A GOP requires robust clinical governance and the development of training, research and health economic data to promote sustainability. Where geriatricians are unavailable to operate a GOP, referring to existing geriatrician-led services can promote favourable network formation Technology can be utilised to address workload, health economic and resource barriers. These enablers are the product of realist review using the available evidence, key stakeholder expertise and the authors' reflections.

Strengths of this review include the novelty of using realist synthesis in the systematic review of GA in oncology settings and, to the best of our knowledge, this is the first of its kind. The vast majority of systematic reviews concerning GA within oncological settings have focussed on effectiveness (64, 65). Because respected international organisations already endorse and use GA in oncology settings, we chose to focus on implementation. We made the assumption that GA is an evidence-based practice. Realist review was chosen to facilitate the combination of heterogeneous literature exhibiting a range of study types with real-life experience and reflection. The lead author (GM) has designed and operates a new GA-based service for cancer patients. This first-hand experience helps to contextualise literature findings, thereby making programme theories more generalisable towards clinical practice and the wider implementation science community. The iterative approach of the steering committee also improved sense-making of the limited implementation literature, noting the absence of ideal study types such as hybrid implementation-effectiveness trials (178). A robust systematic search strategy was undertake utilising a novel implementation filter designed by an information specialist (SG) to help identify relevant papers from a large literature base (>10,000 results). We avoided the need to exclude key MeSH terms (e.g., 'geriatric assessment') to reduce the abstract screening workload (179).

Limitations include those common to systematic reviews, including the search strategy employed and the heterogeneity of studies. The search strategy was not designed to encompass all diagnostic accuracy studies of screening tools used before GA, which have been subject to several systematic reviews (70). We also excluded studies solely focussing on healthcare education, as our search strategy was not developed to capture all healthcare education literature. Some studies may not have been analysed in our review, although, the large number of abstracts screened and our rigorous forward and backward citation searching strategy means that major implementation studies were unlikely to be missed.

Zubair *et al*. (179) undertook a realist review of CGA in UK care homes and found that the effectiveness of CGA in this context requires three components: i) structured/standardised assessment; ii) MDT review; and iii) care delivery coordination. Similarly, we found that a protocolised assessment undertaken by non-specialist staff with carefully summarised results integrated into a tumour-site specific MDT appears effective. Oncological care delivery co-ordination comes either from the integration of geriatrics into oncology (e.g., establishing a GOP) or from autonomising a CSGA service to make and follow-up geriatric-specific referrals.

2.9 Conclusion

We have demonstrated that a whole system approach is required to improve the implementation of GA in cancer settings using four programme theories. At the service-level, utilisation of IT, leverage of non-specialist staff skills and the consensus of individual MDTs helps to view GA as a predictive optimisation tool. At the organisation level, recognition of the cost consequences of GA, such as medicolegal mitigation, research opportunities and data generation for service improvement provide top-down incentives for GA. Finally, insurers, payers, and regulators should make a clear declaration, either way, about the value of GA within cancer care. This review should help guide policy decisions regarding implementation of GA and provide a basis for further implementation research.

2.10 Post-publication comments

A subsequent focussed search was undertaken in September 2022 using PubMed to identify any later published studies, which could change the conclusions of this chapter. In summary, four significant trials have been published since and the methods utilised reinforce the findings herein. Mohile *et al*. (60) undertook a cluster-randomised study of 718 participants and demonstrated lower relative risk of grade 3-5 chemotherapy toxicity. The use of a dedicated team to undertake GA was evident driving implementation, although they were not autonomised to undertake the interventions. There was consequently evidence of some interventions having much lower prevalence of being selected by treating oncologists. The geriatric assessment-driven intervention trial (180) also demonstrated a 10.1% reduction in grade 3+ chemotherapy toxicity. The fidelity between recommendation and implementation was high in this study (76.8%), because the MDT undertaking GA was autonomised to make referrals for GA-driven interventions. Soo *et al*. (181) undertook a multi-centre, open-label RCT in Australia of 154 participants using a dedicated geriatrician to undertake GA at chemotherapy initiation. They found improved HRQoL, but the timing of GA meant that GA could not be used for MDT-level decision-making and generalisability depends on having a dedicated geriatrician available. Paillaud *et al*. (182) undertook an RCT of 499 patients with head and neck cancer undergoing GA-guided interventions by a geriatrician. They were unable to demonstrate improvement in six-month overall survival, functional, and nutritional status. There were significant implementation issues, including availability of geriatricians and low fidelity between intervention suggestions and follow-through by the treating oncologist, again reaffirming the importance of autonomisation.

Chapter 3 – Methodology

3.1 Introduction

The previous chapter presented the findings from a systematic realist review, which generated the basis for the design, implementation, and evaluation of an OGA service. Before discussing further individual studies and their methods in subsequent chapters, this methodology chapter focusses on the underlying philosophical and theoretical basis of this thesis. Further specific details regarding methodological paradigms relating to individual studies are covered later, where relevant. This chapter also focusses on the ethical issues that arose from the study design, their mitigation and justification, and the process of obtaining ethical approval for the study.

3.2 Theoretical basis for the study design and rationalisation

A decision was made to undertake a predominantly quantitative research approach for this thesis and the associated research studies. A detailed discussion of the use of different methods, as opposed to mixed methods, is intentionally deferred until later. This decision was rationalised based on ontological, epistemological and methodological principles, which are described in this section. Firstly, an overview of the relevant principles is presented, followed by justification for choices made regarding their utilisation, with personal reflection on this process. Secondly, the theoretical model choice is outlined and justified. Finally, my background knowledge is discussed in relation to the experiential framework which supports the methodological choices.

3.2.1 Overview of research paradigms

Every research community holds certain beliefs and assumptions regarding ontology, epistemology and methodology. This phenomenon both serves as a mental model and structures unique fields of study and their chosen research methods to find solutions to known problems. Individual researchers also hold personal contexts – assumptions, models and backgrounds based on philosophy, theories and knowledge, generated through experience and existing beliefs (183). Ontology refers specifically to the beliefs of the investigator regarding the nature of reality. Whereas epistemology refers to what we may already know of reality, and then how we can acquire knowledge of the world. Although ontology and epistemology represent a continuum of positions, the chosen methodology is often derived from a particular epistemology (e.g., social constructionism), which may lean towards a particular ontology (e.g., relativism). The researcher's life and personal circumstances may heavily inspire or influence their research interests, the so-called intellectual autobiography, which has been

observed in feminist research (184). Methodology refers to the procedures used to investigate reality and confirm our findings (185). Together these principles constitute research paradigms, which include positivism, postpositivism, constructionism/interpretivism, postmodernism and pragmatism (186), (187).

Positivism is classically associated with quantitative methods and refers to hypothesis testing through controlled experimentation in order to advance scientific knowledge (188). Postpositivism represents a modern development from the critique of positivism in its ability to always extrapolate truth from observation and disprove pseudoscientific theories (189). Positivistic beliefs assume a single reality where the researcher must independently observe and remove influence from the research to the greatest extent possible (188). In contrast, constructivism is more commonly associated with qualitative research, as it assumes that multiple realities are constructed at the individual level and must be reflexively studied by working *with* individuals, but where the researchers own values are inseparable (190). Interpretivism is often used synonymously with constructivism (191). In mixed methods research, foundations based on positivism or constructivism tend to favour quantitative or qualitative methods respectively, possibly at the expense of the other when each are critiqued. However, it has been argued that the underlying philosophy does not always align with particular research methods (192). Critical realism sits between positivism and constructivism with similarity to postpositivism in that there is an objective reality that can be studied to a point of agreement. However, critical realists believe that this is insufficient to understand the world and individual mental phenomenon also occur. Researcher's values and perspectives are part of the research and drive knowledge acquisition. This paradigm formed the basis of the realist review in **Chapter 2**, where the contextual elements served as part of the causation process towards a particular outcome through a particular mechanism (behavioural and mental phenomena).

Pragmatism is often associated with mixed methods research or research that employs different methods. Pragmatism holds that viewpoints regarding reality are diverse, and knowledge is acquired through both independent observation and subjective models. Importance is placed on the research questions and the appropriate methods to draw inferences, where the researcher's influence is important. However, this approach has been criticised for diluting the underlying theoretical considerations of the quantitative and qualitative methods (193). This pluralistic viewpoint of reality is shared with another philosophy termed dialectical perspective/pluralism. However, in this paradigm, knowledge enhancement occurs through a

respectful dialogue of the different philosophical conceptualisations, involved between different stakeholders. Intellectual tension is encouraged, although respectful values must be maintained (e.g., tolerance and acceptance). The overemphasis on epistemology and lack of guidance where divergence of contradictory beliefs occurs has led to criticism of this paradigm (194). The concept of multiple realities has been extended again, where socio-political differences drive strong social justice perspectives. Transformative emancipatory perspective is a paradigm where knowledge of reality is gained through working with individuals who experience the effects of certain socio-political structures. The researcher's values are a core component of this paradigm, but the strong value-based moral underpinnings are criticised as being served as the research purpose, rather than an epistemology (195).

Finally, postmodernism has been used in mixed methods research both as a foundation and to examine and critique the field itself to challenge existing practices and make advancements. Postmodernism evolved from modernism (a time of art and culture movement breaking away from tradition) as a process of questioning the underlying assumptions of a field to promote innovation and progress. Postmodernism accepts that reality does not conform to any structure and any knowledge has value when scrutinised and discussed properly. The researcher's values are important but are equal weighted with other values. However, the process of challenging the field without providing credible alternatives as lead to criticism (196).

3.2.2 Justification of paradigm choices

As previously discussed, the use of OGA has been extensively studied from a postpositivism paradigm, with various solely quantitative studies returning mixed results of efficacy for risk prediction and optimisation. The heterogeneity of CGA as a complex intervention means that meta-analysis is limited. The various implementation challenges identified in **Chapter 2** have contributed to the mixed efficacy within trials to improve outcomes following cancer treatment. When faced with consensus decision-making, authoritative bodies such as ASCO often utilise pragmatism to justify the use of OGA to enhance decision-making and when deciding on individual OGA components to use. For example, they may compromise on the psychometric validity of a particular OGA instrument for the sake of ease of implementation, through choosing a tool that is easy and quick to use. Comparably, much less research has been undertaken using a constructivist approach for OGA. From a postmodernist paradigm, challenging the default position of positivist research for OGA would be welcome, given the vast body of mixed quantitative results. In fact, the numerous systematic reviews undertaken regarding the efficacy of OGA as a risk prediction tool was my inspiration to utilise a realist

approach towards understanding the implementation of OGA. Not only was there an apparent gap in the literature, but also a new lens to explore implementation challenges, utilising my own personal reflexivity in the process. Since this thesis formulated part of a funded, team effort to improve regional outcomes and address inequalities in cancer treatment (TRANSFORMing Cancer Outcomes in Yorkshire, funded by Yorkshire Cancer Research, UK), a transformative emancipatory perspective could be considered. The social injustice here is the apparent ageism that still exists in cancer care (31) and the need to improve objectivity in treatment decision-making within MDTs. However, due to the diverse nature of the research workforce and their individual studies, the social injustice element is perhaps best reserved as the high-level purpose of the research rather than the epistemological underpinning.

Due to the presence of a high-level purpose and a diverse research team, aspects from dialectical perspective have been utilised. A scientific committee was formed holding regular meetings, including members from diverse research backgrounds (including realism, postpositivism, constructivism) and extensive patient and public involvement (PPI) work was undertaken. Despite the apparent use of aspects of many different paradigms, arguably the most fitting philosophical paradigm within this thesis is pragmatism. This thesis examined the problem of OGA at a time where the research community had expressed a need to understand *how* to implement OGA. Research questions of '*should* OGA be utilised' have already exceeded clinical equipoise, therefore from my perspective an alternative approach to positivism was needed. This was supported by my own personal gravitation towards pragmatic approaches in clinical practice and the use of realism in the study discussed in **Chapter 2**. I chose to employ a realist approach because it befitted the research question I was asking. This is not dissimilar to how I would choose a treatment strategy based on the patient in front of me according to evidence, the patient's views and my own clinical expertise. This represents the three pillars of evidence-based medicine (EBM). Because the balance of each EBM pillar can tip accordingly, this generally follows a pragmatic approach, although some would argue that more pragmatism is welcome in the face of increasing complexity, and the need for generalists versus specialists (197).

Chapter 4 presents a health economic evaluation of OGA prior to cancer treatment. This principally uses quantitative methods, although some qualitative discussion points are made in terms of the ethical considerations of assessing OGA as a cost-effective intervention. Pragmatism was used to guide development of the model and in the interpretation of the findings. With the increasing concern over healthcare costs and need for efficiency, a

healthcare economic analysis is a necessary part of business case generation to develop or sustain an OGA service. Again, pragmatically, this method was selected based of its ability to answer the research question and its broadly understood value by a range of stakeholders.

Before focussing on the patient-facing aspects of an OGA service, the organisational aspects must be considered. **Chapter 5** initially details the specific theoretical considerations of implementing an OGA service, and then the development of a digital-first OGA service. **Chapter 6** specifically presents data gained from quantitative patient surveys. The quantitative data represents an objective snapshot of the patient's experience and thoughts at the time of assessment, which is comparable to other studies. However, to catch any important qualitative details, free-text responses were included in the survey, and field notes were taken of important off-hand patient thoughts or opinions. Method selection was pragmatic based upon the previous use of quantitative surveys in evaluating digital OGA processes, their popularity and easy to understand structured metrics. **Chapter 7** discusses the methods and results addressing a positivist research question regarding the modelling of an oncogeriatric population. These research questions required quantitative approaches given their need for statistical verification.

In conclusion, pragmatism allowed the choice of relevant methods to answer disparate research questions. Although this did dilute the overlying epistemology of the research process and the nature of reality, it also generated a diverse, challenging and interesting methodology that was sparse in the field of oncogeriatrics.

3.2.3 Theoretical model

In addition to a philosophical paradigm that supported method selection, a theoretical model was also selected to provide an underlying assumption about oncogeriatrics, its mechanisms and provide a theoretical foundation to support the use of different methods in the research. A detailed discussed of theoretical models is beyond the scope of this thesis, but within implementation science they can be broadly categorised as grand theories, mid-range theories and programme theories. Grand theories seek to develop an all-inclusive and unified conceptual system of the world (198). They are internally diverse, non-specific, high-level and are difficult or impossible to empirically verify. Examples include feminist theory and Marxism–Leninism (198). Programme theories are small, specific and explanatory, like those generated in **Chapter 2** during the realist review process. They are not high-level abstractions like grand theories and are characteristically accessible, practical and insightful towards research context, mechanisms and outcomes. Programme theories can be modified with new

evidence and can include informal elements (199). It is mid-range theories that bridge the gap between programme theories as working hypotheses, and grand theories as master concepts. They may draw inspiration from grand theories but have more specific use and mechanisms, and can be empirically verified (199). Examples include Normalisation Process Theory (200), which is used as a theoretical consideration in **Chapter 5** for the development and implementation of an OGA service.

In the search for a suitable theoretical model for this thesis, I realised that traditional linear thinking oversimplifies the challenge of solving implementation issues in oncogeriatrics. For example, one may consider that if funding could be secured to recruit new staff, a Geriatric Oncology Programme could be implemented to help manage older patients. This demonstrates the case to consider the wider context in which cancer care operates, and the utility of using a theory such as complex adapting system (CAS) theory (175). A CAS is defined as a dynamic, self-similar collection of interacting adaptive agents and their artefacts. There is often an extensive amount of feedback between agents and the system must respond to external pressures (e.g., the COVID-19 pandemic) and biomedical advances (e.g., molecular pathology). The use of CAS theory in this case, helps to frame the implementation problem in the widest possible box, so that opportunities to turn barriers in to facilitators can be captured (175). For example, the nationwide lack of geriatricians, serves as an opportunity to utilise emerging technology (e.g., machine learning) and roles (e.g., physician associates) to implement GA in cancer care. **Chapter 5** discusses in detail how CAS can be applied to oncogeriatrics.

Importantly, this thesis should not be viewed through a traditional systems thinking lens, as different philosophical paradigms and methodological approaches may be required. The use of CAS theory should be viewed pragmatically. Not only does CAS theory harmonise with diverse research questions, their interactions and the overall aims of the thesis, but also with my own worldview as a scientist, technologist and surgeon. Classical medical teaching encourages the systematisation of learning, assessment and presentation and the systems employed within healthcare and clinical practice are dynamic and adaptive. In subsequent chapters the use of systems thinking, and CAS theory will be further qualified, where relevant.

3.2.4 Background knowledge

Experiential elements of my personal and professional background have already been discussed, but it is important to note that all my prior research has been centered around a

positivistic paradigm and employed quantitative methods. This includes a Master of Science degree, focussing on the use of biotechnology within the immunology of Graves' disease. Previously my background knowledge was largely removed from the quantitative research to avoid bias and it was unnecessary to consider this. However, in this thesis my background is important, because I relied on clinical knowledge and experience, alongside technological literacy to generate applications and computational models. Within the experiments presented in **Chapter 5** I was also serving simultaneously as a clinician and researcher to recruited participants. There are benefits and potential harms to my dual role, which are discussed below.

3.2.4.1 Benefits

The unique characteristics of the situation generated by this thesis – where the same doctor who has assessed the patient also undertakes the research may serve some benefits for the patient. The continuity of experience and convenience provided to patients may be beneficial to them, as was highlighted by the PPI group. Having two or more individuals contacting, assessing, and recruiting patients may be disorientating, especially whilst on a cancer pathway. There are also benefits for trans-disciplinary research. Often in the development of computational models there may be researchers from a computer science, bioinformatics or engineering background who are domain experts, but lack the clinical knowledge to realise the application of the models. To counter this, they may liaise with clinical experts who guide the clinical details but are often significantly less familiar with the technical nuances of data science and software engineering. There is significant benefit offered here in generalism and crossing expert boundaries, including development efficiency and future trans-disciplinary work. It also allows a constant reappraisal of the clinical application and a goal-orientated approach to quantitative modelling, which exceeds that of purely intrinsic interest.

3.2.4.2 Harms

In contrast to the above, it can also be argued that generalism dilutes the specialty knowledge required from both the clinical and technological perspectives. To counter this, expert second opinion from both domains was sought to ensure the robustness of methods, assumptions, theory and development. I cannot exclude the possibility that the participants answered research questions differently in the survey instrument utilised in **Chapter 5** differently because I was also their clinician at the time. Here some degree of objectivity, repeatability and therefore generalisability has been sacrificed for participant continuity of experience. However, this can be countered by carefully acknowledging these factors in the interpretation of the results. Furthermore, the use of very specific quantitative survey questions has no

obvious perceived benefit or harm towards my clinical practice from the patient's perspective. It is therefore unlikely that my status as their clinician and researcher at the time had a significant material influence on their responses.

3.3 Research questions

The research questions outlined in **Section 1.9** were generated by refining the overall aim and objectives of the thesis and served as an early justification to employ mainly quantitative methods in the study design. One question clearly gravitated towards a qualitative method, the realist review presented in **Chapter 2**, and the remainder towards quantitative methods. Because the implementation data OGA is so heterogenous, quantitative analysis of the studies (e.g., meta-analysis) was precluded and a qualitative appraisal of the literature was required. Compared with a traditional narrative review, the realist review allowed the incorporation of key stakeholder opinions, the vast literature base and my own personal reflections, whilst still using a systematic process. I must declare that the research questions around data simulation in **Section 1.9** emerged during the conduct of the study and stemmed from lateral ideation during the COVID-19 pandemic. It became increasingly unlikely that the sample size would be sufficient for quantitative data analysis. This was due to constant recruitment suspensions and interruptions to study from clinical redeployment and shelter from home orders. A decision was made to pivot to data simulation to boost the quantitative arm of this thesis, circumvent issues arising from the pandemic and protect vulnerable patients.

3.4 Ethical considerations

3.4.1 Overview

Research studies involving human participants mandates compliance with standards to ensure study participants well-being is protected and they are not exposed to harmful effects (201). This thesis generated interesting ethical considerations due to the use of different methods in the research, my role as both doctor and researcher, the development of a new NHS service and the COVID-19 pandemic. All these issues had to be assessed within one research ethics committee (REC) review, as a whole study (202), which created a complex protocol and required a second REC iteration to respond to changes and time to seek specific PPI consultation (see below). The COVID-19 pandemic resulted in a resubmission to the REC for amendments to the recruitment strategy, patient-facing documentation and the OGA service. The OGA service itself evolved over time to merge with a developing geriatrician-led inpatient service and switched to a remote offering to reduce face-to-face contact in response to shelter-

from-home public health recommendations. Overall, this was considered a low-risk study and ethical issues were easily mitigated.

Three general medical ethical considerations are non-maleficence (avoiding harm), respecting autonomy (deliberated self-rule) and ensuring justice (fairness). Given the General Data Protection Regulation (EU) 2016/679 as tailored by the Data Protection Act (2018), data management and confidentiality were also considered separately, as were COVID-19 amendments. Finally, this section summarises how specific concerns raised by the first REC review regarding power and study administration were addressed and the value of PPI in this regard. Hull York Medical School ethical approval was gained prior to the start of the study. The whole study gained initial ethical approval by the Yorkshire and Humber–South Yorkshire REC (19/YH/0382).

3.4.2 Non-maleficence and autonomy

Patients were recently diagnosed with or investigated for cancer and therefore may have become anxious or stressed being approached for a research study. To counter this, patients had the option to make granular and autonomous decisions. For example, they could undertake an OGA without participating in the research study. They could also decline both an assessment and participation in the research study. It was made clear that this was a new service being studied and not fundamental to their cancer care. This helped to avoid any bad feelings about not using the OGA service or participating in the research.

3.4.3 Justice

Some patients may have had to arrange a visit to the hospital outside of a planned appointment to participate in the study. To address this, patients could have been refunded travel expenses for hospital visits outside of their planned appointments.

3.4.4 Data management

Data included quantitative survey results which were stored as JavaScript object notation (JSON) files for programmatic analysis. Participants' health information remained within hospital systems.

3.4.5 Confidentiality

Confidentiality was considered at both the university and research site (hospital) levels. The Patient Information Leaflet (PIL; see **Appendix Figure 54**) was written in clear and understandable English. The University of Hull was the sponsor of the study and therefore acted as the data controller, which kept the minimum possible identifiable information about

participants for 3-6 months after the study had finished. The rights of participants to access, change or move their information were limited, to ensure information was reliable and accurate. If participants withdrew from the study, information already obtained was kept. The contact details for a designated Information Compliance Officer at the University of Hull were provided.

Hull University Teaching Hospitals NHS Trust (HUTH) collected information from participants and their medical records accordingly. HUTH used participant's name and contact details for study recruitment, administration, data collection and quality control. Individuals from the University of Hull and regulatory organisations could look at participants' medical and research records to check the accuracy of the research study. HUTH provided these details to the University of Hull along with the information collected from participants and their medical records. The only people in the University of Hull who had access to information that identifies participants were the researchers who required this for study administration. All data to be used in the study was anonymised. The study site file, including a copy of the study master index, containing patient confidential information, demographic data and consent forms, was kept in a locked filing cabinet in the research office at the Allam Medical Building on the third floor (swipe card entry to authorised personnel only). Physical encrypted USB sticks were backed up and securely stored in a key-controlled area of the HYMS building, only accessible by the data custodian. All other study documents were kept for five years after the study and will be shredded and disposed of accordingly thereafter. Anonymised findings will be presented at relevant medical conferences and social media (such as Twitter), and a paper prepared for submission to relevant medical journals. Summary findings will be sent to participants that requested a copy.

3.4.6 COVID-19 amendments

Amendments were made to the OGA service to enable a remote offering, and therefore the study administration, recruitment and documentation required substantial amendment. I changed from approaching patients following referral or by face-to-face introduction at scheduled appointments to screening MDT lists to reduce contact. This required an initial letter to alert patients to receiving a phone call offering participation within the OGA service and offering recruitment to the research study. This was to mitigate the professional and practical issues of an unsolicited phone call. This meant that recruitment had changed from predominantly face-to-face, often following clinician referral, to providing patient-facing research documentation by post. The PIL (see **Appendix Figure 54**) had to be modified to

include details of the new recruitment strategy. Unfortunately, the underlying science was also modified, as it became considerably difficult to undertake the necessary physical components of the OGA service and undertake the desired secondary data analysis. In summary, a clinical walking test was no longer practical, so the prospective study of a predictive decision tree had a significantly reduced sample size than was required for diagnostic accuracy studies. This also meant that less data were available for secondary data analysis, which inspired the use of data simulation (see **Chapter 7**). Substantial amendments were submitted and gained ethical approval by the Yorkshire and Humber–South Yorkshire Research Ethics Committee (19/YH/0382, **Appendix Figure 55**).

3.4.7 Patient and public involvement

After the first REC iteration, several substantial issues were raised around study administration. These include the deliberate omission of the word 'cancer' from the patient-facing documentation (a non-maleficence issue), my role as both doctor and study administrator (a power issue) and several minor issues concerning specifics of patient-facing documentation. The latter issues were easily resolved with documentation administration, however, the two other issues warranted specific PPI group discussion. Three patients with a lived experience of cancer were consulted. All were older adult males (> 65 years) who had either experienced living with cancer personally or had a close relative diagnosed with cancer. A discussion was held and minuted around the issues raised by the REC. Because patients were being recruited into the study with *suspected* or confirmed cancer, we found that the PPI group consensus was that omission of the word cancer was acceptable and probably desirable in the patient-facing documentation. This was to avoid creating anxiety in patients who transpire not to have cancer after investigation. The REC's concern was that omission of the word cancer may risk falsely reassuring patients that they do not have cancer, whereas the PPI group felt that this was unlikely. To illustrate this, one member recalled that the constant use of the word cancer can be distressing. Regarding the second issue, the REC's concern was that there was a potential power gradient with me acting dually as the patients' doctor by contacting them to undertake an assessment, and the study administrator offering recruitment. The REC countered that an independent person should contact the patients to offer recruitment, utilising a scripted question and answer format. The PPI group reached consensus that it was preferable for me to act as both their doctor and research coordinator, because it enabled a trust relationship to be formed and promoted continuity. One patient recalled being previously confused by the number of

different team members contacting him regarding different aspects of his care and his research involvement.

3.5 Data collection and analysis

The data collection process can be divided into five phases consisting of sampling, permissions, data sources collected, data recording processes and the administration of data collection (203). The specifics for each method are better described separately in their respective chapters.

3.6 Quality assurance

To maximise the power and representation of the inferences made from this thesis, several considerations were made towards quality assurance. The rigor of the methods is assessed by a process termed validation, which can be complicated using different data sets in research (202). Quality occurs at the results level of the qualitative and quantitative strands, which propagates to the inferences (202). In keeping with the overlying epistemology, a pragmatic approach was taken for quality assurance in this thesis, regarding relevant terminology and approaches. For quantitative studies (e.g., survey and secondary data analysis), validity (the accuracy of inferences based on the data) will depend on the sample sizes available (204). External validity (the ability to generalise the findings outside of the study) may be compromised by lower sample sizes and the unique setup of this thesis. A power calculation was undertaken (see **Chapter 6**) to establish the sample size. Reliability is the ability of the measurement procedures to yield the same result and can be assured trough standardisation (204). In this case the quantitative survey and the original clinical data for secondary analysis followed a set proforma. Missing or incomplete clinical data were dealt with by omission or imputation (205).

3.6.1 Inference generation

Like the individual studies in research using different methods, the generated inferences will be affected by the underlying study quality, but also the specific quality of the inferences themselves (206) and their transferability (202). The quality of the inferences can be assured at multiple levels, that are unique to this thesis: i) consultation with the scientific committee of the research group; ii) consultation with the PPI group; and iii) revisiting the findings of the realist review, which encompassed a significant body of the literature in this field.

3.7 Chapter conclusions

In conclusion, this chapter has highlighted the methodological assumptions taken from personal contexts, study design, ethical considerations and quality assurance. A predominantly

pragmatic philosophy has been utilised along with a CAS theoretical model. My background position as a doctor and researcher is significant and generated unique research and ethical considerations requiring thought around their mitigation and consultation with a range of stakeholders. The main study design considerations produced a predominantly quantitative thesis, but I pragmatically employed a qualitative systematic review strategy using realist theory because of the suitability of this research method to answer the research question.

Chapter 4 – Geriatric assessment prior to cancer treatment: a health economic evaluation

4.1 Chapter introduction

This chapter presents the text of a research paper provisionally accepted by the *Journal of Geriatric Oncology* in October 2022. The text is identical to the original publication, except that headings, subheadings, tables, figures and references have been renumbered in keeping with this thesis. Supplementary text in the original submission has been included in the main body of text.

4.2 Abstract

4.2.1 Objectives

To address uncertainty regarding the cost-effectiveness of implementing geriatric assessment (GA) in oncology practice, we undertook a synthetic model-based economic evaluation.

4.2.2 Materials and Methods

A decision-analytic model with embedded Markov chains was developed to simulate a cost-effectiveness analysis of implementing GA within standard oncological care compared to current practice. This was for patients aged 77 years receiving chemotherapy or surgery as a first-line treatment. Assumptions were made about model parameters, based on available literature to calculate the incremental net health benefit (INHB) of GA, using a synthesis of data.

4.2.3 Results

GA has additional costs over standard care alone of between £390 and £576 dependent upon implementation configuration. When major assumptions about the effectiveness of GA were modelled, INHB was marginally positive (0.09-0.12) at all cost-effectiveness thresholds (CETs). If no reduction in postoperative complications was assumed, the intervention was shown not to be cost-effective (INHB negative at all CETs). When used before chemotherapy, with minimal healthcare staffing inputs and technological assistance, GA is cost-effective (INHB between 0.06-0.07 at all CETs).

4.2.4 Conclusion

Considering emerging evidence that GA improves outcomes in oncology, GA may not be a cost-effective intervention when used for all older adults with cancer. However, with judicious selection of implementation models, GA has the potential to be cost-effective. Because GA tends towards utilitarianism and has no safety issues, it is a suitable intervention for more widespread implementation.

4.3 Keywords

Cost-Benefit Analysis, Cancer, Geriatric Assessment, Decision Support Techniques, Frailty

4.4 Author contributions

I conceived the idea of undertaking a health economics evaluation of geriatric assessment supported by my supervisors Dr Charlotte Kelly, Professor Mike Lind and Professor Miriam Johnson. Mr Steve Parrot provided expert opinion on the modelling and best practices of the economic evaluation. All authors read the final manuscript.

4.5 Introduction

With an ageing and growing population, the number of older adults undergoing treatment for cancer is projected to continue increasing (207). Older adults with cancer have worse outcomes with higher postoperative complications, chemotherapy toxicity, and best supportive care treatment allocation (5, 7). The spectrum of ageing phenotypes means that clinicians can struggle to assess, select, and counsel older adults appropriately for different cancer treatments (19). One solution proposed to counter this problem is geriatric assessment (GA) in oncology practice (13). Numerous studies of the predictive ability of GA (70), and the therapeutic efficacy of GA as a complex intervention in oncology have been reported (62). GA is delivered within oncology with significant heterogeneity, precluding meta-analyses. Moreover, complex, whole-system implementation issues limit widespread introduction (105) and mixed results from randomised controlled trials (RCTs) have created uncertainty over its value (62). The perceived benefit-cost ratio is a frequently perceived barrier (105). Without robust cost-effectiveness data, alongside a national shortage of geriatricians, stakeholders may struggle to justify widespread adoption (105). It is therefore necessary to demonstrate cost-effectiveness evidence for GA in oncology practice. The lack of trials capturing health-related quality of life (HRQoL), precludes a traditional evaluation of single (or multiple) trial data. A pragmatic approach utilising the available evidence to explore the cost-consequences of GA in oncology

practice is therefore desirable, in terms of time and cost constraints. At a time of complex pressures on health services following the COVID-19 pandemic, economic justification for expansion of services is crucial. This can inform stakeholders and researchers of the potential value for money afforded by implementation. Using wide-ranging literature, this study presents a model-based cost-effectiveness analysis. We aim to evaluate the cost-effectiveness of different implementation configurations of GA within oncology practice compared to standard care.

4.6 Methods

4.6.1 Study design

A decision-analytic model was developed that compared different implementation configurations for the inclusion or exclusion of GA within standard oncology care. The perspective throughout this economic evaluation concerned implementation of GA within National Health Service (NHS) oncology departments within the United Kingdom (UK). We modelled the patient population for the most common cancer multi-disciplinary team (MDT) setup in the NHS, where chemotherapy and/or surgery are treatment options. This was selected to provide the most relevance to stakeholders We follow the latest guidance published by the National Institute of Health and Care Excellence (NICE) (208).

4.6.2 Evidence informing economic evaluation

4.6.2.1 Strategy and assumptions

Non-systematic, targeted searches using PubMed identified the evidence used to inform the assumptions of this economic evaluation. Research was selected from the geriatric oncology evidence-base, including grey literature and wider geriatric literature, including perioperative and community geriatrics. The levels of evidence provided by the Oxford Centre for Evidence-Based Medicine guided inclusion. The major studies included are summarised in **Appendix**

Table 17.

Of note, we included a randomised controlled trial (RCT) by Lund *et al*. (209) that did not report a clinically effective reduction in chemotherapy toxicity for the geriatric assessment (GA) arm (28.2% reduction *vs*. control, $p = 0.156$) and hospitalisations were equal in each arm. This may represent a type II error from lack of power for these secondary outcomes, since hospitalisation is an uncommon event. We chose to model this effect, as statistically insignificant clinical outcomes can still be cost-effective (210), provided the results are interpreted with caution (211). A recent meta-analysis of the effects of geriatric care models

on postoperative outcomes in older adult surgical patients, including those with cancer, did not demonstrate a reduction in prevalence of delirium, length of stay, 30-day readmission, or 30-day mortality (62), but did not analyse the overall effect on postoperative complications. There is increasing acknowledgement that implementation factors have a significant effect on the outcomes of an intervention (212). An underpowered RCT with implementation issues has previously reported neutral effects on postoperative complications for preoperative GA intervention in patients with colorectal cancer (109). To model the *potential* benefit of GA on postoperative complications, we chose to use an exemplar RCT of preoperative comprehensive GA (CGA) in vascular patients by Partridge *et al*. (96), which was adequately powered, not subject to implementation issues and deemed to be cost-effective in a recent evaluation (61). Moreover, this RCT is an analysis of a centre of excellence within the National Health Service (NHS); the Perioperative medicine for Older People undergoing Surgery (POPS) model.

Given that GA is a complex intervention, implemented within a complex adapting system, many factors can interact to reduce or negate the expected positive outcomes from GA processes (105). This may partly explain the heterogeneity in delivery and outcomes, and the observation that certain research groups and/or institutions can report beneficial findings, which are non-reproducible elsewhere (62). We took the pragmatic assumption that with the correct implementation context and mechanisms to augment facilitators and overcome barriers, the observed efficacy of GA is possible.

4.6.2.2 Intervention and standard care

We attempted to model two alternative implementation strategies: a) a highly optimised GA undertaken using patient-led, technologically assisted reporting and a trained healthcare worker, with minimal geriatric input and a 'screen, predict and refer model'; and b) the gold-standard geriatrician-led service with a dedicated multi-disciplinary team (MDT). The former is rationalised based on the emerging evidence of the implementation benefits of utilising non-geriatricians (105) and technology (95) in GA within oncology. The latter reflects higher resources, but generally a more desirable model in surveys of oncology practitioners (105). The latter could also encompass the use of screening to select patients for full GA (213). Standard care does not include GA and the assessment and optimisation relies on the responsible surgical or oncological consultant, sometimes supported by a registrar-level

clinician. Patients are referred to their general practitioner or other specialties according to need. It has been recognised that older adults have unmet needs in standard oncological care (214).

In oncology settings, GA is often delivered differently to CGA, originally designed for frail older general medical inpatients (13). CGA is defined as a multidomain, multidisciplinary team (MDT) assessment that identifies and optimises physical, psychological and social issues within an evidence-based and personalised care plan (36). CGA is normally led by a geriatrician with support from a MDT, including nurses, occupational therapy, physiotherapy, social services and other allied health professionals. This model is sometimes replicated in oncology as a geriatric oncology ('oncogeriatric') service (215). GA ideally occurs pre-treatment where data is used within decision-making in the tumour-specific cancer MDT (73). This strategy also enables early general health optimisation, aiming to improve cancer treatment outcomes. This model is considered the gold standard, but delivery requires additional human resources (105),

The comprehensive aspect of CGA is often sacrificed in alternative oncology implementation models, to reduce the duration and complexity of assessment, utilising screening instruments and a trained healthcare worker (101). Specific problems amenable to intervention are managed largely by referral to other specialties or departments (e.g. dietetics or geriatric medicine) (101). Leveraging technology and patient-reporting to aid GA data collection does reduce the time to completion (216) (and potentially the human resources) and appears acceptable and feasible in multiple healthcare settings (217), including the NHS (unpublished data). There is uncertainty whether GA models deviating from traditional CGA have inferior clinical effectiveness compared to geriatric oncology models.

4.6.2.3 Health care utilisation

The main resource input in GA is the staff input required to deliver the service and the expected individual patient-facing interactions necessary. These costs can be estimated using assumptions of typical interaction durations, considering the unit costs per minute for each clinician. For model (a) there is the additional cost of the technology to enable patient- or carer-reported GA.

4.6.2.4 Unit costs

Units of healthcare resource inputs were costed using NHS reference costs and available estimates of unit costs for health and social care services and professionals (**Appendix Table 18**). All costs are reported in Great British Pounds (£) and uprated to 2019/2020 financial year prices where necessary using the Hospital and Community Health Services and NHS cost inflation indices, and then further inflated to 2021 prices using the geometric mean of indices from 2007-2020 (218).

For chemotherapy toxicity admission, reference costs for an unscheduled admission were utilised, depending on the length of stay. A short stay was defined as a one-day admission, a long stay was anything beyond this. In the NHS, episodes of care are grouped under health resource groups (HRGs). Each HRG sets a trim point, representing the length of stay before an excess bed day tariff is applied. Because the length of stay durations modelled were considerably below most trim points, we used single reference costs for the respective duration of stay. An excess bed day tariff for chemotherapy toxicity was not applied for any length of stay. For postoperative bed days, excess bed day costs were used to better reflect the additional costs of a prolonged inpatient stay. For implementation configurations where technology was employed to assist with data collection, either pre- or during a GA consultation, a fixed unit cost per patient was selected based on similar technology platforms available. This system would include a patient-facing web/mobile application to enable responses to GA questions, and a clinician web application to view data and allocate assessments. The exemplar technology used was the e-Consent platform *Concentric Health*, designed to provide paperless procedural informed consent in NHS practice. The cost basis for *Concentric Health* is £2 per consent episode (219), which is assumed to represent a typical GA episode.

4.6.2.5 Health-related quality of life

Few published studies for GA in oncology practice report a suitable HRQoL measure for calculation of quality-adjusted life years (QALYs). A QALY represents a utility value ranging from 1 (full health) to 0 (representing death, or less than zero for states worse than death), derived from health state preferences from a representative population (220). QALYs provide a singular representation of improvement in life years lived and/or their quality and are favoured by NICE (208). Baseline QALY data were calculated using the sample size weighted

mean and standard deviation of the means of all malignant conditions reported in a database of EQ-5D data (**Appendix Table 18**) (221).

Within the timescales reported, no significant differences have been found between GA and standard care groups for European QoL-5 Dimensions (EQ-5D)-5L or HRQoL measures that could be mapped to EQ-5D (e.g. European Organization for Research and Treatment of Cancer [EORTC] QLQ-C30) (209, 222, 223). Additionally, not all dimensions of EORTC QLQ-C30 were used/reported in one study (209) or available after GA (224). One study did report EORTC QLQ-C30 at baseline for 200 older adults (median age 75) for different malignancies undergoing surgery (224). We used a mapping algorithm developed by Crott and Briggs (225) to transform the EORTC QLQ-C30 domains of the Baier *et al*. (224) study to EQ-5D derived utility values for the UK population. Based on the results presented by Baier *et al*. (224) and Monte Carlo simulations, their mean baseline EQ-5D was estimated at 0.87 (standard deviation [SD] = 0.19), whereas the baseline EQ-5D from the database (221) was 0.73 (SD = 0.06). We decided to utilise the lower values derived from the database for two reasons: i) the overall sample size was higher than those patients in the study by Baier *et al*. (224); and ii) patients preselected for surgery may be fitter and therefore introduce selection bias towards higher HRQoL values. Other health economic analyses in perioperative and community geriatrics demonstrate that any short-term improvement in QALYs following CGA tend to be small and non-perpetual after the first year (61, 226). Longer-term differences likely occur through mortality reduction in favour of GA (61, 226). Moreover, patients receiving chemotherapy tend towards a disutility in QALY scores (**Appendix Table 19**) in the first year (227).

4.6.3 Economic analysis

4.6.3.1 Analytical framework

The potential utility in terms of QALYs for GA was calculated, representing cost-effectiveness, providing a common comparator against other interventions for stakeholders to consider. Given that the cost-effectiveness analysis is derived from disparate data, this evaluation also serves as a cost consequences analysis. Costs and outcomes are presented in a disaggregated form to inform different stakeholders regarding the domains relevant to their own budgets **(**

Table 4). To compare the use of GA versus standard care, the incremental net health benefit (INHB) was estimated to model potential gains in QALYs (228). INHB conceptualises that health spending forgone elsewhere represents an opportunity cost to fund a new intervention. The INHB of GA is calculated as the incremental costs of GA above standard care divided by

the opportunity cost, subtracted by the incremental gain in QALYs per patient, calculated as the area under the curve, from using GA over standard care. The opportunity cost represents a cost-effectiveness threshold (CET), which is a predetermined level of excess healthcare system cost sufficient to redirect one QALY from an alternative clinical opportunity (229). Where INHB is positive, the net benefit in terms of QALYs would be greater than the opportunity cost, meaning that GA is more cost-effective than standard practice. A negative INHB would imply that the potential health benefits of GA are insufficient to redirect resources from other clinical activities (229). To address uncertainty for the value of the CET in NHS health economics, cost-effectiveness for CGA was calculated for several possible CET values.

Consequences of geriatric assessment
Prediction of adverse outcomes to assist shared decision-making (13)
Improved data on risk/benefit ratio for procedural informed consent (13)
Opportunity to undertake holistic optimisation prior to treatment (13)
Identification of candidates for surgical or chemotherapy prehabilitation (230)
Recognising and fulfilling unmet needs (13)
Improved patient and caregiver satisfaction with communication (231)
Mitigation of future medico-legal risk
Improved quality of life in geriatric specific domains (209)
Reduced early treatment discontinuation (181)
Reduced chemotherapy treatment modification (232)
Increased advanced directive completion (233)
Big data collection for research and development (216)
Potential positive effects on a range of outcomes, which are centre dependent (62)

Table 4 – Consequences of geriatric assessment.
The consequences of undertaking GA can be considered by decision-makers separate to or alongside cost-utility evaluation.

4.6.3.2 Modelling approach

A decision analytic model (**Figure 10**) with Markov chains (**Figure 11-Figure** 13) were utilised to estimate the INHB for a 77-year-old patient undergoing cancer treatment, based on the median age of patients in a large exemplar study (234). Markov chains are simple to construct and widely used in decision-analytic economic modelling of the health state transitions common in oncology. According to this model (**Figure 10**), a patient may receive a GA in addition to standard oncological care. The GA may take one of four main implementation configurations (**Table 5** and Figure 9), which are individually modelled. A patient may then

receive surgery or chemotherapy as the first-line treatment, with a risk of developing postoperative or chemotoxicity complications (

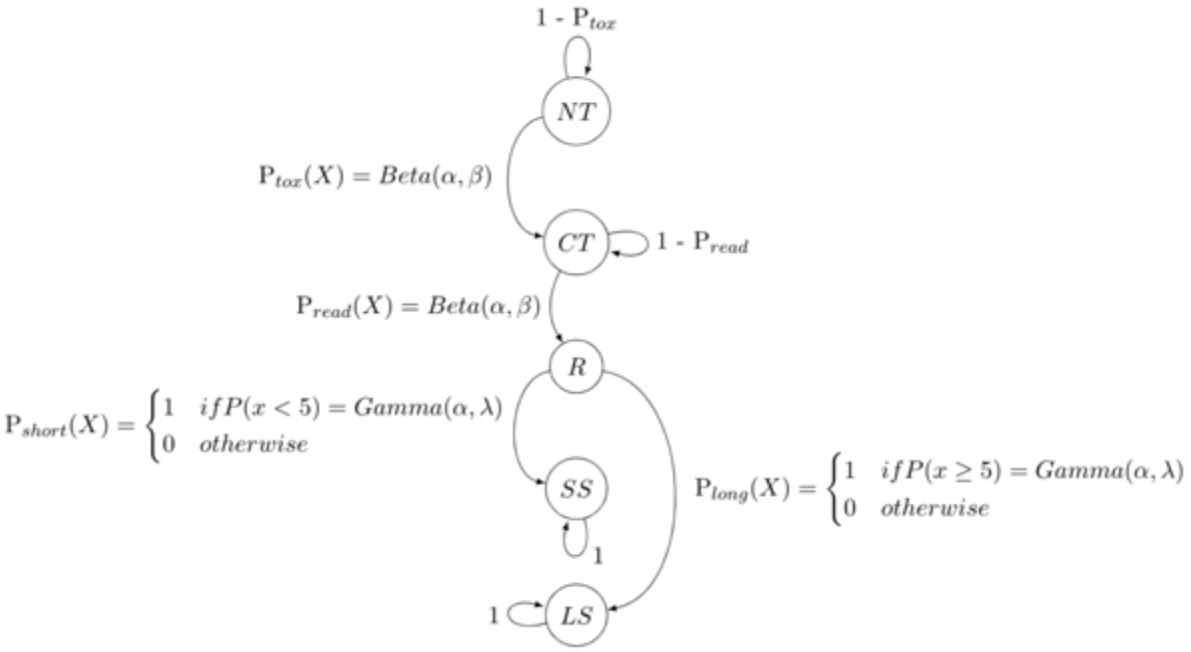


Figure 11). Additional pre-treatment costs result from undergoing GA with standard care, although standard care may still generate some pre-treatment costs (**Appendix Table 18)**. Posttreatment mortality, QALYs (**Figure 12**) and costs relate to posttreatment complications. GA data can also change cancer MDT treatment decision making in around 28% of cases to higher, or more commonly, lower intensity treatment (73). An exemplar study was modelled (**Figure 13**) that reported the changes in management for 375 patients when GA data were used by the cancer MDT (235).

The data from the exemplar study of treatment decision changes (235) was extracted and treatment changes were grouped into state transitions between single modality and multiple modality treatment; and multiple or single modality treatment and best supportive care (**Figure 4**). Weighted mean figures were derived from the National Schedule of NHS costs (2020) for single (£4,152) or multiple (£6,364) interventions across breast, gastrointestinal, gynaecological, head and neck and hepatopancreatobiliary malignancies (236). An uprated and inflated pragmatic figure of £11,081 for best supportive care, based on a systematic review was utilised (237). The estimated difference in costs, rather than absolute costs for all care, were factored into the model for treatment changes following GA.

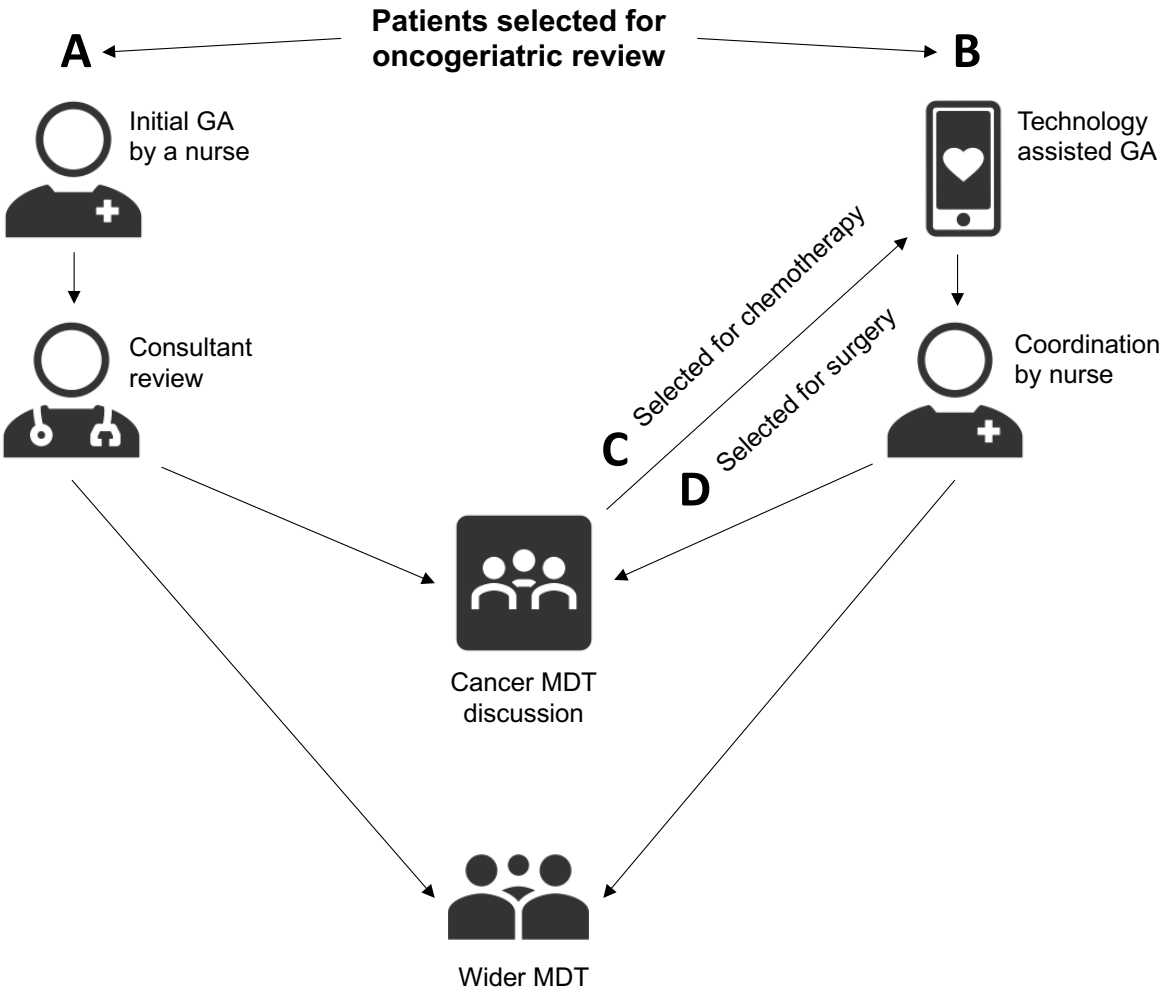


Figure 9 – Diagram illustrating the differences in implementation models in Table 2.

A represents a geriatric oncology model; B a screen, predict and refer' model; C a prechemotherapy model; and D is a preoperative model.

Abbreviations: GA = geriatric assessment; MDT = multi-disciplinary team.

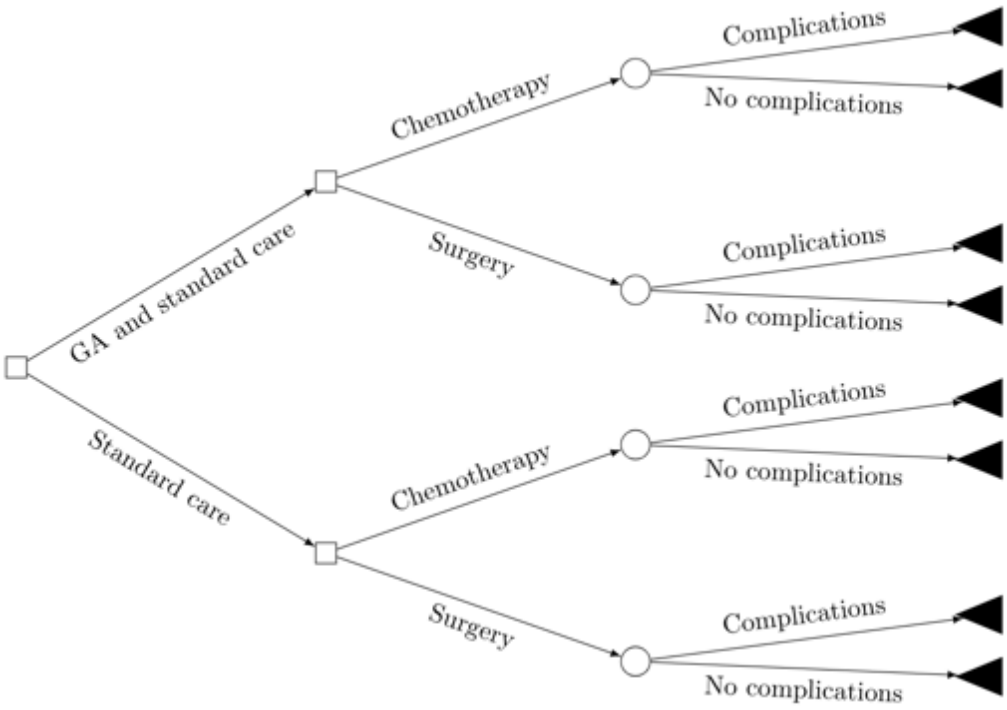


Figure 10 – Decision analytic model.
Patients enter the pathway and either receive GA in addition to standard care or standard care only. Each patient is allocated a first-line treatment, either chemotherapy or surgery and has a risk of developing complications.

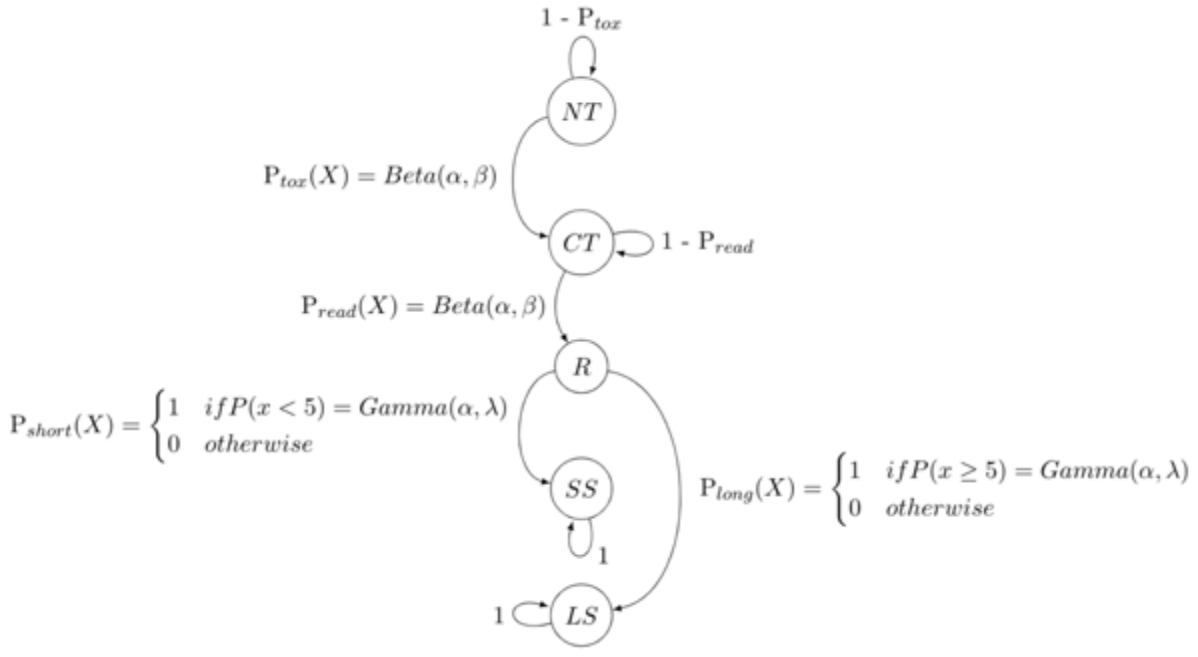


Figure 11 – Homogenous, progressive Markov chain state transition diagram for chemotherapy toxicity.
Patients begin in the no toxicity (NT) state and face a risk (P_{tox}) of transitioning to the chemotherapy toxicity (CT) state during a single cycle of treatment (and the Markov chain). In the CT state, patients face a further risk (P_{read}) of readmission (R) to hospital, and then progress to either a short stay (SS) lasting < 5 days with probability (P_{short}) or a long-stay (LS) with probability (P_{long}) lasting ≥ 5 days within one cycle, which are absorbing states for the purpose of modelling. Transition probabilities are determined by random draws from Beta and Gamma distributions.

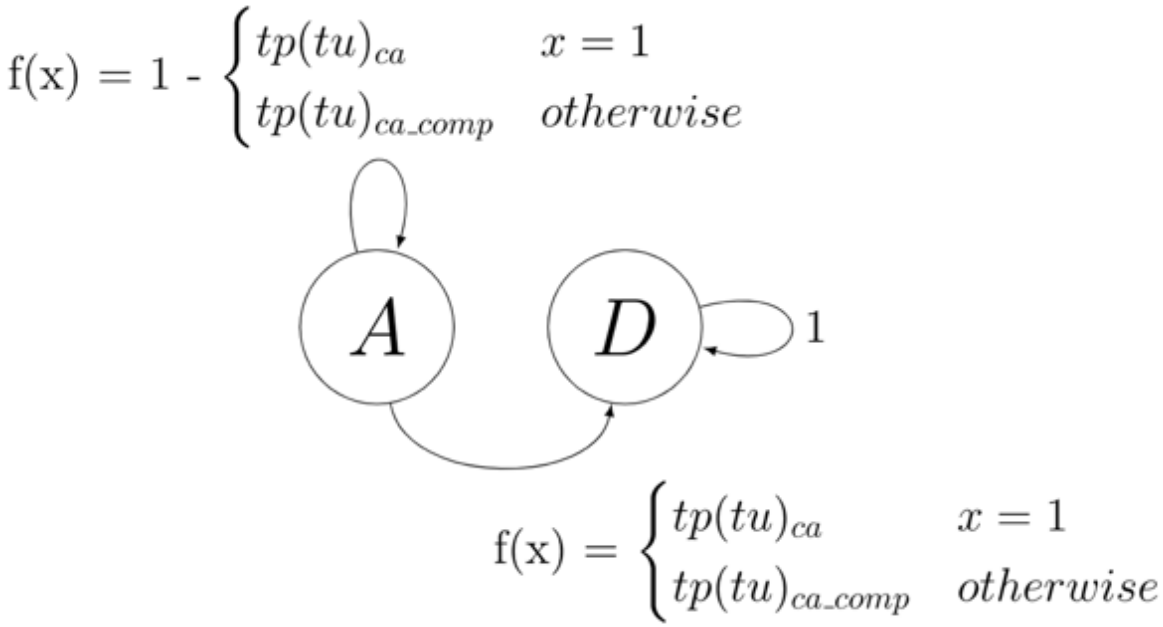


Figure 12 – In-homogenous, progressive Markov chain state transition diagram for 10-year mortality. Patients start in the Alive state (A) and face an annual transition probability, $tp(t_u)$ to the Dead state (D), which is absorbing. The $tp(t_u)$ for each year of the Markov chain is determined by a function, $f(x)$, where x represents the presence (1) or absence (0) of surgical complications. The $tp(t_u)$ for patients who have not undergone surgery is derived from mean age-specific survival rates from UK cancer statistics for 29 common cancers, $tp(t_u)_{ca}$. For patients that have undergone surgery, their $tp(t_u)$ from state A to D, depends on the presence or absence of surgical complications, $tp(t_u)_{ca\_comp}$. $tp(t_u)_{ca\_comp}$.

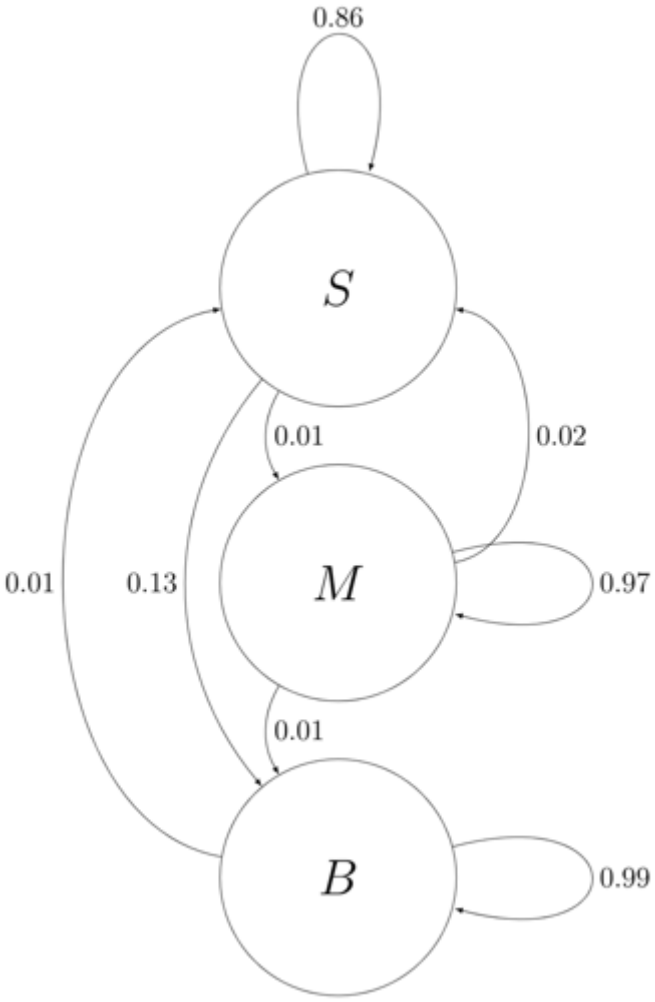


Figure 13 – Homogenous Markov chain state transition diagram for changes in management following geriatric assessment.
Patients start in one of the following initial states derived from national data on treatment allocation for this age group: single modality (*S*) treatment (e.g., surgery only); multi-modality (*M*) treatment (e.g., chemotherapy and surgery); or best supportive care (*B*). Geriatric assessment may cause a change in management according to the transition probabilities above. This change in management is associated with a cost difference.

Model	Description	Assumptions	Additional probabilistic sensitivity analysis (PSA)
A	The most resource intense implementation configuration, requiring a dedicated MDT, representing a geriatric oncology service. A nurse will undertake an initial GA (60 minutes) and a consultant will also review the patient in person (30 minutes), amounting to the highest possible pre-treatment costs from human resources. A technological solution is not employed to aid GA data collection.	• The potential effects of reducing chemotherapy toxicity and surgical complications are modelled using data from exemplar studies. • Differences in costs arising from treatment changes are included by modelling treatment changes from using GA results within the cancer MDT.	• One-way PSA neutralising the effect of GA on post-surgical complications • One-way retaining the effect on post-surgical complications but removing the effect on chemotherapy toxicity rates. • One-way removing the effects of treatment changes at the MDT-level but maintaining the perioperative effects
B	A nurse or other trained healthcare worker is primarily involved in ensuring the GA is undertaken, supported by technology, to reduce the number of clinician-led GAs that need to be undertaken. A Band 6 nurse must dedicate 30 minutes of time to each patient.	• **As for Model A**	• One-way PSA removing the positive perioperative and chemotherapy effects
C	A replica of model B but exclusively for patients selected to undergo chemotherapy. The pre-treatment costs mirror those of model B. Any effect on cancer treatment changes would be lost and the sole intention of this model would be for optimisation prior to chemotherapy, in attempt to reduce toxicity.	• GA would no longer influence the treatment decision-making at the cancer MDT-level. • The potential effects of reducing chemotherapy toxicity are modelled using data from an exemplar study.	• One-way PSA removing the potential effects on chemotherapy toxicity • One-way PSA increasing the human resources (i.e., undertaking model A as a prechemotherapy geriatric oncology model).
D	Like the preoperative CGA model reported by Partridge *et al*.(96) and could take either the form of model A or B. Only patients selected for surgery would undergo a preoperative GA. Like model C, this would essentially be a preoperative optimisation service.	• **As for model C**, but considering potential effects of reducing surgical complications	• One-way PSA removing the potential effects on surgical complications • One-way PSA increasing the human resources

Table 5 – Different models of implementation configurations.
Abbreviations: GA = geriatric assessment; CGA = comprehensive geriatric assessment; MDT = multi-disciplinary team; PSA = probabilistic sensitivity analysis.

4.6.4 Estimating model parameters

The main model parameters were prevalence figures for referrals to other departments or specialities expressed as mean and standard deviation percentages derived from the literature (**Appendix Table 19**), which were modelled using a Beta distribution. Baseline QALY values were represented by a Beta distribution. A Gamma distribution represented length of hospital stay following admission for chemotherapy toxicity, recognising the skewedness of the original data (238) and that the upper limit tends towards infinity. Cancer treatment allocation required a Dirichlet distribution to describe mutually exclusive outcomes as a probability. Finally, Log-Normal distributions were used for the potential effects of GA on outcomes, modelled as risk ratios derived from exemplar studies (**Appendix**

Table 17), as described in a previous study (239). See **Appendix Equation 4-14** for further details.

Where only a 95% confidence interval was presented, the SD was estimated using **Appendix Equation 6**) (240)**.** Where the sample size was unavailable, inappropriate (i.e. the range was derived from several studies) or invalidated the Beta distribution (derived parameters $\alpha > \beta$), the standard error was assumed to be the SD. Monte Carlo simulations were then used to visualise the Beta distribution and check the representativeness of the derived parameters. If only a range was available, the denominator of **Appendix Equation 5** was set as four, known as the range rule for SD (240).

4.6.5 Modelling QALYs and mortality

Any effects on long-term QALYs in favour of GA are likely a result of improved survival, either mediated through the intervention itself or reduced postoperative complications (61, 226). Ten-year QALYs were estimated using a two-state, annually cycling Markov chain (Alive and Dead) (**Figure 11**). Patients begin in the Alive state and face an annual mortality risk, transitioning to the absorbing Dead state. During every Markov cycle in the Alive state patients accrue QALYs. QALYs are summed cyclically to estimate QALYs for GA and usual care respectively. Where chemotherapy was selected, a decrement of 0.32 QALYs for the first year was incurred (227). Only one study demonstrated a decrement of 0.07 QALYs at 12 months following colorectal cancer surgery (241). We therefore assumed that there was no persistent decrement following surgery surgery, as colorectal surgery represents a fair median

between the relative extremes of different tumour site procedures (e.g. breast versus pancreatic surgery). QALYs were discounted at 3.5% per annum, as recommended by NICE (208).

The baseline annual transition probabilities were generated based on predicted estimates of net cancer survival data (242). Weighted mean 1-, 5- and 10-year survival data for 29 common cancers combined were calculated. Mean survival data were imputed between the calculated values from the UK Office of National Statistics (ONS) data (242) using piecewise cubic Hermite interpolating polynomial (**Appendix Figure 49**). We assumed that those with an uneventful postoperative course would adopt the survival probability curve related to cancer. Significant long term effects on 10-year mortality following surgical complications have been reported previously (243). Moonsinghe *et al*. (243) undertook a study of 1,382 surgical patients with a mean age of 63 years undergoing major non-cardiac and non-neurosurgical operations, including cancer procedures. The cumulative 10-year mortality rate reported in their study was recently used in a health economic evaluation of CGA for elective arterial surgical patients (61). Using data from the Moonsinghe *et al*. (243) study we created specific, annually adjusting transition probabilities for patients undergoing surgery who developed postoperative complications.

The cumulative hazard rate curve from Moonsinghe *et al*. (243) was copied from the publication and the coordinates of the plot, were extracted using *WebPlotDigitiser* (v4.4) – an online tool used to extract data from plots (244). Since these data represented four categories of postoperative morbidity, depending on the final morbidity day, the weighted mean was calculated for each time point using the subgroup sample sizes provided. The survival probability was then calculated by exponentiating the negative of the mean extracted cumulative hazard data for each time point in days. The presence of cancer and postoperative morbidity likely augments long-term mortality, possibly mediated through underlying frailty (245). To adjust for the lower mean age in the Moonsinghe *et al*. (243) study, the survival effect was adjusted for 77–87-year-old patients. The ratio between the 10-year mortality risk from postoperative morbidity compared to the baseline risk from 63-73 years of age was calculated using UK national lifetables, with age weighting according to the baseline data from Moonsinghe *et al*.(243) These ratios were then used to adjust the risk of having cancer and postoperative morbidity over a 10-year period for 77–87-year-old patients (**Figure 49**). Finally, the transition probability for each Markov cycle can be derived from the survival function using **Appendix Equation 14**. Because the weighted means from the ONS cancer survival data include different tumour types with significant variability in survival, the weighted SD for each

time point ranged between 18-22.4%. This would lead to significant uncertainty in cancer survival probability at each year of the Markov chain. When plotting the Kaplan-Meier curves including the standard deviation, there was near total overlap between the survival curves. Isolated Monte Carlo simulations of the Markov chain for mortality (**Figure 12**) were undertaken using random draws from a Beta distribution for each year, where the parameters were calculated using the weighted mean and SD from the ONS data. This degree of uncertainty distorted the results significantly, so the yearly transition probabilities of the Markov chain were fixed rather than obtained by random draws from a distribution. The alternative approach of having separate curves for multiple cancers would create unnecessary complexity in the evaluation.

4.6.6 Probabilistic sensitivity analysis

To address uncertainty in the parameters used within the model, a probabilistic sensitivity analysis (PSA) was undertaken using Monte Carlo simulations, generating probability distributions for all parameters (246). PSA is used to generate a confidence level for the outputs of the model by reflecting the uncertainty in the input parameters. Monte Carlo simulations are repetitive runs of a model, where parameters are drawn from probability distributions (246). Fixed parameters were unit costs, mean length of patient-facing consultations with clinicians and yearly mortality probabilities with/without surgical complications. For each implementation configuration, 5,000 simulations were undertaken, generating a distribution of parameter values and estimates of INHB for GA compared to standard care. The mean and its associated probability distribution were used to evaluate the cost-effectiveness of GA and its uncertainty. Three separate CET values were utilised to manage the uncertainty of the desired threshold for NHS health programs: i) £30,000; ii) £20,000; and iii) £13,000 (247, 248). These values represent the upper and lower limit of the range utilised by NICE and a more recently proposed conservative CET respectively (247, 248).

The two main implementation configurations (models A and B, **Table 5**) solely reflect different levels of pre-treatment human resources and therefore pre-treatment costs. It is assumed that the other costs and treatment outcomes are the same regardless of the implementation. A further two models were also used to represent recent RCTs. Model C only includes patients selected for chemotherapy and model D solely for those selected for surgery (**Table 5**). The one-way PSA of the neutral effect of GA on postoperative (62) or other outcomes represented an

additional sensitivity analysis for each implementation configuration. For models C and D specifically, the human resources can be varied by basing the pre-treatment costs on models A and B respectively.

The model was developed and statistically evaluated using the Python programming language (v3.7.3, Python Software Foundation). All code and open-source software dependencies utilised can be found at https://github.com/gordonmckenzie/oncogeriatrics-health-economics. The Equator network CHEERS guidelines for reporting health economic evaluations were adhered to when reporting this study (249).

Costs arising from the identification and optimisation of unmet needs were assumed to be the same regardless of implementation strategy. This enabled an assessment of the cost-effectiveness of GA, even in the case where no effect on treatment outcomes and/or quality-adjusted life years (QALYs) is observed. In this scenario, the cost-consequences of GA (**Table 4**) can be considered by stakeholders. The probability that INHB was less than zero represents the decision error. This was estimated by computing the probability density function (PDF) of the incremental net health benefit (INHB) using Gaussian kernels, and then the integral of a 1-dimensional PDF between 0 and -7 (where the lower limit represents slightly below the lowest value recorded in simulations). The expected cost of uncertainty per patient in QALYs was estimated by calculating the mean QALYs from the distribution where INHB is less than zero.

4.7 Results

Table 6 and Figure 14 presents the cost-effectiveness findings for each implementation configuration.

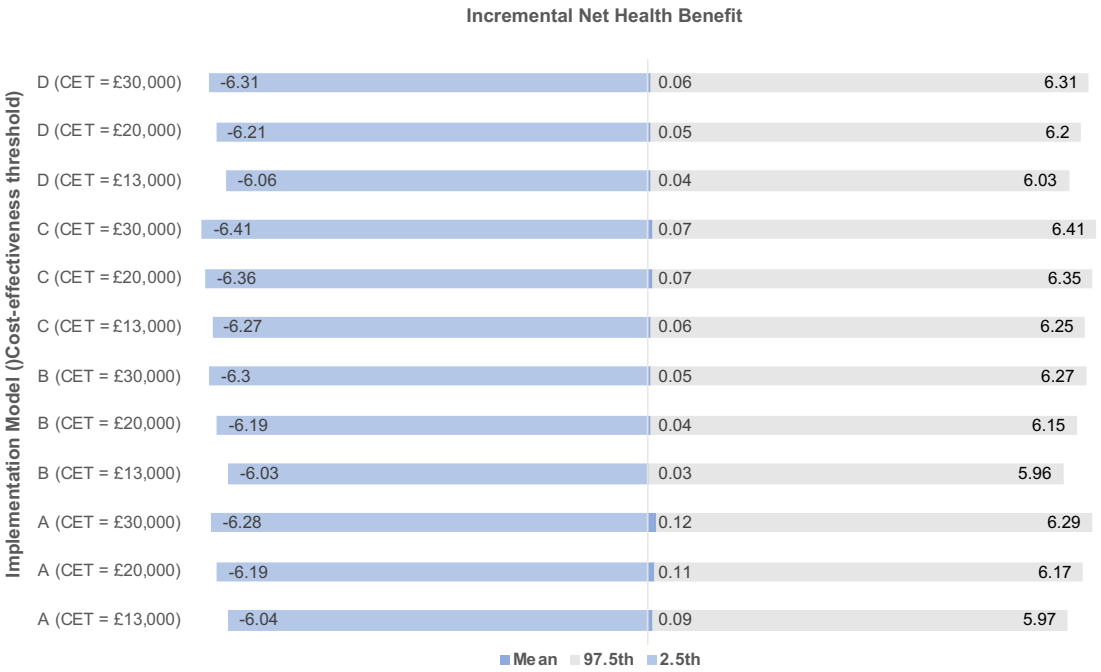


Figure 14 - Tornado diagram representing the difference (mean, 2.5th and 97.5th percentile) in incremental net health benefit between different implementation models according to three cost-effectiveness thresholds (CETs).

4.7.1 Implementation configuration A – The geriatric oncology model

The mean difference (£576) in pre-treatment cost of a geriatric oncology model was higher than standard care alone. The 2.5th percentile of pre-treatment costs is negative, whereby usual care costs more than the addition of GA. This is explained by the rare scenario where usual care uncovers more unmet need than GA. The addition of GA reduces post-treatment costs by £78 per patient, leading to a total cost per patient of £497. Costs associated with changes in management (£373) are balanced against a reduction in costs arising from expected post-operative excess bed days (£356), ITU admissions and 30-day surgical readmissions (£77), due to fewer operations being undertaken. A small reduction in costs (£20) arising from reduction in chemotherapy toxicity is also noted.

Slightly positive INHBs were found at all CETs, meaning that GA would be considered cost-effective if the effect sizes and management changes were reproducible at centres implementing GA. One-way PSA was undertaken by neutralising the effect of GA on post-surgical complications and GA was not cost-effective (INHB < 0 across all CETs). One-way PSA retaining the effect on post-surgical complications but removing the effect on chemotherapy toxicity rates or treatment changes at the MDT-level was also modelled. GA

remained cost-effective at all CETs, therefore highlighting that the perioperative component of GA in cancer care is an important effect.

		Implementation configuration Mean (2.5th and 97.5th percentile values)			
		A	**B**	**C**	**D**
Differences in cost per patient					
Pre-treatment (£)		576 (-735 to 1,486)	390 (-924 to 1,324)	389 (-924 to 1,324)	405 (-924 to 1,324)
Posttreatment (£)		-78 (-6,151 to 6,929)	-102 (-6,270 to 6,929)	-67 (-3,437 to 3,437)	45 (-5,994 to 5,758)
Chemotherapy toxicity (£)		-19 (0 to 0)	-8 (0 to 0)	-68 (-3,437 to 3,437)	0
Postoperative bed days (£)		-356 (-4,679 to 3,893)	-381 (-4,980 to 3,629)	0	49 (-4,661 to 4,728)
Other postoperative costs (£)		-77 (-3,523 to 2,160)	-113 (-3,523 to 2,160)	0	-4 (-3,523 to 3,523)
Treatment changes (£)		420 (0 to 6,929)	401 (0 to 6,929)	0	0
Total pre- and post-treatment (£)		497 (-5,602 to 7421)	287 (-6,100 to 7,151)	322 (-3,275 to 3508)	451 (-5,723 to 6,382)
Discounted QALYs over 10 years		0.13 (-6.47 to 6.54)	0.06 (-6.5 to 6.51)	0.09 (-6.52 to 6.52)	0.07 (-6.5 to 6.52)
INHB of GA compared to standard care (QALYs)					
	CET = £13,000	**0.09 (-6.04 to 5.97)**	**0.03 (-6.03 to 5.96)**	**0.06 (-6.27 to 6.25)**	**0.04 (-6.06 to 6.03)**
	CET = £20,000	**0.11 (-6.19 to 6.17)**	**0.04 (-6.19 to 6.15)**	**0.07 (-6.36 to 6.35)**	**0.05 (-6.21 to 6.2)**
	CET = £30,000	**0.12 (-6.28 to 6.29)**	**0.05 (-6.3 to 6.27)**	**0.07 (-6.41 to 6.41)**	**0.06 (-6.31 to 6.31)**
Probability INHB < 0 (decision error)		0.44	0.44	0.44	0.44
Expected cost of uncertainty per patient (QALYs)		2.82	2.81	2.86	2.91

Table 6 – Economic evaluation results for various implementation configurations.
Abbreviations: QALYs = quality adjusted life years; INHB = incremental net health benefit; GA = geriatric assessment; CET = cost-effectiveness threshold.

As reported by Partridge *et al*. (61), a registrar-led configuration of GA is also possible. A senior (e.g., seven years postprimary medical qualification) non-consultant doctor, specialising in geriatric medicine undertakes the GA (lasting 90 minutes) with consultant support available as required. This had lower total costs than the consultant-led model (£402 vs £497, or a 19.1% reduction), but exhibits a similar cost-effectiveness profile with PSA.

4.7.2 Implementation configuration B – The 'screen, predict and refer' model

The reduction in resources required to undertake the GA using this model reduces pre-treatment costs by 32.3% to £390 per patient. Assuming all beneficial effects of GA are present, the posttreatment cost profile follows model B and GA is again cost-effective at all CETs (INHB 0.03-0.05). One-way PSA demonstrated that GA is no longer cost-effective when the perioperative effect is neutral. Further one-way PSA removing the pre-treatment cost of using technology, (e.g. using a screening tool instead) did not affect the cost-effectiveness. Overall, this model has lower pre-treatment costs and a similar cost-effectiveness profile to model A.

4.7.3 Implementation configuration C – Prechemotherapy model

This model is cost-effective at all CETs. It is marginally cost-effective (INHB = 0.01) at higher CETs, if the effect on chemotherapy toxicity reduction is neutralised. One-way PSA demonstrates that GA is no longer cost-effective when the staff input is increased.

4.7.4 Implementation configuration D – Preoperative model

This model is cost-effective with INHB consistently above zero at all CETs, regardless of human resources. **Table 3** includes the results for a configuration based on model B. When the effect of GA on post-operative complications is neutralised, GA is no longer shown to be cost-effective.

4.7.5 Uncertainty

There was a consistently high probability (0.44) that INHB was less than zero, coupled with a high expected cost of uncertainty, between 2.81-2.91 QALYs.

4.8 Discussion

4.8.1 Significance of this study

The addition of GA to standard care in the management of older adults with cancer may be cost-effective, *if* assumptions based on the potential for GA to reduce surgical complications hold true. Implementation and other complex system factors will likely limit centre-dependent results in achieving the effects that have been reported in specific studies. A recent meta-

analysis (62) did not demonstrate positive effects of GA on postoperative outcomes and numerous underpowered studies reporting neutral results within oncology settings exist. When implemented with minimal healthcare staff input and assisted with technology, GA is potentially cost-effective for pre-chemotherapy optimisation. This finding holds even if GA has no effect on reducing chemotherapy toxicity, although the relationship between healthcare staffing inputs and outcomes following GA is uncertain. Due to the uncertainty in model parameters, the probability of decision error (INHB < 0) and the expected cost of uncertainty was high.

Examining the available evidence and the results of this study, GA may not be a cost-effective intervention for *all* older adults within oncology settings. This is principally due to the lack of evidence in recent meta-analyses and trials that GA consistently reduces chemotherapy toxicity and postoperative complications. The latter effect appears imperative to cost-effectiveness through consequent mortality reduction and increased QALYs favouring GA. The demonstrable efficacy of GA may be challenged by a myriad of factors including: i) complex implementation issues; ii) expedition of treatment in cancer treatment pathways with national targets; iii) QALY decrements with treatment; and iv) intensely competing causes of mortality. One could argue that GA is not required to be cost-effective because it will tend towards utilitarianism (250). By offering deeper insight into older adults' health, which may be unavailable in standard care, GA can change clinical decision-making in a direction most appropriate for a given patient. Furthermore, GA realises unmet needs and promotes general health optimisation where appropriate.

4.8.2 Strengths

This study has several strengths, including a robust synthetic modelling approach drawing assumptions from multiple studies across GA literature. The use of numerous validated statistical techniques maximised data whilst encapsulating uncertainty wherever possible. We utilised detailed modelling architecture with three Markov chains embedded within a decision tree. Furthermore, we have released our source code for others to examine and use freely. We have provided a range of implementation-specific cost figures to inform stakeholders when commissioning services.

4.8.3 Limitations

The limitations of this study arise from the assumptions made about the efficacy of GA to improve certain outcomes, principally chemotherapy toxicity and postoperative complications.

One-way PSA was used extensively to demonstrate where cost-effectiveness is sensitive to a particular assumption. Due to competing causes of mortality within oncology and highly differential mortality rates between different cancers, mortality differences between those with and without postoperative complications were difficult to resolve. The assumption that GA reduces postoperative complications and therefore long-term mortality appears imperative for cost-effectiveness. This assumption was utilised in a recent health economic evaluation by Partridge *et al*. (61), and our analysis found a lower effect than proposed by them. The concept of unmet needs is difficult to model in an economic framework. Synthesising multiple data sources aided this, but expert opinion guided the amount of addressed unmet need in standard care, supported by the combined, varied and senior NHS experience of three of the authors over several decades. A geriatric oncology model (model A in this study) may offer superior effectiveness over a model not involving geriatricians. The provision of GA in cancer care differs widely across the NHS (251) and the relationship between different implementation configurations and outcomes is unknown. This study was a macrosimulation and therefore cannot account for all nuances of oncogeriatric care (e.g. chemotherapy toxicity grading). Notable exclusions were radiotherapy, immunotherapy, endocrine therapy and best supportive care pathways. However, there is less, or sometimes, no evidence available that GA offers any therapeutic benefit in these management options. We were also limited by the available data and wished to avoid making speculative assumptions. For example, we do not have sufficient data for a third arm of Figure 1, where a patient uses GA to decide not to have chemotherapy or surgery. Data was also lacking in the available literature for chemotherapy or surgery-related rehospitalisation and discharge to dependent care settings. Finally, our model applies only to UK-based NHS health practice and the cost data reflects this.

4.8.4 Implications for clinical practice

The decision to implement GA could be based on centre-level economics, with consideration to the cost-effectiveness and cost-consequences reported here. Health organisations must consider implementation factors to successfully embed GA services in cancer care. Our study suggests that the most cost-effective model for centres cautious of the true cost-effectiveness of GA, is a prechemotherapy optimisation model with a nurse-led configuration. This could be assisted by technology where possible. For centres with dedicated geriatricians looking to start a geriatric oncology service, our results indicate that this should also include perioperative geriatric medicine.

4.8.5 Implications for future research

There are many trials protocolised, still in progress or recently reported in abstract. The results and subsequent meta-analysis of these may further support the cost-effectiveness of GA or neutral results may leave it in doubt. This questions the value of further research into the (cost-) effectiveness of GA, given that it is entirely safe and works towards utilitarianism. Future research should always include HRQoL as an outcome and a like-for-like comparison of unmet needs in standard care and GA arms, to aid cost-effectiveness studies. The dose-response relationship between health staffing inputs and clinical effectiveness must be ascertained through further research. Although complex and computationally expensive, microsimulation may be useful for oncogeriatric care models, including further examination of implementation models utilising screening and additional outcomes. Our group are currently working on a microsimulation model using machine learning, and a data pipeline could be created to inform a cost-effectiveness model.

4.8.6 Conclusions

This study and supporting evidence show that the use of GA in cancer care for *all* older adults may not be cost-effective. Where organisations can replicate the findings from centres of excellence, GA may be cost-effective when used preoperatively for patients undergoing cancer surgery. GA may also be cost-effective when used with a reduction in staff inputs and technological assistance before chemotherapy. A large amount of further trial data is pending, and this model can be used for future simulations. With judicious selection of implementation strategy, GA has potential cost-effectiveness in cancer care and tends towards utilitarianism with no safety issues, making it suitable for more widespread local implementation.

Chapter 5 – Developing a digital-first oncogeriatric assessment service

5.1 Introduction

The NHS Long Term Plan promotes digital-first approaches to service delivery, recognising the utility of technology and societal trends towards its normalisation in daily life (252). Drawing from the findings of **Chapter 2** and **Chapter 4**, technology serves a dual purpose in OGA by facilitating implementation and improving the cost-effectiveness. New OGA services being developed should therefore employ technology and existing services could trial embedding technology to improve their efficiency.

Service development in the NHS often formulates a quality improvement (QI) process. There are many similarities between QI efforts and implementation science, with overlapping methods and a shared goal of improving healthcare quality. Improvement and implementation science differ at the level of the problem they are employed to solve and their secondary goals (253). Improvement efforts tend to be focussed on a specific problem, within a specific healthcare system and are recognised at clinician, department, or health system level. Improvement strategies focus on addressing local problems and are often drawn from other industries such as manufacturing (e.g., Lean and Six Sigma) (254, 255).

The concept of Lean healthcare employs the principles from Toyota's Lean Manufacturing to healthcare, both for QI and operational efficiency, which has been popularised since the 1990s. However, successes are often localised with little evidence of sustainability (255). Lean methodologies and therefore by extension QI initiatives tend to focus on internal efficiency rather than external effectiveness without consideration to the end-users (i.e., patients). There has therefore been a movement for healthcare organisations to consider building upon lean with agile. Agile is a project management strategy, frequently associated with software development, with a key focus on developing systems mapped to the end-user requirements. When applied to healthcare, agile is difficult to define but tends to focus on capacity to deal with change to maintain external effectiveness instead of operational efficiency (256). Agile also raises the idea of proactively strategising processes and structures to manage uncertainty.

By contrast, implementation science tends to begin with an under-utilised intervention, which has a significant evidence-base for effectiveness already. Implementation science seeks to identify and address multi-level quality gaps and generate generalisable knowledge beyond the intervention and/or system under study (257). Implementation of OGA should be viewed as a

strategy rather than an intervention as it requires several methods to facilitate change, including QI techniques at the clinical level, extensive engagement with the MDT and wider services, and systems redesign at the healthcare organisation level (257).

A digital-first approach offers specific implementation facilitators, as one of the most cited barriers to implementing OGA is the time taken to complete the assessment. A systematic review of OGA in radiation oncology identified three pilot studies, which recorded that OGA takes between 80-120 minutes to be completed (69). Even an additional 5-10 minutes within frequently overbooked oncology clinics may be impractical. At an assessment-level, an OGA essentially comprises both a questionnaire and a physical examination component. Digitalisation of the questionnaire component towards patient-reporting may serve many theoretical advantages, which have some evidential basis. However, there are also some potential disadvantages, which may become implementation barriers to digitalisation (

Table 7).

Advantages
• Reduced clinician time
• Preferable to some patients **(258)**
• Environmentally friendlier
• Can be undertaken remotely using web-based or native smartphone applications
• Increased 'thinking time' for patients
• Improved clinical coding (useful for profiling, tariffs and mortality rates)
• Easier to store and share information between MDT members
• Easier to extract and analyse data for audit, research, business intelligence and data science
• Potential gateway for measurement of patient reported outcome measures
• Potential for automation of summarisation processes
• Potential for automation of e-referrals
• Potential for integration with electronic consent and digitalised, patient-centered decision support tools **(259)**
• In keeping with the NHS Long Term Plan for digital enablement **(252)**
Disadvantages
• Higher opportunity cost
• Integration with legacy electronic health records can be difficult
• Some older patients will be unable to use devices (e.g., cognitive or physical limitations)
• Requires specialist update and maintenance
• Raises cybersecurity, data safety and information governance issues

Table 7 – Advantages and disadvantages of digitalisation of oncogeriatric assessment.
Digitalisation of the oncogeriatric assessment has both advantages and disadvantages. *Abbreviations: NHS – National Health Service*.

To the best of my knowledge, no OGA has ever been developed to be utilised early in the cancer pathway and provide sufficient breadth to cover all cancer treatments. A digital-first OGA for use within the NHS has not yet been developed. The aim of this chapter was to develop a digital-first OGA service. This will be achieved through the following objectives: -

1. To establish the theoretical underpinnings of implementation of an OGA service
2. To establish the baseline implementation factors involved in implementing an OGA service
3. To establish the minimum questions required for the patient reported questionnaire component of the OGA
4. To establish the minimum physical components of the clinical examination component of the OGA
5. To develop and operationalise an OGA service

5.2 Methods

5.2.1 Theoretical considerations

The conceptual basis of OGA extended from CGA, which was never actually designed for older adults with cancer. Given the historical lack of agreement on the components of OGA, significant heterogeneity in its form, implementation and outcome measures developed. This entropy is represented as the inability of many systematic and umbrella reviews to undertake meta-analysis of OGA when applied to surgical settings (70). High level organisations such as ASCO have recently attempted to rationalise the components of OGA, although did not provide data on assembling this into an implementable system (13). This serves as an opportunity to apply principles from CAS theory and high-level recent evidence into the design of a patient reported OGA system. The need for a whole-system approach for integrated OGA considering clinical, organisation and strategic levels was highlighted in a systematic review using concept analysis (260) and was emphasised in **Chapter 2**.

From an axiological perspective, OGA only holds value for two purposes: i) identification of vulnerabilities for optimisation before cancer treatment; and ii) prediction of outcomes. The vulnerabilities identified by OGA are mainly optimised by actors external to the cancer MDT, which due to competing priorities may be unable to offer timely intervention. This therefore introduces a hidden tertiary value in OGA, which is to generate business data for QI to realise unknown and unmet needs. The prediction of outcomes creates a feedback loop for both patients and clinicians to use in shared decision-making. Modelling OGA as a system is a useful

construct, which may help to reduce the entropy and therefore heterogeneity of OGA and improve its value. A goal-oriented approach can be taken to rationalise each question of a patient reported OGA with a value: either towards identification of a vulnerability or predicting an outcome. A high-level construct is also of value when applying gerontology to cancer care. The 'geriatric giants' were coined by Bernard Isaacs in 1965, namely: immobility, instability, incontinence and impaired intellect/memory. However, 'modern geriatric giants' also encompass four new geriatric syndromes of frailty, sarcopenia, anorexia of ageing and cognitive impairment (261). More recently, in order to clearly express the role of geriatric medicine, the 5Ms construct was conceived: mind, mobility, medications, multi-complexity and matters most (262). The latter refers to patient-centred care and focusses on the role of geriatric medicine as a centralisation of different specialisms. A new system of OGA should consider these high-level constructs in its design thinking.

Drawing analogies with software design, an OGA system essentially comprises of a patient-side (e.g., 'application') and clinician-side (e.g., 'server'). The patient-side must consider the user experience (UX) in all aspects of its design. The patient-side of OGA is essentially a form for data collection, using both patient reported and objective clinical data variables. The clinician-side centres around the computing and stratification of risk; the establishment of vulnerabilities for optimisation, mapped to downstream referral targets; and/or generation of business intelligence for local QI processes. Considering this model, the patient-side of an OGA can be divided conveniently into five major components, determined by their suitability for patient-reporting and pragmatic configuration: i) cognitive screening; ii) patient reported questionnaire; iii) co-morbidity and medication review; iv) physical examination; and v) targeted investigations. The clinician-side comprises four major components: i) risk computation; ii) brief intervention and referral generation; iii) risk stratification and summarisation; and iv) communication back to the MDT.

Linear conceptions such as the recommendation to undertake OGA by influential bodies like ASCO and SIOG fails to account for the complex, heterogenous and resource-constrained systems that must implement OGA. In contrast, systems thinking aims to be nonlinear and encompass the various interactions, relationships, perspectives and boundaries of a system (263). OGA is itself a third-level subsystem, operating within a parent subsystem (oncology), which operates within a particular healthcare parent system. The hospital operates within a community with various interactions with other services and the third sector. This can be conceptualised as a CAS due the dynamic, interacting and context-dependent clusters of

entities. Since OGA is intrinsically linked to other changing and evolving systems, including the cancer MDT, allied-health professionals, medical specialists, psychological services, social services and the third sector, viewing it as a CAS may aid its implementation (**Figure 15**).

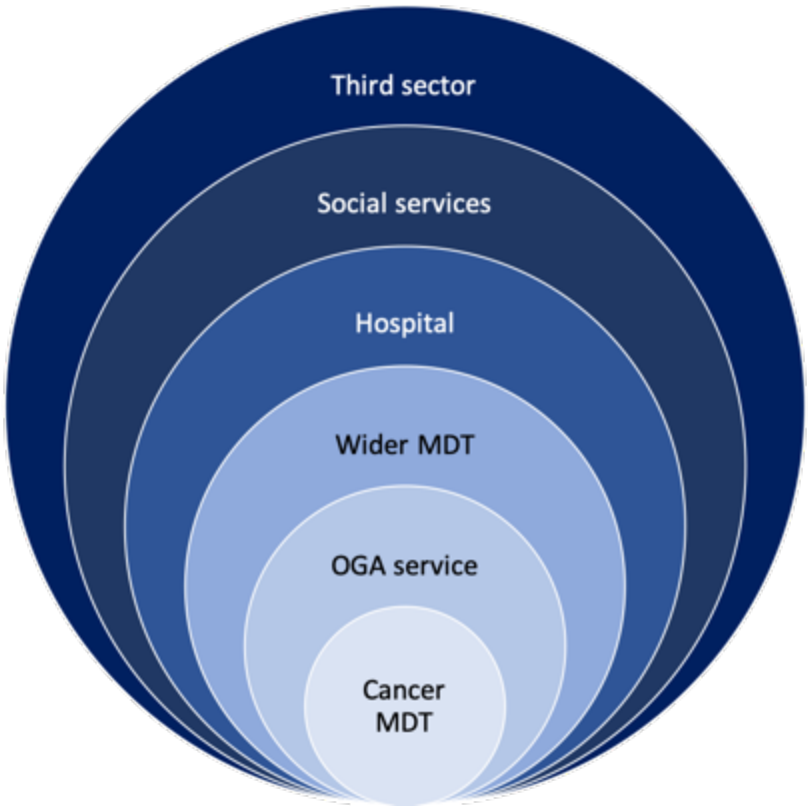


Figure 15 – Oncogeriatric assessment within a complex adapting system.
Oncogeriatric assessment (OGA) can be viewed within a complex adapting system with an OGA service serving as a gateway between the cancer MDT, wider MDT (e.g., allied health professionals, medical specialists), the hospital, social services and the third sector.

OGA within a CAS is not necessarily a hierarchical linear relationship. By modelling interactions using social network analysis, considering the patient as the most significant agent within a network, OGA can be further visualised as a CAS (**Figure 16**) (264). Graph theory is the mathematical modelling of relations between objects, made up of nodes (also known as vertices or points) and edges (also known as links or lines) (265). Modelling OGA within a cancer pathway demonstrates significant bidirectionality between nodes, which themselves are systems, rather than discrete objects or simple actors. Although there can be significant regional variation in services offered (266), generally patients can often self-refer to mental health, social and third sector services. The OGA service therefore exhibits a gateway role to other systems of professionals, including allied health professionals and other medical

specialists. These nodes represent a wider cancer MDT, generated through the OGA service and the patients themselves. The OGA service can also serve as an educational platform, empowering patients to seek the help they need for optimisation or their own general well-being within a cancer pathway. The separate systems operating around OGA exhibit interdependency, and the independency and the role of collaboration becomes evident, which has been identified as an enabler to OGA implementation in **Chapter 2**. Important feedback loops exist between the patient, specialist and cancer MDT, so that the OGA service can influence the actions and decisions of these agents (264).

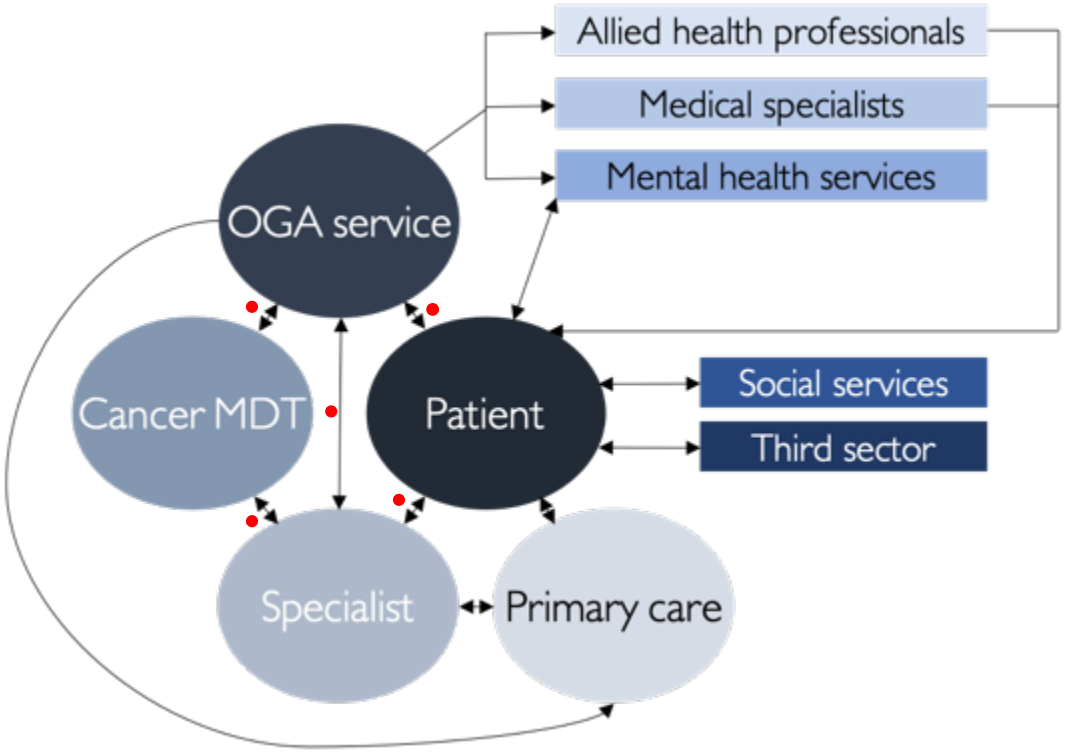


Figure 16 – Undirected graphical network model of OGA within a complex adapting system.
The patient is represented as a node since their agency will have the greatest effect on the network. The OGA service has a gateway role for referring to systems that the patients cannot access themselves, unlike social services and the third sector. Mental health services can frequently be accessed by self-referral or clinical referral. There is significant bidirectionality of edges throughout the network of this complex adapting system. The red dots mark significant feedback loops that can profoundly influence the relevant receiving nodes.

The core nodes (patient, primary care, specialist and cancer MDT) are well established and are likely to undergo changes that synchronise with each other within the CAS. This means that the OGA service will need to establish or normalise with the core nodes to obtain stability and exhibit adaptability to adjust to external factors. The OGA service, as a gateway node, generates edges that were previously not frequently utilised nor established. By generating new edges the OGA service begins to show evidence of emergence (i.e., spontaneous creation of

order and functionality from the bottom of a system) (264). Within the wider cancer MDT, points of failure do not affect the stability of the core nodal network, and this represents adaptability. For example, where implementation barriers or latterly health system failures (e.g., financial or capacity issues) prevent referrals to allied health professionals, the core nodes within the CAS can still operate. However, with the introduction of the OGA service, other useful utilisations of the network can still occur.

5.2.2 Service development

This thesis arose out of a unique set of circumstances whereby I was dually funded to provide both clinical services (20%) and academic research (80%). There was an opportunity within the research-participating institution (Hull University Teaching Hospitals NHS Trust; HUTH) to develop and implement an OGA service. I was employed by HUTH via an Honorary contract and was a middle-grade doctor (Specialty Registrar in Otolaryngology) who could therefore operationalise an OGA service with acceptable clinical governance within HUTH. A proposal was developed through the engagement with key stakeholders, initially as part of the realist review. The OGA service was protocolised according to current literature, key stakeholder input and clinical experience, including the senior clinicians assuring governance within HUTH. The service was registered as a service evaluation within HUTH. Key stakeholder engagement continued monthly to identify improvements and further develop the business case.

5.2.3 Key stakeholder engagement

Numerous informal stakeholder consultations were undertaken as part of the realist review in **Chapter 2** and additional meetings occurred. These were informal and unrecorded because they formulated part of a process of internal service development in my capacity as a clinician. To provide a framework for the summarisation of key stakeholder engagement, a custom discovery approach was utilised. Custom discovery is a business principle, propagated as the core purpose of start-up enterprises and was recently reported for use in developing the business case for a digitalised OGA system (267). There are four phases in a customer discovery process, which is iterative following revisions: i) generating hypotheses; ii) testing hypotheses; iii) testing a product concept; iv) evaluating feedback from customers regarding the product. Hypotheses are guided by a business model canvas, segmenting a business model, such as a digital-first OGA service, into: i) key partners; ii) key resources; iii) key activities; iv) value propositions; v) customer relationships; vi) customer segments; vii) distribution

channels; viii) cost structure; and iv) revenue stream. In this context, the value propositions refer to the value or benefits that a digital-first OGA service can bring to a cancer centre (268).

Key stakeholders consulted informally for advice and opinion included my supervisors (a consultant medical oncologist and a palliative care physician), members of the full Head and Neck Cancer MDT (including five consultants from otolaryngology, oral maxillo-facial surgery and clinical oncology), a consultant colorectal surgeon, the medical director for oncology services (a consultant haematologist), cancer business manager, four IT services personnel, clinical safety officer, clinical coding manager, two HUTH digital managers, a senior occupational therapist, clinical lead for therapy services, two physiotherapists, clinical lead for dietetics, three dieticians, two cancer nurse specialists and three consultant geriatricians.

5.2.4 Baseline formative evaluation

Formative evaluation has been defined as "*a rigorous assessment process designed to identify potential and actual influences on the progress and effectiveness of implementation efforts*", which supplements summative evaluation obtained from conventional efficacy/effectiveness research methods (269). Extensive summative data is available on OGA, confirming its role in generating data on vulnerabilities and outcomes. However, formative evaluation data is only just starting to emerge (92). Formative evaluation can be used at the developmental stages for several reasons, including understanding the context of a local implementation setting, identifying the need for an intervention. The Medical Research Council guidance on complex interventions, recommends the use of theory in their design to help understand causal assumptions and build a generalisable knowledge base for a wider academic readership (270).

NPT is an action theory developed to help explain how an intervention can be normalised and become embedded into routine practice (271). Normalisation of the OGA service was identified as important within the CAS to obtain stability and adaptability to adjust to external factors. NPT has four main components which work dynamically, inter-dependently and in the wider context of an intervention: coherence (this ability to make sense of complex intervention); cognitive participation (how likely actors are to engage with a complex intervention); collective action (the work undertaken to enable the intervention to be implemented); and reflexive monitoring (cost benefit appraisal undertaken formally or informally by actors) (271). NPT has been used in the implementation of CGA previously, both

hospital wide and within surgical pathways (92, 94). NPT was therefore utilised in the design of the OGA service to help aid normalisation.

The formative implementation evaluation was based on two sources of feedback, which were collected through professional network interactions, rather than formal qualitative interviews. One source of feedback was derived from the Head and Neck MDT members, which focussed on the optimisation of the presentation and content of the summarised information provided to them. The second source was consultations with clinical staff members who were referral targets of the OGA service. NPT was supported by design theory, which has been drawn from the business community as a novel way of solving problems in healthcare. Design thinking emphasises empathy with users, diverse collaboration and encourages rapid hypothesis testing and prototyping with end-user derived insights (272).

5.2.5 Software design and development

The technical details of the software design and development are better deferred to **Chapter 6,** which specifically focusses on evaluating the usability and acceptability of the patient reported component of the OGA and its respective UI and UX considerations.

5.2.6 Patient and public involvement

Several patients who have lived experience of cancer were involved in the design of the service by helping to validate both operational and research design assumptions of the OGA service and its associated studies.

5.2.7 Ethical considerations

Formal ethical review was not required to operate the OGA service *per se* because OGA is considered routine care internationally and similar services already exist within other NHS institutions. However, favourable opinion was sought from the Research Ethics Committee for the research study running in parallel (see **Chapter 6**), who had no concerns regarding the implementation of the OGA service (see **Appendix Figure 55**).

5.2.8 Literature review and analysis

Non-systematic targeted searches using PubMed and Google Scholar were used to identify important studies across disparate disciplines to develop the question set used for the evaluation of a digital-first patient reported OGA in **Chapter 6**. The levels of evidence provided by the Oxford Centre for Evidence-Based Medicine guided inclusion. A qualitative synthesis and narrative discussion are presented below of the decision making for the selection of questions and components of the OGA.

5.3 Results and discussion

5.3.1 Cognitive screening

In the context of OGA, the cognitive screen serves the purpose of identifying cognitive impairment, namely dementia or mild cognitive impairment (MCI) (273). Dementia is a clinical syndrome characterised by usually progressive, deteriorating mental function that interferes with activities of daily living (ADL) (274). Diagnosis of dementia requires impairment in two or more cognitive domains (memory, language, behaviour, visuospatial or executive function), significant functional decline that affects ADL and the exclusion of another disorder or adverse effects of medication (274). Between 29-76% of people with confirmed or probable dementia are estimated to be undiagnosed in primary care (275). MCI is cognitive impairment that does not fulfil the diagnostic criteria for dementia, although 50% of people with MCI will later develop dementia (274).

Cognitive impairment is a vulnerability in cancer care and although some treatments can be beneficial in early-stage disease, it is not suitable for optimisation before cancer treatment. Computer based tests require further validation, therefore this domain must currently be clinician-led, based on patient responses (276) and is therefore considered separately. Detection of this vulnerability is also important for predicting outcomes and is recommended by ASCO guidelines. Cognition is an established domain of CGA and impairments in two or more CGA domains is considered indicative of frailty (277). Frailty has significant predictive power for postoperative outcomes (18, 245), therefore cognition screening serves value towards frailty detection or confirmation.

Pre-existing cognitive impairment increases the odds of postoperative delirium (odds ratio [OR] 2.7, 95% CI 1.9-3.8) and falls (OR 2.13, 95% CI 1.56-2.90) (278, 279). Postoperative cognitive dysfunction (PCD) represents cognitive decline within three months after surgery and may be subclinical. A systematic review found that the incidence of PCD is 11.7% (95% CI 10.9-12.5), although it has not been associated with preoperative cognitive impairment (280). Cognitive impairment has not otherwise been consistently associated with postoperative complications or mortality in older patients with cancer (66, 68, 70). However, cognitive impairment is a strong predictor of nursing home admission in the next three years according to a meta-analysis of older adults within the USA (OR 2.54, 95% CI 1.44-4.51) (281).

On balance, detection of cognitive impairment within an OGA probably favours sensitivity versus specificity. This is to avoid missing frailty or potential lack of decision-making capacity.

There are a variety of cognitive screening tools, of which the Mini-Mental State Examination (MMSE) (282) and Montreal Cognitive Assessment (MoCA) (283) are the most common. The MMSE requires licensing and therefore incurs a cost for use. Several systematic reviews tend to favour the MoCA (**Appendix Figure 50**) for its sensitivity (84%), specificity (74%) (276) and ability to differentiate between vascular MCI and vascular dementia (284). The MoCA cut-off score of 23/30 (versus 26/30 traditionally) appears to improve diagnostic accuracy for older adults and/or those of lower education (285). The ASCO guidelines for geriatric oncology recommended the Mini-Cog (286) for cognitive screening, however, a recent Cochrane systematic review found insufficient evidence for the use of the Mini-Cog for detection of dementia in primary care (287). An important referral following positive cognitive screening (in the absence of known cognitive impairment), recommended by NICE, both for MCI or suspected dementia is to a memory assessment service (e.g., memory clinic or community mental health service) (274). There is a need to integrate with the existing referral criteria of local services, therefore the use of alternative instruments may be considered.

Decision-making capacity should be determined for the decision being made at the stage of their cancer treatment. Where cognitive impairment has been detected, guidance to the MDT should be made to confirm capacity at that point for a particular decision. Finally, before attempting a patient reported questionnaire (digital or paper), it is important to consider an individual's suitability for this. In the context of cognitive impairment, it may be appropriate to fall back to a clinician-led questionnaire or even use collateral sources (e.g., relative or carer). For this reason, cognitive assessment should be undertaken first in the OGA process.

5.3.2 Patient reported questionnaire

Beyond cognition, the ASCO guidelines for geriatric oncology recommend a minimum assessment of instrumental ADL (IADL), a single question for falls, a depression screening tool, specifically the Geriatric Depression Scale (288), and an assessment of unintentional weight loss for nutrition (13). A recent umbrella review of CGA in surgical patients (70), also agreed that nutrition and mood assessment were of most value preoperatively. All these domains are focused on identifying vulnerabilities for optimisation and are suitable for patient-reporting. However, excessively abbreviating an OGA may miss some important domains, which could lead to missed pre-treatment optimisation and/or decision-making opportunities. The following additional considerations should be considered for UK clinical practice and an OGA that occurs early in a cancer pathway: -

1. Vulnerabilities in basic ADL may warrant a needs assessment from social services and/or involvement with hospital occupational therapy services (289).
2. A limited social network and/or mobility/transportation issues may mean that hypofractionation, brachytherapy, or stereotactic radiotherapy is better suited where radiotherapy is an option (69). Frequent outpatient visits may be more difficult in these circumstances (258). Exploration of social support is therefore valuable.
3. In the context of surgery as an option, questions assessing functional capacity, breathlessness, alcohol and smoking are warranted (290). These domains may also be relevant to other treatments as well.

The ASCO guidelines also recommend using a validated non-cancer, all-cause mortality prediction score and a chemotherapy toxicity risk prediction score (e.g., CARG) (13). Some of these scoring systems require answers to simple questions, which could be patient reported. All these requirements should be factored into the questionnaire to produce one complete patient reported component. This organisational process helps to reduce entropy and promote emergence within OGA. The domains, example questions and their rationale were mapped to generate a patient reported questionnaire (**Appendix**

Table 21). A detailed discussion of each individual domain follows.

5.3.3 Falls screening

Falls are a common geriatric syndrome and around one third of community-dwelling adults aged over 65 years fall each year, with potentially serious consequences (291, 292). Falls and their injurious sequelae are common in older adults with cancer and those receiving chemotherapy or androgen deprivation therapy may be at higher risk of falling than non-recipients. Injurious falls may be even more likely in patients with advanced cancer or those receiving palliation (293). However, a recent systematic review was unable to conclude if falls were more prevalent in older adults with cancer versus age-matched controls from the general population (293). A recent meta-analysis found that cumulative post-test probability from different measures (history, self-report and performance-based) held most clinical utility in combination for predicting falls, rather than using single measures in community-dwelling older adults (294). A history of falls is the most consistent risk predictor of future falls in patients with cancer (293, 295). Asking a single question regarding falls in the last six months maps into the CARG toxicity prediction score (**Appendix T**Error! Reference source not found.) and is the minimum question for falls recommended by ASCO guidelines (13). A

Delphi consensus from the ASCO guidelines recommended that patients deemed at risk of falling should be informed of their potential higher risk of falls during cancer treatment and provided with educational material. A referral to physiotherapy or occupational therapy may be warranted for pre-treatment strengthening exercises and/or home safety assessment and appropriate adaptations (13). In UK clinical practice, this may not be pragmatic due to the capacity and waiting list limitations of falls clinics competing against cancer pathway targets.

Local referral criteria may vary, but within HUTH a fall of unknown cause is needed for referral, therefore exploration of the details of a fall in the last six months are required from history and/or the medical record. This single question strategy therefore only serves as a prompt for more detailed falls assessment. Pre-treatment falls prevention interventions may also be considered prehabilitation, which lacks robust evidence of improved outcomes (54-56). There are several trials ongoing to further assess the impact of geriatric interventions on outcomes (13). Given that the impact of falls intervention before cancer treatment is unclear, it could be argued that, outside of a trial, the significant cost implications of additional referrals are not currently justified in NHS practice. Considering these circumstances, where there is little opportunity to offer falls prevention intervention before cancer treatment, a single question carries more value when mapped to the CARG chemotherapy risk prediction score. However, any patients that have fallen in the last six months without explanation, assessment or intervention may be referred to a falls clinic according to good clinical practice. This should not need to compete with cancer pathway targets or be prioritised as a pre-treatment intervention, where services cannot fulfil this expectation.

From a QI perspective, gathering suitable data towards developing a business case for expanded services holds value. Priorities over resource allocation within healthcare organisations is a matter for senior management, and the identification of unmet needs can help guide business decision-making. To identify unmet needs and those at risk who may benefit from falls prevention interventions, a screening process recommended by the American Geriatrics Society/BGS for primary care can be utilised (296). This consists of a clinical algorithm, which can be converted to self-reporting and combined with other aspects of the OGA system (**Figure 17**). This algorithm was recommended for use in a recent systematic review of falls in older adults with cancer to help standardise both clinical practice and research methodology (293). Fear of falling was not included in the original algorithm, although may be considered as an additional screening question, given its associations with limitations in undertaking ADLs and increased risk of institutionalisation and future falls (297).

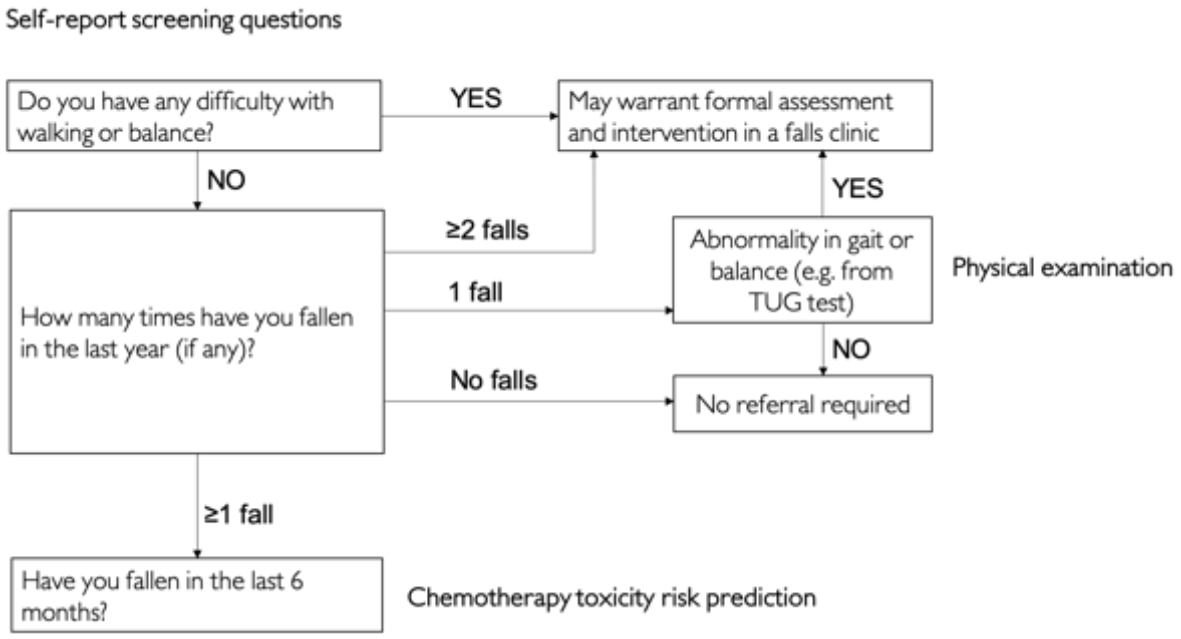


Figure 17 – Modified clinical algorithm for falls assessment within a oncogeriatric assessment.
Patients are initially asked to self-report on their walking and balance and number of falls in the last year, which determines the need for referral to a falls clinic or other multifactorial falls risk assessment and intervention service. An assessment of gait or balance abnormalities using a physical examination e.g., Timed Up and Go (TUG) test, can help to confirm which patients may benefit from a falls assessment who have fallen in the last year. Finally, for those that have fallen in the last year, clarification of whether this occurred in last six months is necessary to map with the Cancer and Ageing Research Group score (if used). Those that screen negative (i.e., no walking or balance issues or falls in the last year), do not require referral and do not attract three points on the CARG score (**Appendix TError! Reference source not found.**). Adapted from the Panel on Prevention of Falls in Older Persons, American Geriatrics Society and British Geriatrics Society (296)

5.3.3.1 Nutritional assessment

Malnutrition is defined as a state where deficiency of energy, protein and/or other nutrients causes objectively adverse effects at a biochemical, physiological, functional and clinical level (298). Malnutrition is common and affects over 10% of people aged over 65 years – a group of which over half of the annual £7.3 billion cost of malnutrition is expended (299). Among patients with cancer, malnutrition may affect between 15-80% (65). Malnutrition is associated with a multitude of negative outcomes, including increased infections, morbidity, post-operative complications, functional decline, recovery times, length of stay, readmissions, mortality and healthcare costs (300). Recent meta-analyses found that malnutrition increases the risk of all-cause mortality in patients with cancer (relative risk [RR] 1.73, 95% CI 1.23-2.41) (300) and falls in community-dwelling older adults (RR 1.64 , 95% CI 1.18-2.28) (301).

Screening for malnutrition is recommended by ASCO guidelines and an umbrella review of preoperative CGA, due to its ability to be modified before treatment commences (13, 70). There is no single validated malnutrition screening tool for older adults with cancer, although the Mini Nutrition Assessment (MNA) was still found to associate with higher risk of all-cause mortality (RR 2.13, 95% CI 1.34-3.39), however, this may be an overestimation (300). The MNA is the most validated nutrition screening tool for older adults and the short-form consists of six questions, three of which are suitable for patient-reporting (**Appendix**

Table 20) (302). The remaining questions regarding neuropsychological problems are probably best ascertained from the medical history. Depending on the mode of presentation or recent medical history, many patients on a cancer pathway will have suffered from acute disease in the past three months, so in most cases this will be positive by default. Body mass index (BMI) can be measured objectively during a physical examination in the clinician-side of the OGA.

5.3.3.2 Psychological assessment

Depression is common in patients with cancer, affecting on average between 8-24% (303). Depressive symptoms have been associated with higher risk of falls (RR 1.52, 95% CI 1.19-1.84) (304), higher odds of postoperative complications (OR 1.77, 95% CI 1.22-2.56) (305) and postoperative pain (OR 1.71, 95% CI 1.32-2.22) (306). However, the effect of treating depression to improve cancer-related or treatment outcomes has not yet been demonstrated. Systematic reviews and meta-analyses have demonstrated that pharmacological or psychological interventions have little evidence of effectiveness for depression in patients with cancer (307, 308). Collaborative care interventions, including pharmacological and psychological interventions with integrated delivery and follow-up have demonstrated better effectiveness, retention and longer-term effects (309). A more compelling reason to identify depressive disorders in patients with cancer is the risk of suicide mortality. A meta-analysis recently reported a pooled standardised mortality ratio (SMR) of 1.55 (95% CI 1.37-1.74) in patients with cancer (310). Suicidal mortality differed by cancer subtypes: upper gastrointestinal and hepatopancreatobiliary (SMR 2.06, 95% CI 1.32-3.23), colorectal (SMR 1.57, 95% CI 1.26-1.97), thoracic (SMR 3.07, 95% CI 2.20-4.28), breast (SMR 1.24, 95% CI, 1.03-1.48) and prostate (SMR 1.71, 95% CI 1.38-2.12) (310).

Diagnosing depression can be challenging in older adults with cancer due to the overlap of cancer symptoms, treatment side effects and older adult presentations of depressive disorders (e.g., pseudodementia) (311). Screening for depression is recommend by ASCO guidelines and

from an umbrella review of CGA in surgical patients, given its potential for treatment to commence before treatment (13, 70). The Geriatric Depression Scale (GDS) is the most used measure of depression among older adults, although there are concerns about its use in patients with cancer (312). The ASCO guidelines recommend the GDS, however, the evidential basis to this recommendation was lacking. A systematic evaluation by Nelson *et al*. (313) found that the Center for Epidemiologic Studies of Depression-Revised (CESD-R) (314) measure potentially offers the highest reliability, although the eight other common measures assessed were not optimal. Another systematic review of the psychometric properties of tools for detecting emotional distress in patients with cancer further supported the high generalisability, validity, reliability, criterion measure and judgement of the CESD-R tool (315). A study by Saracino *et al*. (312) with 201 older patients with cancer, using GDS, CESD-R and the Hospital Anxiety and Depression Scale, found that CESD-R has the most utility. CESD-R and was able to detect major depressive disorder with over 80% sensitivity and specificity. However, all three patient reported tools studied were poor at detecting minor depression, with the worse findings for the GDS (312). Until further validation data is available for measuring depression in older adults with cancer, the CESD-R (**Appendix**

Table 23) appears to be the most useful tool and was selected for inclusion in the OGA.

5.3.4 Functional status

Functional status can be defined as the level of activities an individual can perform to meet the physical, psychological, social, spiritual and intellectual needs of daily living (316). Functional status can also be extended to functional capacity and functional performance. Functional capacity represents the maximum capacity to perform needs of daily living, whilst functional performance represents the actual daily activities undertaken (317). Functional capacity can be measured by maximal exercise testing and is quantified by metabolic equivalents (METs). One MET is equal to the basal metabolic rate (i.e., metabolic demand at rest), and the ability to perform ADL can be used to estimate functional capacity. For example, four METs is the ability to climb two flights of stairs or run a short distance. In the context of known ischaemic heart disease, preoperative risk stratification and management are determined by the functional capacity (318). Measuring METs is therefore a useful component of OGA, as METs that are under four may require preoperative cardiac stress testing in the context of known coronary artery disease (319). Higher levels of preoperative physical activity are protective and associated with shorter length of stay (OR 3.66, 95%CI 1.38-9.6) and with better postoperative quality of life (OR 1.29; 95%CI 1.11-1.49) (320).

Measuring functional capacity fits well with the Rockwood Clinical Frailty Scale (CFS), which was developed to provide a common understanding of frailty between different clinicians to promote acceptance (321). Rockwood *et al*. (321) validated the predictive power of the 7-point CFS (**Appendix Figure 51**) prospectively in 2,305 older adults. The CFS was revised in 2008 to become a 9-point scale ranging from 1 (very fit) to 9 (terminally ill) and frailty categorised as 4 (mild) 5 (moderate), 6 (severe) and 7 (very severe). The power to predict mortality and other outcomes was further validated by systematic reviews in other older adult populations (322, 323). Both functional capacity and performance factor into mortality risk prediction models, such as the Suemoto index **(Appendix Table 26**) (71), representing the role of functional status as a proxy to poor outcomes.

Functional performance can be measured by self-reported ADL, although health perceptions can confound these results (e.g., someone with a poor view of their health may have poor functional performance relative to capacity) (317). Two commonly used scales for measuring functional performance are the Katz (basic) ADL (ADL) scale (324) and the Lawton instrumental ADL (IADL) scale (325). Both scales are over 40 years old and are often bundled into CGA, being the most common instruments used to assess ADL (326). Basic ADL (BADL) are those considered essential for living and include bathing, dressing, toileting, transferring, continence and feeding (324). Disability to undertake BADL means that assistance will be required to live in the community and is associated with lower well-being and health-related quality of life (326). Around one third of all adults with cancer have BADL disabilities, which are mostly related to personal hygiene, walking, transfers and bathing (326). IADL are more complex skills required for independent living, including telephone use, shopping, food preparation, housekeeping, laundry, transportation, medication self-administration and financial handling (325). Around half of all patients with cancer have IADL disabilities, which most commonly relate to housework, shopping and transportation (326).

Generally, deficits appear in IADL first followed by BADL and cognitive impairment tends to limit the IADL tasks (e.g., medication self-administration), whereas physical limitations can greatly affect BADL and functional capacity (327). IADL also tend to be affected earlier in the cancer trajectory versus BADL (328, 329). Morris *et al*. (330) demonstrated the progression of IADL, through to IADL-ADL transition and ADL dependency in a study of 762,023 interRAI (a suite of CGA tools for community-dwelling adults) assessments. They identified a general pattern of progressive dependency affecting IADLs initially, including shopping and housework, meal preparation, managing finances and managing medications respectively. This

was followed by BADL losses in hygiene, toileting, locomotion and finally eating (330). Given the interaction between different domains of the OGA and the ability to define frailty from the number of domain impairments, functional status assessment is considered an essential OGA component (70, 331). Modern IADL may even extend to smartphone, computer and/or internet use and the ability communicate with email. IADL deficits were found to predict mortality in a systematic review, although the results could not be meta-analysed due to heterogeneity (74).

Chemotherapy stresses functional reserve, therefore, the ASCO guidelines (13) recommend to screen for IADL disability to predict functional decline. This is seemingly based on a single prospective study of 364 patients aged ≥ 70 years receiving first-line chemotherapy for cancer (332). Hoope *et al*. (332) found that low pre-chemotherapy IADL scores were independently associated with functional decline (OR 2.87; 95% CI 1.06-7.79), as measured by a decline in the Katz ADL scale after the second cycle of chemotherapy. However, this single study excluded 17.8% of recruited patients due to logistical, organisational and patient factors. A systematic review by van Abbema *et al*. (66) only analysed the study by Hoope *et al*. (332). However, IADL impairment is included in the CRASH chemotherapy toxicity risk prediction model and a single question from IADL (dependency in medications) maps into the CARG score (**Appendix Table 22**) (66). An umbrella review of preoperative OGA recommended undertaking functional status assessment, based on its link to adverse outcomes (70). However, BADL or IADL impairments have not demonstrated predictiveness of postoperative outcomes. Instead, they tend to associate with mortality in cohorts, with nearly 50% receiving non-surgical cancer treatments. Huisman *et al*. (70) attribute this finding to selection bias, whereby surgical candidates tend to be fitter and more independent.

Functional decline is defined as developing difficulties with ADL, diminishing autonomy and increasing disability. Functional decline has been associated with numerous poor health outcomes including increased length of hospital stay, mortality and quality of life (333). Functional deficits factor into many frailty indices and frailty significantly predicts nursing home admission, as found in a recent meta-analysis (OR 5.58, 2.94-10.60) (334). Another meta-analysis found that three or more ADL dependencies predicts nursing home admission in the US (OR 3.25, 95% CI 2.56-4.09) over a 2–6-year interval (281). A systematic review suggested that multimorbidity (two or more chronic conditions) predicts future functional decline in community-dwelling older adults, which is worsened by the number and severity of conditions (333). Death was found to be preferable to severe functional impairment in nearly three quarters of older adults with chronic disease (335).

There is significant heterogeneity in the use of ADL tools in the literature. Hopman-Rock *et al*. (336) undertook a systematic review of the psychometric properties of various BADL instruments for older community-dwelling adults. The tool with the highest reliability, validity and responsiveness was the Functional Autonomy Measurement System (SMAF), followed by the Katz 5-items. However, the SMAF is a comprehensive 29-item scale, unsuitable for patient-report and takes approximately 40 minutes in total. The Katz 5-items, takes the Katz 6-items and excludes continence, as some argue continence should not be considered an ADL (337). To the best of the authors knowledge, the Katz 5-items has not been specifically validated for true patient-report (i.e., not led by clinicians). However, the questions are easily modified into patient-report format by splitting the responses and making the wording first person (**Appendix** T**able 24**). The same process can be used for the Lawton IADL scale (**Appendix Table 25**). Using a clinician-led self-report tool could be criticised as invalidating the tool in the absence of validation for this administration method. However, a clinician would frequently rephrase the measure into questions, and therefore the wording in many self-report tools (like the 5-item Katz or Lawton IADL scale) are never actually true to their original wording.

There is a lack of robust evidence for the overall predictive power of functional performance towards postoperative or post-chemotherapy outcomes in older adults with cancer. Total dependence in ADLs predicts postoperative pulmonary complications in general (OR 2.51, 95%CI 1.99-3.15) (338). Individual domains from BADL and IADL are useful to map into separate predictive models (e.g., Suemoto Index, CRASH and CARG). In the general older adult population, a meta-analysis demonstrated that difficulties in BADL (OR 2.09, 95% CI 2.09-2.45) or IADL (OR 2.10, 95% CI 1.68-2.64) double the risk of falling (339). Identifying vulnerabilities for pre-treatment intervention or generation of data on unmet needs for QI requires screening across the spectrum of BADL and IADL. Given the significant epidemiology of ADL disability in patients with cancer identified by Neo *et al*. (326) in a meta-analysis of 19,246 patients, there is clearly substantial need for OT input in cancer care. Both Neo *et al.* (326) and Hopman-Rock *et al*. (336) recommended against using selected items to assess ADL performance, due to the inability to pool data in ADL disability studies and reduction in reliability and validity. For example, Roehrig *et al*. (340) proposed a forward selection model involving six ADL items versus 18 items, drawn from the Barthel index (another common BADL scale) and Lawton's IADL scale. Outpatient-based OTs will be better placed to offer home-based interventions where specific deficits have been identified. Some patients may benefit from a needs assessment offered by social services and patients can be

advocated to self-refer for this where specific assistance needs have been identified. To better understand the predictive or optimisation power of BADL and IADL, a consideration of each commonly affected domain follows.

5.3.4.1 Personal hygiene and bathing

Personal hygiene has been demonstrated to be the first loss within BADL and therefore represents an early feature of progressive functional decline (330). Falls occurring in the bathroom have been significantly associated with hospitalisation, probably due to the number of environmental hazards (341). Bathing difficulty is a strong predictor of nursing home admission, as found in a large American database of 18,801 individuals over 50 years of age (342). Various simple aids and adaptations including bath seats, raised toilet seats, handles and rails can be installed to facilitate independence in bathing.

5.3.4.2 Walking and transfers

Locomotion is a mid-loss BADL (330) and around one in five older adults with cancer reported difficulty in getting out of a chair in one large American study, which could easily be remedied by installing chair raisers (343). Nearly two in five in the same study reported difficulty in walking and the use of a frame or other assistive walking aid could greatly improve this (343). However, this also requires environmental hazard assessment to prevent falls, which imparts the need for dedicated OTs working within cancer pathways to also undertake home visits (341). Given the possibility of elevated falls risk during cancer treatment, proactively addressing transfer needs for patients at higher risk of falling seems a necessary output of OGA.

5.3.4.3 Transportation

Transportation independence is an IADL and dependency or inability to travel is associated with several negative factors in cancer care. Transportation issues can present a barrier to receiving cancer treatment, especially those involving frequent hospital visits such as radiotherapy (344). The authors of a systematic review of OGA in radiation oncology pragmatically recommended that hypofractionation, brachytherapy, or stereotactic radiotherapy may be considered where transportation capabilities are poor (69). Transportation issues can also create financial difficulties for follow-up appointments (345), which may be unnecessary in some older adult outpatients with cancer. Information regarding financial support should be made available to patients and their caregivers (e.g., from the Macmillan website) or holistic needs assessment offered by Macmillan nurses. Consideration should also be given towards remote video consultations if possible. Transportation and

financial problems extend to family members, which can create stress for family caregivers in the context of regular hospital visits (346). Limitations in self-care have been associated with the highest risk of driving cessation (347). In the context, of a patient who does not drive and has difficulties with transportation, consideration of social support is important.

In summary, functional status factors into both the Suemoto Index (all-cause 10-year mortality) and CARG chemotherapy toxicity risk prediction models. Functional status can be extended to functional capacity and functional performance. Functional capacity can be estimated using METs, which has utility in preoperative risk stratification. Functional performance can be patient reported using adapted Lawton ADL and Katz 5-item IADL questionnaires. In the absence of clear consensus over which tools to use, these measures were chosen for their prevalence, ease of administration, suitability for patient-report and evidence for validity (where available).

5.3.5 Symptomatic enquiry

Symptomatic enquiry is common in CGA, but often neglected in OGA, probably due to this being considered a standard part of clinical care (13). Patients presenting to an outpatient clinic early in their cancer pathway may have distressing symptoms including pain, nausea and vomiting, breathlessness and bowel disturbances. In a qualitative study of patients with lung cancer, significant early symptoms were present for some time before presentation to primary care (348). Fortunately, these symptoms can be addressed with conservative and medical treatments. Given the investigative focus of early cancer care, there is the potential risk of unaddressed symptom control, patient distress and reduced quality of life (QoL). For example, the index presentation to primary care may focus on establishing the clinical grounds and counselling for initiating an urgent suspected cancer pathway. The first outpatient appointment with a specialist will also tend to focus on cancer risk assessment and investigative next steps, rather than symptom control. There may also be diffusion of responsibility as to who should manage cancer-related symptoms and/or those from other co-morbidities. The burden of symptoms, which includes the effect on daily life, decreases QoL, tends to increase with the stage of cancer and may be indicative of tumour stage (349, 350). Heterogeneously defined integrations of palliative care with oncology for symptom screening and management and early involvement have been identified in systematic reviews (351, 352), highlighting the overall drive towards better symptom management. However, the referral criteria and timing remain undefined (352).

Various cancer symptom instruments exist to assess symptoms (353), which can be incorporated into OGA to aid symptom detection and management at an early opportunity. Symptom assessment using an instrument, as opposed to traditional historical inquiry by the clinician, falls into the realm of patient reported outcome measures (PROMs). A systematic review of the routine collection of PROMs in general has demonstrated value in oncological settings, especially for identifying unrecognised needs, enhancing patient-provider communication and improving patient satisfaction (354). It could be argued that the patient reported questionnaire of the OGA is a PROM, although it is just one component of a dedicated system. PROMs are also welcomed by patients, although numerous barriers have been identified including technical and logistical issues (355).

A systematic review of cancer symptom PROMs was unable to recommend a specific tool. However, this review offered significant utility in identifying a psychometrically sound tool, validated for patient self-report with potential for digitalisation (353). Kirkova *et al*. (353) evaluated 21 instruments and recommended several instruments for initial clinical assessment of which the Memorial Symptom Assessment Scale (MSAS) fits the purposes for OGA. The MSAS has both internal validity and construct and content validity (353). Furthermore, the MSAS offers the additional benefit of being studied for proxy assessment, although further studies of the reliability for this delivery method are required (353). Although not formally addressed in prior studies, the MSAS in its original form may lack usability due to its complex layout. Digitalisation of the MSAS could help to simplify the delivery of single questions to enhance user experience. Furthermore, digitalisation enables automatic computing of scores and highlights areas of concern for the clinician to act upon.

Breathlessness should be quantified differently to other general symptoms explored in the MSAS. Breathlessness is a common and distressing symptom with widespread impact on patients and carers and presents a challenge for clinicians. The aetiology of breathlessness is most commonly from long-term cardiorespiratory disease or cancer. Despite optimal management of the underlying treatment, breathlessness can persist and cause disability, known as chronic breathlessness syndrome (356). Undiagnosed and established breathlessness can be identified and quantified using the modified Medical Research Scale breathlessness scale (357). If breathlessness is of unknown origin, preoperative echocardiography may be indicated and early review by an anaesthetist may be required (319). If breathlessness limits activity in chronic obstructive pulmonary disease (COPD), preoperative evaluation is

necessary and early referral to a respiratory consultant and anaesthetist is advised (358). Where services exist, consideration should also be given towards referral to a breathlessness service.

Although inclusion of the MSAS would be optimal, to keep the time taken to complete the questionnaire shorter, I decided to include only breathlessness. Future iterations could include the MSAS.

5.3.6 Self-reported health

A single question on self-reported health maps into the Suemoto Index (**Appendix Table 26**) for 10-year all-cause mortality. However, this question has independent value on mortality prediction. A meta-analysis revealed that compared with people reporting "excellent" self-rated health status, those reporting "good" (RR 1.23, 95% CI 1.09-1.39), "fair" (RR 1.44, 95% CI 1.21-1.71) or "poor" (RR 1.92, 95% CI 1.64-2.25) health status had higher mortality after adjustment for co-morbidities, functional status, cognitive status and depression (359).

5.3.7 Social circumstances

Social circumstances, including financial circumstances, formulates a traditionally important part of the CGA to contextualise other domains. The ASCO guidelines do not make any recommendations on use of any instruments or screening questions due to lack of evidence, although they recommend this assessment to help enable non-oncological interventions (13). The effect of adverse social circumstances on outcomes have not been highlighted in the systematic geriatric oncology literature (70). However, the significant effect of social relationships on mortality has been demonstrated in a meta-analysis for social isolation (OR 1.29, 95% CI 1.06-1.56) and living alone (OR 1.26, 95% CI 1.04-1.53) in the general population (360). Studies on social networks of community-dwelling older adults tend to demonstrate low density (i.e., actual connections divided by all possible connections), reciprocity (i.e., if X knows Y, Y knows X) and high isolation (i.e., no gain or loss of connections) (361).

Recognising the complexity and copyright issues concerning instruments assessing social circumstances, the BGS has compiled a set of important questions (362). These questions appear to map well to assessing key factors that are useful to guide cancer treatment, such as social isolation. Where social support is poor, hypofractionation, brachytherapy or stereotactic techniques can be considered for radiotherapy (363). Social isolation is variably defined, although both the structure (i.e., size and frequency of social support connections) and function (i.e., subjective quality and or perceived value) should be considered. The BGS questionnaire

on social circumstances lacks exploration of the function of social support, although a single additional question concerning sufficiency could address this. There are several questions that may not be suitable in the early phase of a cancer pathway concerning enquiry about probate and funeral care.

Social isolation is experienced by about 7-17% of older adults (364). Loneliness focusses on the emotional aspect of perceived loss of absence of social integration. Loneliness is more common than social isolation, affecting about 40% of older adults and also has a significant effect on mortality (OR 1.32, 95% CI 1.14-1.53) (360). To assess social circumstances, an adapted BGS questionnaire was utilised (**Appendix**

Table 21) adjusted for sensitivity in the OGA process and including quality of social support. A lack of social support may also be grounds for a needs assessment from social services.

5.3.8 Hearing

Nearly one third of adults 65 years and over are affected by disabling hearing loss globally (365). Hearing described as fair or worse maps into the CARG chemotherapy toxicity risk prediction score (**Appendix** Error! Reference source not found.). A systematic review found that hearing loss increases the odds of falling (OR 2.39, 95% CI 2.11-2.68), although publication bias may be evident (366). A meta-analysis of an estimated 20,264 participants found an association between age-related hearing loss and cognitive impairment (OR 2.00, 95% CI, 1.39-2.89) and dementia (OR 2.42, 95% CI, 1.24-4.72) in cross-sectional studies (367). These associations were lower in prospective cohort studies and an RCT is warranted to examine the potential benefit of intervention on cognitive outcomes. Correcting sensory deprivation is also a recognised preventative measure for postoperative delirium (368). Unaided poor hearing or inadequate aiding can be quite easily optimised before treatment.

5.3.9 Vision

Visual impairment is common and underreported in older adults and has been attributed to a range of adverse outcomes including falls, in-hospital delirium, reduced functional performance and reduced quality of life (369, 370). Community surveys indicate that the aetiology of low vision may be treatable with cataract surgery or simple refractive correction through prescription of glasses (371). The link between visual impairment and falls is paradoxical. A systematic review of RCTs undertaking falls prevention interventions in community-dwelling older adults identified that interventions to improve vision appeared to *increase* or have no effect on the risk of falls. The only evidence of benefit on all falls was for

active participants changing from multifocal to single lens glasses, in one RCT subgroup analysis (292). A meta-analysis showed that hospitalised older adults with visual impairment were at significant risk of developing delirium (OR 1.89, 95% CI 1.03-3.47), demonstrating the importance of ensuring sensory aids are available for older adult inpatients (370). Isolated or CGA-based screening of community-dwelling older adults for visual impairment using patient reported tools or visual acuity testing has not demonstrated benefit in a Cochrane systematic review of RCTs (372). Clarke *et al*. (372) concluded that this negative observation was probably due to the low uptake of interventions recommended following screening. In summary, screening for visual impairment within OGA lacks evidence and the potential risk of increasing falls through intervention is concerning, therefore visual impairment screening was not included in the patient reported questionnaire.

5.3.10 Smoking

Meta-analyses have demonstrated that active smoking status has a significant effect on postoperative delirium (OR 1.8, 95% CI 1.3-2.4), postoperative pain (OR 1.33, 95% CI 1.09-1.61) and other outcomes (**Appendix**

Table 27) (278, 305, 306). A meta-analysis of continued smoking on outcomes for patients with head and neck cancer undergoing radiotherapy showed a significant effect on mortality (RR = 1.85, 95% CI 1.55-2.21), locoregional failure (RR = 2.24, CI 1.42-3.52) and late toxicities in qualitative synthesis. A similar effect was seen in a meta-analysis of patients with localised prostate cancer where current smoking was associated with higher risk of biochemical recurrence (HR 1.40, 95% CI 1.18-1.66), metastasis (HR 1.89, 95% CI 1.37-2.60) and cancer-specific mortality (HR 1.89, 95% CI 1.37-2.60) (373). Though data were limited by indirect comparisons in a systematic review, the use of targeted therapies (erlotinib and gefitinib) and smoking was associated with higher mortality rates in non-small cell lung cancer (374). Smoking was associated with increased risk for chemotherapy-induced peripheral neuropathy, although this was based on a single study in a meta-analysis (375), and radiation pneumonitis in radiotherapy for lung cancer (376). Smoking cessation is recommended at any time and may improve post-treatment outcomes. However, a systematic review of interventions for preoperative smoking cessation found that interventions beginning 4-8 weeks preoperatively with weekly counselling and nicotine replacement therapy are more likely to improve postoperative morbidity and long-term smoking cessation (377). In summary, smoking has a significant effect on postoperative outcomes, oncological outcomes and mortality and has also

been associated with elevated adverse treatment side effects. Screening for smoking and promoting cessation is therefore an important component of the OGA.

5.3.11 Alcohol

Alcohol is significantly associated with worse postoperative outcomes (**Appendix**

Table 28) and therefore an important issue for integration within OGA (378). There are a variety of screening tools, although Alcohol Use Disorders Identification Test-C (AUDIT-C) demonstrated better detection versus the Cutting down, Annoyance by criticism, Guilty feeling, and Eye-openers screening test within OGA (379). Whilst procarbazine can interact with alcohol to cause disulfiram-like reactions (380), there is limited evidence of the effect of heavy alcohol consumption on non-surgical treatment outcomes. AUDIT-C was integrated into the patient reported OGA (**Appendix**

Table 21) and self-referral to alcohol services was recommended. However, preoperative alcohol cessation intervention should not compete with cancer treatment because there is little evidence that it improves postoperative outcomes from a recent Cochrane systematic review (381).

5.3.12 Incontinence

Urinary incontinence is common in older adults and is defined as the involuntary loss of urine (382). There are five main subtypes of urinary incontinence: stress, urgency, mixed, overflow or functional. Stress urinary incontinence is more prevalent in women and relates to urethral sphincter weakness, typically exacerbated by increased intra-abdominal pressure from sneezing of coughing (383). Urgency urinary incontinence is associated with symptoms of urgency (sudden desire to void urine which is difficult to defer). Urgency or urgency urinary incontinence are symptoms of overactive bladder syndrome, which is also associated with frequency, nocturia, depression and anxiety (384). Overflow urinary incontinence is caused by chronic urinary retention from incomplete bladder emptying and can cause continuous urinary incontinence. In men, lower urinary tract symptoms are frequently used to describe storage, voiding and post-micturition symptoms. Frequent causes are prostate pathology and overactive bladder syndrome (385). Mixed urinary incontinence may involve elements of different underlying pathologies (382). A systematic review showed that urinary incontinence is associated with increased odds of falling (OR 1.45, 95% CI 1.36-1.54), although this was only true for urge (OR 1.54, 95% CI 1.41-1.69) or mixed urinary incontinence (1.92, 95% CI 1.69-2.18), not stress urinary incontinence (386). A systematic review of screening tools for urinary

incontinence recommended the International Consultation on Incontinence Questionnaire – Urinary Incontinence Short Form (**Appendix**

Table 21) as a reliable and simple tool for both men and women. This tool has good psychometric properties and is suitable for patient-report (387).

Faecal incontinence is defined as involuntary loss of stool and affects about 15% of people aged 70 years and older and many prefer to be asked directly about faecal incontinence (388). Faecal incontinence is associated with risk of nursing home admission (389) and is commonly caused by constipation and consequent faecal impaction (390). A simple single screening question can be used to identify faecal incontinence (**Appendix**

Table 21), and then further assessment can be decided accordingly (291). In summary, whilst urinary incontinence or faecal incontinence optimisation are not necessarily going to compete with cancer targets, they are important issues for older adults that relate to other geriatric syndromes. The inclusion of incontinence screening within OGA also helps to preserve some parity with traditional CGA.

5.3.13 Spiritual needs

Spirituality can be defined as the beliefs, values, behaviours and experiences of an individual, which is related to ultimate meaning (391). Spiritual needs formulate a traditional component of CGA, although are omitted in some abbreviated OGA bundles (392). Addressing spiritual needs has been identified as an important component of comprehensive cancer care and is recommended by NICE in supportive and palliative services (391, 393). Within cancer care, spirituality can modify distress and improve patient experiences, therefore the hospital chaplaincy or spiritual care professional should be considered part of the interdisciplinary team, which could also help address psychosocial issues (391). Religiousness and spirituality have also been found to be protective in depression (394). A systematic review demonstrated the breadth of tools to undertake a spiritual assessment (395). Of those identified, the mnemonic FICA tool scored the highest and seemed most appropriate for integration into an OGA. This was based on a short time for completion (4-5 minutes), simple structure (Faith and Belief, Importance, Community and Address in Care), validation and neutral questions (395). The latter refers to the fact that OGA will operate before a serious condition has been diagnosed. The FICA tool also helps to identify social support structures, which may be an important mitigation in some treatments such as chemotherapy and radiotherapy. The FICA tool can be integrated into the OGA and patients can be offered referral to the chaplaincy or other spiritual

care professional. However, I made the decision to not include the FICA tool due to concerns over this type of questioning early in the cancer pathway and the need to manage the questionnaire length.

5.3.14 Co-morbidity

Co-morbidity, the presence of another medical condition with an index condition and multimorbidity, are common in older adults with cancer (396, 397). In the UK, 54% of the population aged over 65 years has multimorbidity, and this is expected to rise in the next 20 years, in particular for complex multi-morbidity (four or more diseases) (398). Co-morbidity adds further complexity for older adults with cancer by complicating diagnosis, optimisation, and treatment (397). Co-morbidity has been associated with increased postoperative complications, mortality and chemotherapy intolerance (66, 70). A systematic review of patients with early breast cancer found that patients with higher co-morbidity scores compared with no co-morbidity had lower odds of receiving chemotherapy (ORs 0.63-0.88), lower quality of chemotherapy and had higher odds of toxicity and hospitalisation (ORs 1.42-2.23) (399). A systematic review of colorectal cancer patients found that patients with co-morbidity had a higher risk of 30-day, overall and cancer-specific mortality compared to those without (400). Up to a 7-fold increase in mortality may be present in patients undergoing radical cystectomy for bladder cancer who have combined high-risk co-morbidity and performance scores versus those with low scores (401). A meta-analysis demonstrated that the presence of one co-morbidity or more increases the odds of neutropaenic events during chemotherapy by 54% (OR 1.54, 95% CI 1.09-2.09) (402). A systematic review of decision-making in cancer MDT meetings found that discussion of co-morbidities was limited and that some treatment decisions may be more conservative than necessary due to co-morbidity (403). The use of competing risk assessments in shared decision-making has been raised (401) and better integration of co-morbidity assessment in MDT decision-making is thought to be capable of improving outcomes for patients with co-morbidity (403).

The ASCO guidelines recommend a clinical review of co-morbidities or the use of a validated tool and placed the highest utility on the Cumulative Illness Rating Scale-Geriatrics (CIRS-G) by expert Delphi consensus (13). The choice of instrument used appears important, as associations between co-morbidity and mortality were attenuated or absent where the Charlson Co-morbidity Index was used in systematic reviews of surgical and non-surgical older adults with cancer (66, 70). However, mortality can be predicted from other indices without using lengthy and time-consuming tools such as the CIRS-G (71). To avoid duplication of effort and

potentially conflicting mortality prediction from different instruments, the use of a co-morbidity review may be reframed to focus on highlighting optimisation and competing risks early in a cancer pathway. This approach carriers more relevance towards surgery, although all patients with suspected or confirmed solid tumours should be considered surgical candidates until decided otherwise (404). A goal-orientated approach to co-morbidity assessment may highlight candidates for geriatrician evaluation to optimise multi-morbidity before any cancer treatment. Given these considerations, high-level international guidelines or systematic reviews were identified that provided recommendations for perioperative management across all major organ systems. Using this literature and that derived from expert opinion where high-level evidence or guidelines were unavailable, a Cancer Pathway Comorbidity Assessment System (CPCAS) was developed (**Appendix**

Table 29). The CPCAS was designed to further stratify risk for surgery, highlight important issues for chemotherapy and radiotherapy, and then highlight optimisation opportunities. This contrasts with the focus hitherto on using co-morbidity to predict mortality. Instead, the CPCAS becomes a 'living' tool requiring review as new evidence arises. Given the evident struggle with capturing, presenting and considering co-morbidity in the cancer MDT, a process to robustly capture significant co-morbidity holds value for assessment purposes (403).

5.3.15 Medication review

Medication review and co-morbidity assessment are an integrated process, and this viewpoint is shared in the ASCO guidelines (13). Some authors do not recognise medication and co-morbidity review as part of a GA and instead view this process as routine (68). However, in the context of multi-morbidity and polypharmacy, this opinion lacks empathy for the clinician undertaking a routine assessment in the early stages of a cancer pathway. Surgeons or oncologists are unlikely to have detailed, up-to-date knowledge of perioperative medicine or appropriate polypharmacy management. The agenda of a 2 Week Wait or first oncology appointment will rightly tend to focus on subsequent investigative or treatment steps versus medication management.

In the umbrella review of preoperative OGA undertaken by Huisman *et al*. (70), polypharmacy had no association with outcomes. A systematic review of predictors of chemotherapy intolerance did not find any association with medication use and polypharmacy does not feature in recent toxicity prediction models (e.g., CARG) (66). A large population-based study including 266,499 patients 65 years and older found increased 90-day mortality in patients with

polypharmacy (HR 1.21, 95% CI 1.14-1.27). However, frailty and co-morbidity appeared to significantly confound this finding (55). The lack of a set definition of polypharmacy is one explanation for this, where five or more medications is commonly used (405). Numerical definitions of polypharmacy may not be the best way to consider the influence of medications on outcomes. Consideration of potentially inappropriate medications (PIMs) may be more valuable, which is understudied in cancer patients (406). Polypharmacy is associated with falls in the general population, although this was not found in a systematic review of patients with cancer (407), indicating the possibility of population specific risk factors. One further consideration is that polypharmacy is not necessarily a negative marker of disease state and may be beneficial (e.g., cardiovascular disease) (408).

Given that polypharmacy has not demonstrated predictive value, the potential to optimise or simply manage medication before cancer treatment may have value. As an OGA service ideally needs to assess patients before a final treatment decision has been made, the exact treatment is unknown at the time of assessment. This makes it difficult to draw up a plan of medication changes following review without knowing the trajectory. For example, some agents such as angiotensin converting enzyme inhibitors (318) for hypertension should generally be held on the morning of surgery and some stopped five days before surgery (e.g., vitamin K antagonists), with bridging therapy accordingly (409). Further details regarding perioperative prescribing can be found in a book chapter that I co-wrote with a perioperative geriatrician (410). There is an expectation that preoperative assessment or the treating surgeon should manage these medication adjustments in many circumstances, although local protocols vary. Any modifications around the time of chemotherapy or targeted cancer therapies are highly dependent on the agent used and would in many cases be managed by the treating oncologist and/or pharmacy team. However, with the rise of oral anticancer agents for the treatment of colon, breast, gastric, ovarian and lung cancers, specific medications are associated with significant drug-drug interactions (411, 412). There may therefore be value in highlighting these interactions in accordance with the current medication list (**Appendix**

Table 30).

In the context of the OGA service, medication review towards optimisation could be considered as an isolated short-term intervention. A systematic review and meta-analysis of RCTs of isolated medication reviews demonstrated no conclusive effect on clinical, economic or QoL outcomes (413). Although Huiskes *et al*. (413) found a decrease in drug-related problems, one

important consideration is the interaction with primary care. Some drug regimens may have taken time and much trial and error to develop, including interaction with secondary care specialties. Without extensive care, there is the risk of destabilising a medication regimen that was optimised for tolerance and disease burden. Given that *management* versus optimisation aims to avoid drug-related problems, this appears to be a better strategy for OGA. Significant primary care compliance (>94%) with medication management recommendations has been identified in an audit of a UK-first, CGA-driven community service for individuals with frailty (Dr Dan Harman – personal communication). There may be value in providing medication management recommendations to primary care instead of making changes in outpatient settings.

There are several well-studied interventions to improve the appropriate use of polypharmacy in older adults. Medication appropriateness can be assessed using an implicit (judgement-based, e.g., Medical Appropriateness Index) (414) or explicit (criterion-based) tool. Popular explicit tools for PIMs include Beers criteria, which is maintained by the AGS as the AGS Beers Criteria® (415) and the Screening Tool of Older Person's Prescriptions (STOPP) criteria (416). In contrast, there are also tools to identify under-use of medications, also known as potential prescribing omissions (PPOs) and these can also be implicit or explicit. The Screening Tool to Alert doctors to the Right Treatment (START) is frequently paired with the STOPP criteria (416). However, a recent Cochrane review found limited and low-quality evidence that any of these interventions resulted in clinically significant improvement, including hospital admission, PIM reduction and quality of life. A small effect on PPO reduction was found, although this effect was limited by risk of bias (417).

In summary, the co-morbidity and medication review should be goal-orientated, utilise the CPCAS, avoid brief medication intervention and instead focus on highlighting PIMs and PPOs to primary care. Integrated assessment of co-morbidity and medication from a perioperative medicine, inappropriate polypharmacy, radiotherapy contraindications and drug-drug interactions perspective offer better value than prediction of outcomes. This makes the early but fair assumption that all suspected or confirmed solid tumours could be surgical candidates and/or suitable for curative or palliative systemic treatment.

5.3.16 Physical examination

The physical examination of traditional CGA is extensive, systematic, and traditionally undertaken by clinicians trained in general and geriatric medicine. Physical assessment can

include abdominal, cardiovascular, colorectal, neurological, podiatric, respiratory, rheumatological and vascular examinations. Given OGA may not be delivered by geriatric specialists, basic physical examinations that have a predictive role or identify optimisable pathology in the pre-treatment settings are favoured.

The MNA (**Appendix**

Table 20) requires height in kilograms and weight in meters to calculate BMI ($\frac{weight}{height^2}$) and accurate measurements are often not known by older adults. BMI is also required for calculation of the Suemoto Index (**Appendix Table 26**) and CARG chemotherapy toxicity risk prediction score (**Appendix Table 22**)**.** Uncontrolled hypertension can delay surgery and medical management should be optimised as soon as possible before elective surgery (**Appendix Table 29**) (418). Angiogenesis inhibitors (e.g., bevacizumab) are used for treatment of lung, colon and renal cell carcinoma and are associated with cancer drug-induced arterial hypertension (419). Patients with pre-existing hypertension have a higher risk of this occurring, as seen with the tyrosine kinase inhibitors sunitinib and sorafenib (420, 421). Anthracyclines and trastuzumab are associated with cardiotoxicsity and chronic heart failure, and hypertension appears to be a risk factor (422). During treatment with anthracyclines, SIOG recommend regular monitoring of ejection fraction by echocardiography in patients 70 years and older, with risk factors such as hypertension (423). Management of pre-existing hypertension is therefore recommended before chemotherapy begins (424). Measurement of BP is quick, easy and extendable to include standing BP measurement. This serves benefit in detecting orthostatic hypotension, which was positively associated with falls (OR 1.73, 95% CI 1.50-1.99) (425) and mortality (pooled HR 1.36, 95% CI 1.13-1.63) (426) in meta-analyses. Orthostatic hypotension may be treatable simply by medication adjustment. Non-pharmacological therapies are often recommended first-line, although have low-quality evidence of efficacy for treating orthostatic hypotension in a recent meta-analysis (427). Second line management options include midodrine and fludrocortisone, which again had limited and low-quality evidence in older systematic reviews (428, 429).

Given the measurement of BP at this early stage, other basic physiological parameters may be considered for their predictive utility. Heart rate variability, for example measured using the standard deviation of all normal sinus R-R intervals on an electrocardiogram or other specialised equipment, is a proxy of vagal nerve activity. Higher heart rate variability has been found in a meta-analysis to predict longer survival in patients with cancer in a meta-analysis

(HR 0.70, 95% CI 0.60-0.82). However, this is not particularly useful in the context of OGA, and studies were heterogenous, thereby limiting generalisability (430). Oxygen saturations on air measured by pulse oximetry may have value in predicting postoperative pulmonary complications along with other factors. The Assess Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) risk score (**Appendix Table 31**) was externally validated in the Prospective Evaluation of a RIsk Score for postoperative pulmonary COmPlications in Europe cohort (431). The score comprises of age in years; preoperative peripheral oxyhaemoglobin saturation measured by pulse oximetry (SpO_2) breathing air in supine position after resting one minute (or in patients on oxygen, SpO_2 after 10 min without oxygen); respiratory infection in the last month; preoperative haemoglobin concentration; surgical incision site; surgical duration in hours; and type of surgery (scheduled or emergency). Older adults undergoing elective major cancer surgery (assuming >2-3 hours surgical duration) will automatically attract a score of between 19-26, making them generally low risk at baseline. The oldest old (>80 years) are moderate risk at baseline. Those likely to be considered for thoracic or upper gastrointestinal score will automatically become moderate risk (≥26 points, 2-4 times higher risk), scoring between 34-41 without consideration of other factors. If preoperative SpO_2 is considered as well, this can then differentiate some patients into the high-risk category (≥45 points, 5 to 11 times higher risk), scoring between 42-65 points (431). Given this early predictive role of the ARISCAT score for postoperative pulmonary complications, which is augmented by knowledge of preoperative SpO_2, SpO_2 should be included within the OGA. To the best of the author's knowledge there are no data on the predictive value of outpatient respiratory rate in community-dwelling older adults.

OGA frequently includes an objective physical function (e.g., TUG test) measure, which does have predictive value (68). The TUG test is quick and easy to carry out, requires minimal training and no specialist equipment (**Figure 18**). A TUG test > 10 seconds is a recommended test for frailty endorsed by the British Geriatrics Society and demonstrates 93% sensitivity for identifying frailty (432, 433). In a multicentre, prospective study of 280 patients 70 years and older undergoing elective cancer surgery, TUG time >20 seconds was an independent predictor for major complications (OR 3.43, 95% CI 1.14-10.35) (434). The TUG test identified twice as many patients at risk of postoperative complications than American Society of Anaesthesiologists (ASA) physical status classification system (434). Soubeyran *et al*. (435) undertook a prospective, multicentre study of 348 patients and found that TUG test >20 seconds was associated with higher odds of 6-month mortality (OR 2.55, 95% CI 1.32-4.94)

after first line chemotherapy (435). An unstable or prolonged TUG test (>13.5 seconds) may be helpful to rule in a higher falls risk, with higher pre-test probability, although TUG test is not a significant predictor of falls (436). TUG test may therefore help guide the need for peri-treatment physical therapy assessment for strengthening exercises and promote discussion of home safety regarding falls risk in the post-treatment period (437). In summary the minimal physical components of an OGA should comprise of height and weight (to calculate BMI); supine, lying and three-minute standing BP; SpO_2 on air; and the TUG test.

1. The patient begins by sitting back in a standard armchair in an area with sufficient clear space
2. A line 3 meters away is marked on the floor
3. The time it takes for the patient to stand up from the chair, walk to the line at a normal pace (walking aids are permitted), turn around, walk back to the chair and sit down again is measured.

Figure 18 – The Timed-Up and Go test.
The Timed-Up and Go test is quick and easy to carry out consisting of three steps.

5.3.17 Targeted investigations

5.3.17.1 Vitamin D deficiency

Vitamin D is essential for musculoskeletal health, both through promoting gut absorption of calcium and phosphorus and enabling mineralisation of new osteoid tissue in bones (438). Vitamin D has two main forms: vitamin D_3 (cholecalciferol) and vitamin D_2 (ergocalciferol). Light (natural or artificial) containing ultraviolet B radiation acts on 7-dehydrocholesterol within the skin to synthesise vitamin D_3 (438). Both forms of vitamin D forms can be obtained from some natural foods (e.g., oily fish), fortified foods (e.g., fat spreads) and supplements. The liver converts vitamin D into 25-hydroxyvitamin D (25[OH]D), and then the kidneys and other tissues convert this to the biological active metabolite 1,25-hydroxyvitamin D (1,25[OH]2D). Parathyroid hormone regulates 1,25[OH]2D production via the kidneys. Serum 25[OH]D is the best measure of vitamin D availability (438).

Older adults are at higher risk of vitamin D deficiency (hypovitaminosis D) due to age-related effects on vitamin D metabolism and less exposure to sunlight, which mainly leads to musculoskeletal complications including osteomalacia (439). Osteomalacia results from osteoclastic breakdown of bone to raised serum calcium levels, which can progress or augment osteopenia and osteoporosis (440). Less severe hypovitaminosis D or vitamin D insufficiency can also led to hypocalcaemia, secondary hyperparathyroidism, bone loss, muscles weakness, falls and fragility fractures (440). Evidence is not robust enough to confirm the role of

hypovitaminosis D on non-musculoskeletal complications (438). A systematic review of meta-analyses and RCTs on vitamin D supplementation and non-skeletal disorders found that data on improving cancer outcomes were scarce, although supplementation may augment resistance to acute infections (441).

The new advice from Public Health England based on the Scientific Advisory Committee on Nutrition 2016 report (438) is that the *general adult population* are recommended to take a daily supplement containing 400 international units (IU) of vitamin D throughout the year to ensure that 97.5% of the population can maintain a serum 25(OH)D concentration ≥ 25 nmol/L when UVB sunshine exposure is minimal. There are no specific population-level recommendations for older adults (65 years and over). Testing is recommended by major guidelines based on risk of vitamin D deficiency and likely benefit of treatment (438, 440, 442). The TUG test would be an ideal opportunity to identify symptoms of osteomalacia and other domains of the OGA will identify risk factors. Hypovitaminosis D is diagnosed when serum 25[OH]D levels are less than 25 nmol/L (438). Following biochemical confirmation of hypovitaminosis D, other investigations may be relevant, although these may be more appropriately arranged from primary care. Treatment of hypovitaminosis D is recommended with a fixed loading dose of vitamin D (up to about 300,000 IU), split daily or weekly, followed by lifelong maintenance treatment of about 800 IU a day. Treatment of vitamin D insufficiency is recommended in multiple scenarios () and involves lifelong maintenance with 800 IU a day without loading (438, 440, 442). In all other circumstances, alternative diagnoses should be considered for symptoms mimicking osteomalacia and preventative measures including vitamin D supplementation and adequate calcium intake should be recommended (443).

5.3.17.2 Other blood tests

In patients with a new diagnosis of MCI or suspected dementia, laboratory tests (e.g., serum B12) are recommended to identify reversible causes, and may be required by local guidelines before referral to a memory assessment service (444, 445). Although some patients may have had recent basic laboratory haematological or biochemical blood tests for other reasons, others may require a full blood count and renal profile to complete the CARG chemotherapy toxicity tool (**Appendix Table 22**). Given that patients are seen early in a cancer pathway before diagnosis or treatment planning, a shared decision-making discussion is necessary to explain that blood tests can be offered for predictive purposes, although may not be required. Finally, some patients may have anaemia of unknown aetiology, or this may be identified from new laboratory tests. In this situation an anaemia screen should be arranged depending on the

haematological indices, including serum ferritin, B_{12} and folate levels (446), replacement of which can be managed in primary care. Based on established guidelines, unless unexplained iron deficiency anaemia is the reason for cancer pathway initiation, all patients using the OGA service should be referred by their GP using a suspected cancer pathway for consideration of endoscopic investigation for occult gastrointestinal bleeding (447). Female patients with post-menopausal bleeding should be referred to gynaecology using a suspected cancer pathway, given that 91% of cases of endometrial cancer present with this symptom (448).

5.3.17.3 Other point-of-care tests

Consideration should also be given to the utility of common point-of-care tests within OGA. Urinalysis using urinary dipsticks is a simple point-of-care test often recommended within traditional CGA bundles for case-finding among patients who are not under investigation for genitourinary symptoms. Screening can identify abnormalities such as microscopic haematuria or proteinuria that can lead to investigations for serious diagnoses such as bladder cancer or chronic kidney disease. A Cochrane systematic review was unable to find any RCTs or other studies that adequately assessed the benefits (i.e., earlier detection and improved prognosis) or harms (i.e., unnecessary and costly investigations or treatments) of routine urinalysis for screening purposes (449). In summary, given the lack of evidence and need to ensure the OGA process is lean, and each component offers value, routine point-of-care urinalysis should not be offered.

5.3.18 Risk computation

5.3.18.1 Overview

The data collected in the cognitive screen, patient reported questionnaire, co-morbidity review and physical examination can all be utilised for risk computation. Several validated risk scores that have been previously discussed can be used to predict 10-year non-cancer mortality (Suemoto Index; **Appendix Table 26**), chemotherapy toxicity (CARG score; **Appendix Table 22** and postoperative pulmonary complications (ARISCAT score, **Appendix Table 31**).

5.3.18.2 Life-expectancy

There are alternative personalised life-expectancy calculators to the Suemoto Index, including the Gagne index (1 year), Lee Index (4 and 10 years), Schonberg index (5, 9 and 14 years) (450). However, these calculators are validated on data from USA populations and thus their generalisability to other populations are doubted. The Suemoto Index was developed using data captured from 35,367 community-dwelling adults in five global longitudinal studies: Survey

on Health, Ageing and Retirement in Europe, Brazilian Sao Paulo Survey on Health, Well-being and Ageing, Mexican Health and Ageing Study, US Health and Retirement Study and English Longitudinal Study of Ageing (ELSA) over a median of 8.6 years (71). Ten-year non-cancer mortality form the Suemoto Index can be subsequently judged against predicted 1-, 5- or 10-year mortality of the cancer itself at the population-level (451), although the cancer MDT will have staging and grading information to estimate cancer survival more accurately (242). In the testing dataset (one third of participants), the c-statistic was 0.76, which means that the Suemoto Index could discriminate those participants who died versus those who lived 76% of the time.

In the context of incurable disease, clinical prediction of prognosis tends to overestimate survival, with an accuracy within four weeks in just 61% of cases (452). The Palliative Prognostic Index (PPI) was developed to predict survival in the context of terminal cancer among 245 patients (mean age of 66 years) with an expected survival of six months of greater. The variables included within the PPI are the palliative performance scale, oral intake and three disease-related symptoms: oedema, dyspnoea at rest and delirium. A PPI score of >4 predicts 6-week survival with 80% sensitivity and 77% specificity. A PPI score of >6 predicts 3-week survival with 80% sensitivity and 85% specificity (453). In the context of palliative radiotherapy, a further tool can be used to help decide on the benefits, harms and burdens of radiotherapy. The number of risk factors tool was developed to predict life expectancy for older adults (median age 68 years) referred to radiation oncology for palliative radiotherapy and consists of three risk factors: primary cancer site (breast versus non-breast), site of metastases (bone-only versus other) and the Karnofsky performance score (>60 or ≤60). One, two and three risk factors predict median survival of 60 weeks, 26 weeks and 9 weeks respectively (454).

5.3.18.3 Frailty and lifestyle factors

The identification of frailty can be made from the presence of two or more OGA domain impairments and/or using the CFS (**Appendix Figure 51**). The presence of frailty conveys significant risk for adverse postoperative outcomes (**Table 1**), as does preoperative smoking (**Appendix**

Table 27 **26**) and heavy alcohol consumption (**Appendix Table 28).** Decision-making that includes surgery as an option can be supported by risk prediction of short-term mortality, major adverse cardiac events (MACEs) and post-operative delirium. The National Confidential

Enquiry into PeriOperative Death (NCEPOD) Surgical Outcome Risk Tool (SORT) was developed and internally validated using prospective data from 16,788 UK patients undergoing non-cardiac, non-neurological inpatient surgery (455). The SORT tool predicts 30-day postoperative mortality. A validated risk-predicting tool is also recommended to predict risk of a perioperative MACE (30-day risk of death, myocardial infarction or cardiac arrest) in patients undergoing noncardiac surgery (319). The Revised Cardiac Risk Index (RCRI, **Appendix Table 32)** has been selected as it is easy to calculate and is suitable for use outside of its original cohort, having undergone external validation (319, 456). A recent systematic review continues to place value in its utility (457). The risk of a MACE without any factors is 3.9% (95% CI: 2.8-5.4%) for patients aged 45 years and over who are undergoing elective non-cardiac surgery. Postoperative delirium occurs in around 18% of patients (278). A postoperative delirium risk assessment (**Appendix Table 33**) can be made based on the findings of a recent systematic review and meta-analyses (278, 458). The medical risks of surgery are frequently neglected from surgical consent, however there are now medicolegal requirements for these to be discussed (see **Section 1.4.6**).

5.3.19 Brief intervention and referral generation

Following risk computation, referrals can be generated based on impaired domains and co-morbidity and medication review using CPCAS (**Appendix able 29**). However, the referrals generated will depend on what stage of the cancer pathway (**Figure 4**) a patient is within at the time of OGA. For example, referrals for preoperative co-morbidity optimisation before shared decision-making are not appropriate, given surgery may not be the desired or appropriate options. In contrast, brief intervention and/or referral to dietetics for malnutrition is appropriate, regardless of diagnosis or treatment options (459). Referrals are locally governed, protocolised and dictated by availability and capacity (**Table 8**). A previous Delphi consensus of geriatric oncology experts provided data on how to map domain impairments to process options (460), although outside of research some referrals may not be appropriate locally due to capacity and funding limitations. Magnuson *et al*. (461) undertook a pilot RCT of OGA-driven geriatric interventions versus usual care of 63 patients analysed with follow-up data. Uptake of 409 recommended interventions to the primary oncologists was poor (35.4%) and those implemented were mostly oncology-based or logistically more feasible. Although this study demonstrated the feasibility of algorithm-based or protocolised OGA, there was no difference in grade 3-5 chemotherapy toxicity incidence, hospitalisation, dose reductions, dose

delays or early treatment discontinuation between intervention and control arm. There were significant methodological limitations including insufficient power, observer bias from non-cluster design, imbalance in baseline vulnerability in the intervention arm and low fidelity of recommended intervention implementation (461). This study gives further support to the importance of developing alternative OGA delivery models to abstract the burden of assessment, referral generation and brief intervention from the primary surgeon or oncologist.

Brief interventions can include the provision of written and/or verbal advice (where formal referral is not indicated or limited by local capacity issues) and suggestions for additional council or privately funded services. Dietary advice is recommended by NICE based on a Cochrane review of RCTs that found that dietary advice with or without oral nutritional supplements appeared to improve weight, body composition and grip strength, but not survival (462). Dietary advice focuses on encouraging the consumption of calorific and nutrition-rich foods (e.g., cheese) to increase energy and protein intake without increased the volume of food. Nationally developed and local leaflets are easily available for patients to take away. Snacking and frequent smaller meals are also encouraged, and other factors can also be considered such as food preparation barriers and swallowing disorders (463). Certain indications for patients with cancer-related malnutrition (e.g., cachexia), dysphagia or pre-operative preparation for undernourishment are prescribable indications for oral nutritional supplementation (ONS), in addition to diet (464). ONS is available, both prescribable and over the counter, in a range of nutritional profiles, flavours, thicknesses and can be flexibly used with diet. NICE endorse a comprehensive guide to managing adult malnutrition in the community based on a traffic light system and the Malnutrition Universal Screening Tool, which maps well to data from the MNA (465).

There are well-established services that may be suggested for older adults who live alone, including: i) personal emergency response systems (PERS); and ii) Meals-On-Wheels. PERS can be used to get immediate assistance following a serious home-based accident, such as a fall, or worsening of a chronic condition, to prevent emergency department admission due to delayed response (466, 467). The most frequent configuration of PERS is a bracelet or pendant wearable device with a help button. Depressing the help button activates a system installed within the home using the landline telephone to connect to a call-centre operating 24/7. A call handler can either contact an informal carer (e.g., family) or emergency services depending on the context of the call for assistance (467). Qualitative studies reveal the value to older adults living alone, such as handling a situation where they need help quickly (468), feelings of

reassurance and interconnectedness (469). Surveys suggest high levels of satisfaction with the service (470), although there is also evidence of non-use and feeling of irrelevance in older adults (469, 471). Some councils may fund or discount basic systems, but where spending is required outside of the NHS or social services, this decision can be left to the patient with support from others.

Home-delivered meal services (colloquially called Meals-On-Wheels) are privately run businesses that enables customers to have a meal delivered to their home. Some councils may fund this service, although this is declining with budget cuts to adult social services. Systematic reviews have demonstrated evidence of benefit from Meals-On-Wheels for older adults' nutritional status, in terms of increasing total daily energy intake, protein and calcium consumption (472-474). Meals-On-Wheels was used as a recommended intervention in the RCT by Magnuson *et al*. (461), although services such as this and PERS were less frequently implemented by oncologists.

In summary, referrals based on OGA findings were made flexibly depending on local capacity and individual needs. Brief interventions such as dietary advice are beneficial when access to dietetics is limited. Suggestions can be made for services that are council- and/or privately funded and patients can self-refer to local psychological, drug, alcohol and smoking cessation services. Recommendations were also made to primary care via a patient's GP.

Referral	**Criteria**
Alcohol Services	Advised for patients who abuse or are dependent on alcohol. This tends to be self-referral.
Audiology	This can be a self-referral for existing hearing aid users or a new referral from primary or secondary/tertiary care.
Dietetics	Malnutrition identified on Mini Nutritional Assessment
Falls Clinic	In general, all patients with an unexplained fall in the last 6 months who have not recently attended or scheduled.
Geriatric Medicine	Complex multimorbidity and polypharmacy. Referrals will join the general outpatient waiting list if no fast-track geriatric liaison services exist.
Memory assessment service (memory clinic or community mental health team)	Evidence of mild cognitive impairment or clinical suspicion of dementia (undiagnosed) requires a single point of referral as per NICE guidelines (274). May be subject to long waits for an appointment.
Occupational Therapy[1]	Impairments in ADL or IADLs, although outpatient therapy services may not exist.

Pharmacy	Polypharmacy, anticancer therapy initiation or radiotherapy. Outpatient pharmacy review is not common outside of research scenarios and a systematic review has not demonstrated robust impact on medication-related outcomes (475).
Physiotherapy	Evidence justifies referral for preoperative exercise-based intervention prior to lung resection in lung cancer as it reduces postoperative complications (RR = 0.45, 95% CI 0.28-0.74) and hospital length of stay in days (mean difference 4.83, 95% CI 3.7-5.9) (476). Outside of a trial this may not be funded locally.
Mental health services[2]	Suspicion of depressive or other mental health disorder.
Smoking Cessation	Advised for patients who are active smokers regardless of diagnosis or treatment. This tends to be self-referral.
Social Services[1]	Impairments in ADL or IADLs. Patients can self-refer for this and can be given support to do this if necessary.

Table 8 – Referral criteria following oncogeriatric assessment.
Referral criteria are locally determined and variable. Broad criteria are outlined above as a guide. Considerable flexibility is required for external referrals and long delays to be seen should be expected. [1]Overlap exists between the outcome of a needs assessment from social services, which may include domiciliary occupational therapy input, and hospital occupational therapy services. Where outpatient occupational therapy does not exist/have capacity, social services can be used instead. [2]Mental health services are regionally variable. Some oncology centers and primary care groups may offer self-referral mental health and wellbeing services. Otherwise, a referral from primary care is required. Local psychological therapies services may also be offered as part of the Improving Access to Psychological Therapies programme. Abbreviations: NICE = National Institute for Health and Care Excellence; ADL = activities of daily living, IADL = instrumental activities of daily living.

5.3.20 Risk stratification and summarisation

Once all risks have been computed and decisions regarding referrals have been made, a process of risk stratification and summarisation follows. Multiclass systems have been used for risk stratification, classically using three groups: fit, vulnerable and frail (477-479). These systems are based on clinical expertise and consensus opinion, and all agree that fit patients can receive standard cancer treatment. Vulnerable patients are thought to derive benefit from treatment after optimisation or receipt of modified treatment. Frail patients have been thought to only derive benefit from palliative care (480), although the SIOG working group for the management of prostate cancer recommended adapted treatment in this group (478). Excluding frail patients from surgery is not appropriate, as frailty was an inclusion criterion in a recent RCT of colorectal cancer patients undergoing surgery (109). Other studies have grouped vulnerable and fit patient into a 'non-frail' or 'fit' group (binary classification) with worse survival and treatment response or withdrawal rates in the frail groups (481-483).

Ferrat *et al*. (484) used latent class analysis to combine OGA components into four health profiles: relatively healthy, malnourished, cognitive and mood impaired and globally impaired. When compared to other classes, global impairment was associated with 1-year mortality and the receipt of palliative treatment. This same group compared the prognostic performance of

four different classification methods (binary and multiclass) and found poor to moderate agreement between them, although 1-year mortality was best predicted using the four-class system (485). Predictive performance for 6-month unscheduled admission was similar between the different classification systems. However, classification bias and lack of data on chemotherapy toxicity limited the study and this RCT did not assess the impact of following classification systems on decision-making, morbidity or mortality (485).

I initially developed a new three-class risk stratification system based on a traffic light system with red (high risk), amber (intermediate risk) and green (low risk) classes. Traffic light systems are frequently used in medical practice as an explicit method of stratifying risk, as found in the NICE guidelines for feverish illness in children (486). A traffic light system maps well to the three-class 'fit', 'vulnerable' or 'frail' system. However, given that frailty was an inclusion criterion of a recent RCT of surgical patients (109), we argue that frailty on its own should be mapped to an intermediate risk category. Green represents 'fit' or non-frail, as a clear indicator of low risk, whereby an older adult should be treated like a younger counterpart, regardless of chronological age. I reserved the highest risk category and use 'red' as a signal that a particular *curative* cancer treatment should be delayed, or best supportive care is more appropriate. Red is used for patients who have expressed an early wish for best supportive care with mental capacity, or through a valid legal instrument without mental capacity. Red is also used where surgery should be delayed in the context of severe recent morbidity, such as stroke or percutaneous coronary intervention with a drug-eluting stent in the past three months. This is a shared and MDT decision, although an appropriately salient signal is required to emphasise the seriousness of a co-morbidity. In the context of older adults, there are few absolute contraindications to chemotherapy, radiotherapy, targeted cancer therapies or immunotherapy. Where these exist, they are agent-specific, and these nuances are handled by the treating oncologist in downstream decision-making. Amber is consequently a broad category for all patients, representing various degrees of vulnerability or frailty and is intended to highlight a need for discussion and shared decision-making. The CFS was proposed to represent the spectrum of fitness, vulnerability and frailty pictorially and categorically in a conceptually clear way, across different clinicians.

However, when the traffic light system was proposed to clinicians from a head and neck cancer MDT, many concerns were raised. These included the need to show the result of a 'red light' to a patient and consequently creating anxiety over treatment outcomes. Furthermore, an amber prediction creates a 'grey-area', where there is uncertainty about how best to manage patients.

There were also questions regarding how much time and resources should be allocated to investigating patients with amber predictions to determine if they tend towards fitness or frailty. For this reason, the focus pivoted to providing the summarised predictions for surgical outcomes and chemotherapy toxicity.

Incorporating raw data from the OGA into a cancer MDT meeting or shared decision-making discussion is not appropriate. This is due both to the large number of discussions that must take place in a set timeframe and the unfair expectation of non-geriatric trained professionals to interpret OGA data. All data were provided to the MDT via a document uploaded to the EHR. Additional more detailed considerations and recommendations can be contained within the same document and accessed later in the cancer pathway.

5.3.21 Communication

The OGA generated several communication outputs: i) immediate patient feedback; ii) summary to the relevant cancer MDT; iii) detailed report of findings to be placed on the EHR/medical record; iv) a letter to the patient's general practitioner (GP). Immediate patient feedback was important because poor professional communication was identified as a barrier to shared decision-making in oncology (487). In an RCT involving 286 patients with cancer, electronic patient reported HRQoL measurement was undertaken in outpatient clinics with or without feedback. A control group received no HRQOL measurement before a clinical encounter. In the group who received feedback on their HRQOL measures a significant positive effect on emotional well-being, HRQOL scores and the liberation of clinical conversations (488). Given the apparent benefit of feedback, patients were informed immediately after the OGA about what referrals are recommended and given an overall summary of their biopsychosocial health. Cancer-related prognostic, investigative or treatment discussions did not take place at this stage, as this was for the cancer MDT to discuss with the patient. The summary (and more detailed report) described in **Section 4.2.2** was uploaded to the EHR for use in the MDT. As a matter of good clinical practice, the patient's GP was sent a summary of the OGA findings, along with any recommendations for referrals or medication changes to be initiated from primary care.

The use of ORs and RRs are useful in predictive outcomes as they help to support statements about predictive outcomes and associations with single value quantifiable data, wherever possible derived from the highest level of evidence. However, these statistical reporting measures can be challenging to convey and are frequently misunderstood by both patients and

doctors. They are also frequently misused (489). OR measures the association between an exposure and an outcome, expressed as the odds for that outcome occurring, against those in the absence of the exposure (490). The precision (but not the significance) of the OR can be estimated using a 95% CI, with large CIs representing low precision and vice versa (490). Meta-analyses commonly report the OR where regression models are used, which is calculated as the confusion matrix (*ad/bc)* where the exposure either causes an outcome (*a*) or no outcome (*c*) and the control group either has the same outcome (*b*) or no outcome (*d*) (491). Where multiple ORs interact, the additive biological and statistical effects can be difficult to calculate, unless ORs can be reliably converted to RRs (492). The RR is easier to convey in terms of 'risk' versus 'odds' and many people have an intuitive grasp of risk. The RR (also called risk ratio) is calculated as the ratio of the risks in two groups: exposure and control. ORs cannot be approximated well to the RR when the initial risk (which is the prevalence of the outcome) is high (489). When using the RR, the absolute risk can be calculated, which is easier to understand. The absolute risk requires the prevalence of the outcome to be known and can be expressed with a common denominator (e.g., X in 100 people) further using an infographic to visualise these statistics better. Considering this issue with the way ORs are presented and the need to graphically represent RRs using absolute risk, it is perhaps more useful to uniformally report the benefits and harms of a treatment to patients, as found in many NHS leaflets.

5.3.22 Customer discovery

The business model canvas is presented in **Table 9**. The value propositions map to the cost-consequences of the OGA, outlined in

Table 4. The customer discovery process highlighted that the primary customer from a business perspective is the unitised cancer MDT, as they work in consensus. Other customer segments include working with geriatricians, either through referrals and inter-departmental networking or more formal planned activity commitments. Allied health professionals also need to be engaged through agreed referral scope or direct integration into the service, possibly as leaders of the service. Finally, senior cancer business managers are customers as a budget will need to be agreed for operations. From an operational perspective the primary customers are the patients (and their carers as a dyad). The dyadic relationship is important in the use of technology in cancer care (493). The customer relationships mainly refer to operations in this context, whereby patients (and their carers) can be engaged through face-to-face, telephone, automated or individualised virtual assessments, depending on their digital accessibility and preferences. Distribution channels are those for patients to use the digitalised OGA service

(e.g., via the hospital website), distribute research/implementation knowledge (e.g., conferences) or commercial marketing (e.g., other hospitals). The key partners, activities, and resources (discussed in detail in prior sections of this chapter) consider both initial focusses, but also longer-term strategy. Interestingly, *IBM®* offer an oncology MDT solution (*IBM® Watson Health for Oncology*), however, it does not currently offer OGA functionality out-of-the-box and bespoke customisation is expensive. Costs can be derived from the unit costs outlined in **Appendix Table 18** and the overall INHB calculated in

Table 6. An additional costing structure may apply if the software required was engineered in-house or outsourced to a developer, as **Chapter 4** assumes purchasing software-as-a-service. Revenue streams include the opportunities for health organisations to receive funding streams for new innovations and commercialise their own innovations. The latter is similar to how Somerset NHS Foundation Trust developed and commercialised their Somerset Cancer Registry (494).

Key partners	Key activities	Value proposition	Customer relationships	Customer segments
Hospital digital services **Freelance software engineer, technology company or university computer science department** **Strategic partner (e.g., *IBM*® offer a Watson Health for Oncology product)** **Clinical coding department** **Hospital governance department** **Patient and public involvement group**	**Software development** **Questionnaire approval** **Embedding into practice** **Integration with existing electronic health record** **Clinical safety process** **Explore software as a medical device certification**	**Prediction of adverse outcomes to assist shared decision-making** **Improved data on risk/benefit ratio for informed consent** **Opportunity to undertake holistic optimisation prior to treatment** **Identification of candidates for surgical or chemotherapy prehabilitation** **Recognising and fulfilling unmet needs** **Improved patient and caregiver satisfaction with communication** **Mitigation of medico-legal risk** **Improved quality of life in geriatric specific domains** **Reduced early treatment discontinuation** **Reduced chemotherapy treatment modification** **Increased advanced directive completion** **Big data collection for research and development** **Potential positive effects on a range of outcomes, which are centre dependent** **May be cost-effective with correct implementation configuration**	**Some patients require telephone or face-to-face support to undertake oncogeriatric assessment** **Some patient/carer dyads can undertake oncogeriatric assessment during an outpatient visit** **Patient/carer dyads with technological accessibility can have an automated experience, initially via SMS, email or letter**	**Patients and their family/caregivers as a dyad** **Cancer multidisciplinary teams as a unit** **Geriatricians/oncogeriatrics** **Allied health professionals** **Senior cancer service managers**
Key resources			**Distribution channels**	
World literature **Hospital guidelines** **Cancer guidelines** **Perioperative guidelines** **Geriatric medicine guidelines**			**NHS England Clinical Entrepreneur programme** **Hospital website and social media** **App stores** **Hull York Medical School or other academic institutions** **Cancer/technology meetings/conferences** **Patient groups** **Appointment letters**	

Cost structure		Revenue streams
Cloud hosting provision **Software engineering** **Penetration testing**	**Additional referrals to other services** **Some geriatrician planned activities** **Band 6 nurse to operate service**	**Resale of software-as-a-service to other institutions** **Government innovation funding** **Pharmaceutical industry funding**

Table 9 – Business model canvas for OGA service.
Abbreviations: IBM® – International Business Machines Corporation; NHS – National Health Service.

5.3.23 Normalisation process theory

NPT was used in the initial design of the OGA service (**Appendix Table 32**) based on an existing framework (271). In the development evaluation, through consultation with key stakeholders, it became apparent that referrals to some allied health professional teams, including physiotherapy, OT, dietetics and falls clinic would not be practical. This was due to the pre-existing capacity of those services being limited and the fear of raising patient expectations of receiving a referral from these teams, and then this not being fulfilled before cancer treatment. However, there were still other useful referral options available and the OGA service still had a core purpose to provide predictive assessment. The OGA service served as an opportunity to collect business intelligence towards generation of cases for funding priorities, and then staff recruitment to fulfil unmet service needs. Instead of becoming an implementation barrier, this was turned into a QI opportunity.

When design theory was considered, empathy was considered for both the MDT members and their patients. The MDT members, especially medical professionals, have limited consultation time with patients and therefore must prioritise the biomedical model with little time even for complete co-morbidity or medication review. Patients are frequently referred to them along 2 Week Wait pathways and the focus of the consultation is naturally towards investigative management. MDT meetings tend to be long with 30-40 patients to discuss and (often overbooked) outpatient clinics either side. Breaking bad news and shared decision-making often follow on from each other, sometimes straight after an MDT meeting. Outpatient clinics have often been operating in one way for many years and radical changes to their operation are difficult to implement. There is unfortunately little time to consider OGA within MDT meetings or consultations. MDT members are not trained in geriatric medicine, but are facing increasing numbers of complex, older adults. For OGA to be integrated into the MDT, its data needs intense summarisation. Furthermore, the information needs to be accessible so it can be understood by other MDT members, including nurses and allied health professionals. The recommendations made from OGA cannot simply be fed back into the MDT or to the specialist. The OGA recommendations need to be arranged as part of the service to prevent the adherence issues demonstrated in other implementation studies (102). In summary, the key pain points for MDT members are the need to abstract the burden of undertaking OGA away from them, the summarisation and accessibility of OGA data and the autonomy of the OGA service to make referrals.

The burden of appointments for patients within the cancer pathway needs to be kept minimal and the OGA service was flexible enough to avoid conflict with investigative appointments (e.g., radiology, endoscopy or day case procedure). The OGA service had to operate in the window before the main MDT discussion meeting (**Figure 4**) and be sensitive to the uncertainty of this time for patients. However, the identification of vulnerabilities of older adults in urgent outpatient settings still holds significant healthcare value and is an interesting model within itself.

5.3.24 Impact of COVID-19

The COVID-19 pandemic significantly interrupted the OGA service provision, firstly by prompting the suspension of recruitment to the research studies in March 2020 and secondly by suspending the service. The former was to prioritise research studies focussing on COVID-19 and increase healthcare staff availability. The latter was due to my redeployment to clinical practice for three months full-time, and then three months less-than-full-time. In September 2020, the service and associated research studies were resumed, although recruitment was significantly affected through decreased patient numbers presenting to cancer services and the need to maintain COVID-19 safety. The OGA service operated in a telephone-only approach and data collection using the tablet device was no longer possible. There was insufficient time to redesign the service to operate remotely using a web application and to enable patients to undertake the assessment on their own devices. In December 2020, study recruitment and the OGA service were again suspended during the second wave to reprioritise the NHS COVID-19 response. Consequently, it was not possible to resume the service in its original form and a decision was made to sunset the OGA service. However, progress was made with integrating with a consultant-led oncogeriatric liaison service, so study recruitment for in-depth interviews (not reported in this thesis) remained open, although the focus shifted towards inpatient service provision. Future plans include the operationalisation of an outpatient focus for the consultant-led oncogeriatric service.

5.3.25 Summary of main findings

A new, digital-first OGA service was developed and operationalised in a tertiary NHS cancer centre. This employed the development of a patient reported questionnaire suitable for administration on a tablet device. The questionnaire mapped to numerous existing predictive models and includes instruments selected on their diagnostic accuracy, value towards prediction and/or optimisation, and their suitability for patient-reporting. The OGA service was successfully operationalised and used by NHS patients (see **Chapter 6**). A mid-level and a

grand theoretical consideration were utilised, including a baseline appraisal using NPT, and CAS theory to contextualise the wider system development considerations. A comprehensive narrative synthesis and discussion of individual OGA component was undertaken using high level evidence wherever possible. This showed the importance of balancing diagnostic accuracy against extrinsic value and implementation factor during instrument or question selection. Numerous key stakeholders were consulted throughout the process, which culminated in extensive feedback. Important findings included the issues created by onwards referral to other healthcare professionals or services from realising unmet needs. Many services are already at maximum capacity and the potential extra caseload generated from an OGA services needs to be carefully considered. However, the OGA service can generate the data required to create business cases for service expansion. Finally, the way information is conveyed to the MDT and patient needs careful consideration. Predictive data should be conveyed to the MDT first so this can be contextualised with cancer treatment decision-making. However, information relating to optimisation of existing health conditions should be conveyed to the patient first so that they understand the reason for recommendations and potential referrals.

5.3.26 Comparison to previous studies

The inability to refer to OT and physiotherapy, either as a pre-treatment intervention for specific vulnerabilities, opportunity for prehabilitation or through falls clinic, re-emphasised the assessment value of OGA. Outpatient OT and physiotherapy services for older adults were recently subject to an RCT. Pergolotti *et al*. (495) evaluated 45 older adults (median age 74 years) with a recent diagnosis or recurrence of cancer within 5 years. Although intervention with OT/physiotherapy improved activity expectations and self-efficacy, no significant effect was seen on functional status, global mental health, or ability to participate in social roles. The timing of the intervention was likely an issue in this study where 65% of participants were in active treatment. Whilst empowering patients towards activity, treatment-related effects (e.g., fatigue) likely confounded the results. Significant implementation barriers were also evident, including recruitment and access to treatments. **Chapter 4** showed that GA can be cost-effective with the right implementation configuration, and especially when utilised as a preoperative optimisation intervention. This supports the notion of bringing forward therapy involvement earlier in the cancer pathway.

The notion of risk-taking in decision-making has been researched from a business perspective previously. Diamandis and Kotler (496) discuss findings from neuroeconomics in their book

Abundance: The Future Is Better Than You Think. Two forms of mindset regarding risk are propagated, those fearful of mistakes and those fearful of losing opportunities. The former tends towards incremental progress, whereas the latter is typical of entrepreneurs with an exponential mindset. The process of implementing the OGA service was driven by opportunity (the correct setting, person and timing), iterative thinking (overcoming barriers, including technology, stakeholders' concerns and research design) and intrapreneurialism (the risk-taking mentality to capitalise on an opportunity *within* an organisation). Medicine is a risk aversive discipline; however, it is also decorated with many intrapreneurs. For example, Professor Barry Marshall whose self-experimentation with *Helicobacter pylori* enabled the discovery of the causative effect of the same pathogen in peptic ulcer disease (497). The overlap between implementation science and intrapreneurialism is a potential area for further research.

Implementation and improvement science also interlap with change management. With healthcare moving away from top-down change processes and the recognition of CAS theory in explaining the numerous factors determining change failure, change management is often used as a guiding principle rather than prescribed (498). Whilst the development of the OGA service did not formally use change management, it resonates with several components of Kotter's 8 step model of change, one of the most frequently used models of change management (498) in healthcare. The embodiment of a research project within the change process aided expedition of change by creating urgency, with some clinicians viewing it as important to me personally to rapidly enact the OGA service. Building on short term wins was also possible, as I was able to operate the service independently and integrate into clinics and healthcare settings rapidly. A recent systematic review of change management models in healthcare (498), found that an enabling culture had elements of authentic leadership, including engaged staff, MDT involvement and conflict resolution. All these characteristics were present when developing the OGA service.

5.3.27 Strengths

The strengths of this research include the effort in creating a digital-first OGA service, which was novel within the NHS and in keeping with the NHS Long Term Plan (252). I made extensive use of theory, which is recommended by the Medical Research Council in the design of complex interventions (270). The use of a both a mid-level and grand theory enabled me to reconsider both low- and high-level assumptions and provides a basis for further implementation research. The extensive key stakeholder involvement was made possible by

avoiding the formality of qualitative research and instead focussing on the clinical priorities. The OGA service resumed the conversation and indirectly promoted the opportunity for integration with a new consultant-led oncogeriatric liaison service with future potential for an outpatient focus. A thorough reappraisal of the oncogeriatric and geriatric medicine literature regarding assessment instruments, their diagnostic accuracy and value in OGA was necessary and useful. This is the especially the case with the increasing use of predictive models such as the CARG chemotoxicity prediction tool and Suemoto Index in decision-making.

5.3.28 Limitations

Limitations include the lack of a systematic search strategy and umbrella review of OGA instruments, although due to the heterogeneity involved this would be extremely difficult to design and undertake. The process of design, consultation, and operationalisation of the OGA service was undertaken at a single NHS centre. The findings may therefore not generalise to other centres, although the implementation facilitators and barriers identified are common to NHS healthcare services. The operationalisation of the OGA service was significantly disrupted by COVID-19 resulting in the sunsetting of the original conception. However, an outpatient service will resume soon under the leadership of a consultant geriatrician. The current climate in healthcare is globally inconducive to significant service changes, due to ongoing service pressures from COVID-19.

Although a baseline NPT appraisal was undertaken and CAS theory was utilised, this was not subsequently supported by quantitative, qualitative or mixed methods research. However, I maintain that taking a purely research-centred approach in the design of the service may have been a barrier to the rapid success in engaging with stakeholders and operationalising the service in the timeframe available. Although patients were involved in validating assumptions of the overall service operation, including the formal research components, co-design was not undertaken of the software used to collect data. This was because the priority was on getting the overall OGA service architecture correct initially. In keeping with a minimum viable product (MVP) approach propagated by Agile and Lean methodologies, minor software UI and UX changes can come in later iterations. However, system-level changes are harder to improve upon during operationalisation. General considerations for the design of software products for older adults were considered and only core features were implemented initially. **Chapter 6** presents the results of formal research into the UI and UX characteristics of the software.

The results of the OGA were not directly fed back to the cancer MDT during discussion of assessed patients. This was because of several MDT concerns: i) increasing the already stretched MDT meeting time; ii) uncertainty around the application of geriatric medicine by non-geriatricians; and iii) uncertainty about the use of predictive models in decision-making. These are common implementation barriers outlined in **Chapter 2**. The future involvement of an oncogeriatric consultant may help circumvent some of these issues.

Finally, the OGA service was not a comprehensive perioperative geriatric medicine service. The important benefits in reduction in postoperative complications and mortality required for cost-effectiveness as found in **Chapter 4** were therefore unlikely to exist. Although these findings came after the design of the OGA service, future services should prioritise perioperative geriatric medicine in their model.

5.3.29 Applications to clinical practice

There are several findings directly translatable to clinical practice from this research. Firstly, I demonstrated the successful use of multiple approaches to service design, encompassing the use of mid-level and grand theories, implementation science, quality improvement, design thinking, customer discovery and project management. Often highly successful organisations are not only innovative in their products, services or technology but also in their change management and organisational psychology. They constantly experiment using different methods to optimise their internal processes and organisational harmony.

Secondly, I have shown the power of a single healthcare intrapreneur to design, implement and lead a new service in a healthcare organisation. During this thesis, I was awarded a place on the highly competitive NHS England Clinical Entrepreneur programme, run by NHS England and NHS Improvement's Innovation, Research and Life Sciences group and now delivered jointly with Anglia Ruskin University. I feel this validates the success in leadership and innovation from new service design and delivery. It is easy to forget that this could have equally been a case of implementation failure and never operationalised.

Finally, I have challenged the practice of bundling a mixture of convenient instruments into the OGA process or including components because they were historically done in CGA. Instruments should not be selected primarily for convenience, but instead a critical appraisal of their diagnostic accuracy, validation, implementation, suitability for patient-reporting and value towards OGA outcomes (e.g., prediction or optimisation) should take place.

5.3.30 Priorities for future research

This chapter also generates many priorities for future research. They way older adults can be assessed is changing, with the convergence of wearables to monitor activity, germline genomic analysis and the use of AI. Future research should study how complex data feeds can be integrated into OGA. Although germline genomic analysis in OGA is probably not cost-effective currently, the cost of the technology is decreasing and new findings of the relevance of germline genomics to treatment and cancer outcomes is emerging (499). Software will be essential to help collate, integrate and summarise such disparate data for interpretation by the patient and cancer MDT. The use of AI conversational agents to undertake the OGA process could also improve the depth and breadth of data collected, tailored to the individual patient. For example, the use of probabilistic graphical modelling (PGM) to explore the cause of falls in-depth and thoroughly assess for mental health disorders is interesting. The study of digital-first OGA services on outcomes, especially those important for cost-effectiveness, such as perioperative complications will be important. Future RCTs should be designed accordingly to mitigate the many implementation issues presented in this chapter and **Chapter 2**.

5.4 Conclusion

In this chapter, a narrative literature review, theoretical, business and implementation science principles were utilised, to provide the basis of the development of a new digital-first OGA service encompassing a patient reported questionnaire. The design process and lessons learned have been reported, including highlighting the power of a single healthcare intrapreneur to design, implement and lead the development of a new digital-first NHS service. In keeping with a lean-agile approach, every component of an OGA should be evaluated for its value towards the purpose of OGA, namely outcome predictions or optimisation. Additional components, interventions or collaborations can come later, but rapid implementation relies on making design decisions that can be guided by theory, evidence, experience, or outcomes.

Chapter 6 – Evaluating a digital patient-led oncogeriatric assessment

6.1 Introduction

In **Chapter 5**, the narrative literature review and rationale for the design of the patient reported questionnaire and new OGA service was presented. Several feasibility studies conducted in the USA have demonstrated acceptability of digitalised and patient reported CGA, although the need for assistance varied from 3-49% (155, 500, 501) and patient completion time was between 15-36 minutes. Hurria *et al*. (500) compared patient reported OGA administered via a web-based application on an iPad device with paper and pencil OGA in 100 adults ≥65 years with cancer. They found no differences between completion time, 67% preferred computer-based OGA and test-retest reliability was high, except for the social activity scale. Bhatt *et al*. (501) undertook a prospective study of 99 patients aged 36-75 years using a survey application on an iPad device. They noted iPad failures in three patients necessitating use of computers and 3% required assistance. McCleary *et al*. (155) undertook computer-based OGA on 38 patients aged 70-89 with gastrointestinal cancer with a tailored list of questions developed from a cancer-specific patient reported CGA (106, 502). The OGA was patient reported and administered before an oncology physician appointment or during chemotherapy using a touchscreen computer. This represents an exceptionally late sampling point in the UK cancer pathway (**Figure 4**) and the findings that OGA did not influence clinical decision-making is unsurprising. This represents what has been termed a Type III error, whereby the negative result may have been due to implementation failure *versus* effectiveness failure (503). Shahrokni *et al*. (258) undertook preoperative digitalised, patient reported and abbreviated CGA on 636 older patients (median 80 years old). They found acceptability of 59% were able to complete the assessment at home, demonstrating feasibility for remote reporting. Further studies are still ongoing and not currently fully reported (e.g., Alliance A171603) (504).

Three of these studies exhibited educational bias through the majority of college-educated patients they sampled (155, 258, 500). In contrast, around one in six adults in England have very poor literacy skills (505). Bhatt *et al*. (501) included younger patients (median age 59.5 years), introducing significant confounding from age. Patient-report time is important for UX (technological perspective) and patient experience (clinical governance perspective), however, from a pure implementation standpoint this is not as important as the clinical time-reduction of patient reported OGA *versus* a clinician-reported CGA (digital or paper). Overall, these studies suggest acceptability of digital, patient reported OGA in those who volunteered for the study

although highlight the necessity for personnel to be available for assistance and the need to evaluate and validate new digital, patient reported OGA assessment tools in NHS settings.

The aim of this chapter is to report the results of the evaluation of a digital patient-led oncogeriatric assessment in an NHS setting. This was achieved using a quantitative survey with qualitative free text responses to capture important UI and UX feedback and to formally assess the acceptability, feasibility and usability of this approach in NHS patients.

6.2 Methods

6.2.1 Software design and development

An application was developed for the Android operating system (version 10; Google, CA, USA) on a Samsung Galaxy Tab A (8.0", 2019) tablet device using the Kotlin programming language (version 1.5.31, JetBrains, Prague, Czechia) and Android Studio (version 4.0.1, Google, CA, USA). The application was engineered to take the array of questions developed from **Chapter 5** and display these to the patients with appropriate responses. Core features included: i) forward and backward navigation through the questions, both to allow progression and changes; ii) a tree-like algorithm that allows certain questions to be skipped or included, depending on previous answers; and iii) the seamless integration of the quantitative survey after the patient reported questionnaire, for consenting patients only. The intended outcome was the development of a MVP, following an Agile project methodology.

Responses were saved in JavaScript object notation (JSON) and plain text format for upload to a HUTH computer via universal serial bus connectivity and subsequent processing. JSON was selected to enable programmatic analysis of the data, whereas plain text was human readable and suitable for direct upload to the EHR to persist the responses. After the response had been uploaded to a HUTH computer and persisted within the EHR or a HUTH hard drive, it was policy to delete the data from the tablet device. This ensured that no patient data were persisted on the tablet device, which was nonetheless password protected and stored in a secure location. A realtime, bidirectional communication between server and application was initially proposed and prototyped using REST principles and WebSockets. However, this was abandoned due to governance and cybersecurity barriers, which would have been difficult to satisfy in the timescale available.

Application design principles made use of Android Material Design components (Google, CA, USA) and general principles for software development for older adults (e.g., high contrast colours) (506). Colours chosen reflected NHS Identify Guidelines (507) to remain consistent

with the NHS UX, with the primary colour being NHS Blue (RGB: 0/94/184) and secondary being NHS Aqua Green (RGB: 0/164/153). NHS Dark Grey (RGB: 66/85/99) was chosen for the back navigation button and NHS Mid Grey for explanatory text. Examples of the UI features are shown in **Figure 19** and the predominant UI viewed by the patient is annotated in **Figure 20**. All other text was NHS Black (RGB: 35/31/32). The HUTH logo was displayed at the top left of the screen as the branding, to reassure patients that the software was operated by an NHS Trust. A progress bar gave a visual indication of the assessment time remaining.

Android applications default to the Android system font, Roboto, a Google Font (Google, CA, USA). Frutiger®, which is the recommended primary NHS font (507) is commercially licensed, as is Arial® the secondary recommended font. A sans-serif font, Open Sans, was selected, which has similar accessibility and clarity to Frutiger® and available for free download from Google Fonts (Google, CA, USA) and incorporation into the OGA application. Font size within Android is determined by the screen density of the device screen, $\frac{screen\ width\ in\ pixels}{screen\ height\ in\ inches}$, measured in dots per inch (dpi) and the font size measured in scale-independent pixels (sp) in Android. To convert between the familiar pixels (px) unit and sp, the formula is, $px = \frac{(sp * screen\ density)}{160}$ (508), where the screen density of the tablet device was 288 dpi. The question font size was set as 20sp (36px) and that of the explanatory text was 15sp (27px). Yeh (509) studied 32 people >65 years old and assessed button position and font size responses on a tablet device compared to younger counterparts. Yeh (509) found that 22px font size offered comparable performance between older and younger participants, therefore a font size of at least this value was selected.

Navigation buttons were bottom-right aligned, as previous research has suggested this is familiar place, although better performance for top-aligned buttons was noted by Yeh (509). I assumed that many older adults would be familiar with modern applications including Google, social media platforms and other websites, where a common design pattern is to place important buttons (e.g., 'Next', 'Login'…) at the bottom right of the screen, therefore this design decision was upheld.

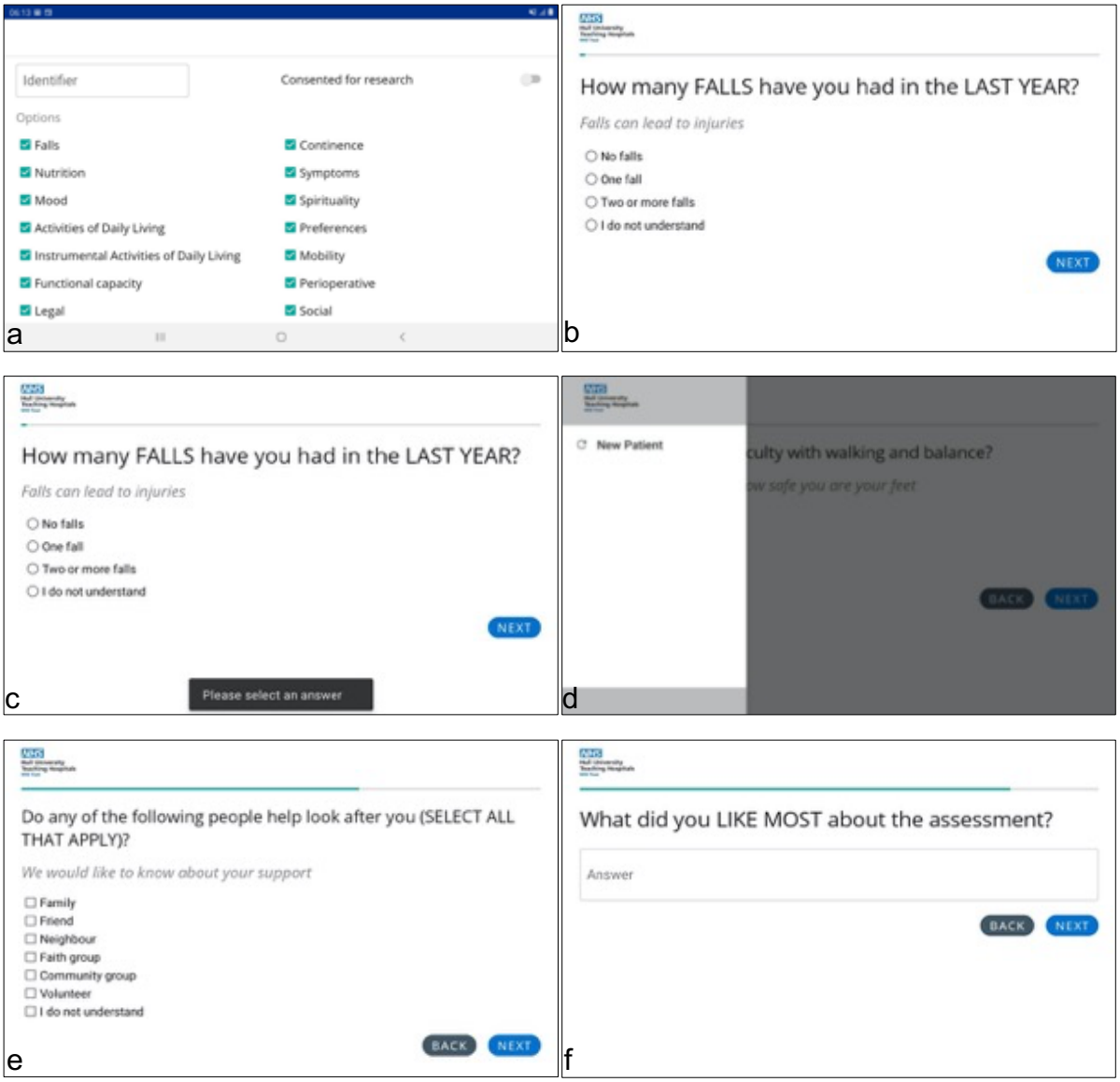


Figure 19 – Collage of screenshots of the OGA Android application.
Screenshots taken from a Samsung Galaxy Tab A (8.0", 2019) running Android Version 10 and the OGA application (Version 1). Screenshot a) The landing screen on opening the app allowing the identifier to be associated with a new assessment, confirm whether the patient has consented to research and select which components of OGA are required (default is all); b) A typical question in kiosk mode, see **Figure 20** for detailed annotation; c) The error message displayed when attempting to navigate away from an unanswered single answer question; d) The hidden navigation drawer obtained by tapping the hospital logo, to start a new patient episode; e) A multiple-answer checkbox style question, where no answers are acceptable; f) A free-text question from the survey, which is only displayed to patients if the 'Consented for research' switch is activated in Screenshot **a**.

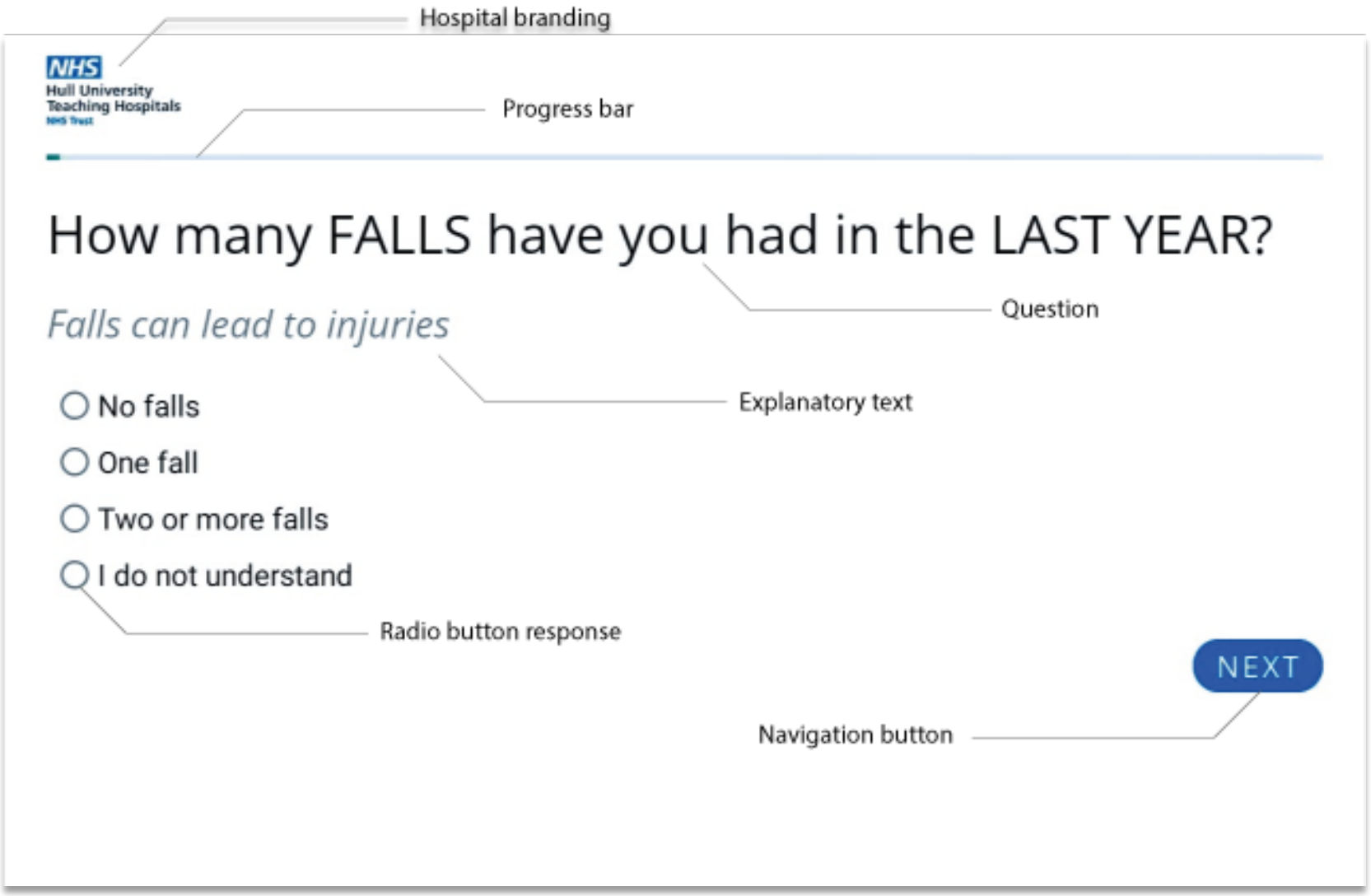


Figure 20 – Annotated screenshot of the user interface of the OGA application.
Screenshot taken from a Samsung Galaxy Tab A (8.0", 2019) running Android Version 10 and the OGA application (Version 1).

6.2.2 Service operation and recruitment

The design of the OGA service is described thoroughly in **Chapter 5**. The first OGA service operated within HUTH between the 22nd of January 2020 and the 12th of March 2020 where the pre-COVID-19 version of the service operated. This version included data collection of the survey results presented in this chapter. Patients using OGA service who fulfilled the eligibility criteria in **Figure 21** were eligible for recruitment.

Inclusion criteria:

- All patients who use the OGA service
- Written informed consent given

Exclusion criteria:

- Unwilling to participate in research
- Insufficient mental capacity to provide informed consent
- Insufficient English to undertake the research survey and an appropriate translator/translation facility is unavailable

Figure 21 – Inclusion and exclusion criteria for study recruitment.

Patients over the age of 65 years with confirmed or suspected cancer were identified through existing HUTH clinical systems, including the 2 Week Wait list and the Somerset Cancer Registry. Patients from the thoracic and head and neck MDTs were proactively fast-tracked for an appointment with the OGA service through appointment letter and/or telephone call. Patients could also be referred into the OGA service from other MDTs. With their appointment letter, patients also received research documents, including an invitation letter (**Appendix Figure 53**), patient information leaflet (**Appendix Figure 54**) and consent form (**Appendix Figure 56**). It should be noted, these research documents reference other study components. These were either abandoned due to COVID-19 disruption (e.g., analysis of eFI data and TUG test result prediction) or have not been reported in this thesis due to time constraints (e.g., analysis of in-depth interviews). Patients were contacted by telephone or face-to-face during a planned appointment (if appropriate) where they were invited to participate in the research study. I answered any questions regarding participation, and those patients willing to participate underwent informed consent using the signed paper consent form. Consented participants proceeded with the remainder of the OGA appointment.

I interpreted all the results, calculated relevant prediction scores, identified optimisation opportunities and made appropriate referrals following OGA. A letter summarising the OGA encounter, and relevant clinical details was produced and uploaded to their EHR (Lorenzo, DXC Technology), which could be viewed by the cancer MDT. Raw data of their OGA responses from the tablet application was also permanently stored in their EHR. A copy of the clinical letter was also sent to the patient's general practitioner with an additional letter informing them of their research participation (**Appendix Figure 57**).

6.2.3 Survey questions and participant data

A survey was used to acquire additional information on educational status, experience of digital assessment, access to the internet at home and any internet-connected devices used. The survey also explored suggestions for improvement of the digital hospital questionnaire as part of the OGA service, in terms of the format and delivery of the hospital questionnaire. The questions used for the survey are presented in **Appendix Figure 58**. Age, gender and clinicopathological details were collected from the clinical record.

6.2.4 Survey data collection

For patients that had consented to the survey, the survey was activated whilst the tablet device was prepared for the OGA questions. Immediately following completion of the OGA questions, participants were automatically transitioned into the survey questions on the tablet device, which has an identical UI and UX to the OGA questions. Most questions were multiple choice radio buttons, but some were multiple choice checkboxes, where more than one response was necessary. Two questions were free text questions using textboxes and participants could either type this themselves, instruct their assisting carer/relative or vocalize this to the study administrator who would record this verbatim. Even in the context of assistance, wherever possible the survey questions were answered where relevant or marked 'I do not know' (e.g., if they did not have to change any responses). If they required partial assistance (e.g., the study administrator or carer/relative had to take over control of the tablet device), the survey was still undertaken as if they had used the tablet device. This was to maximise data collection.

6.2.5 Statistical considerations

Recruitment for the research survey was planned to occur for the first 218 patients. The sample size was calculated based on an estimation that the overall population to attend OGA service appointments would be around 500 patients in a year of operation (approximately 10 patients per week). A similar research study undertaken within HUTH using CGA in an oncology

setting had around a 70% recruitment rate (510). Based on calculations using a 95% confidence level and 10% margin of error, 81 patients would be required to be sampled for an *exploratory* sample for the purposes of patient feedback on the OGA service hospital questionnaire. Acceptability of digitalised hospital questionnaires can be measured by the proportion of respondents answering 'disagree' or 'strong disagree' to the survey question 'would you have preferred to do the questions on paper?' (**Appendix Figure 58**), as undertaken by Shahrokni *et al*. (258). For the purposes of sample size calculation this was considered the primary outcome measure. The acceptability of the digital assessment must be *representative* to establish the value in introducing this technology locally. Therefore with 5% margin of error, 218 patients are required to undertake the research survey. All basic statistics were calculated using Microsoft Excel (v16.47.1, Microsoft).

6.3 Results

6.3.1 Overview

Between the 22nd of January 2020 and the 12th of March 2020, the pre-COVID-19 version of the OGA was utilised, and 17 patients who met the eligibility criteria were approached and 12 patients were recruited. Reasons for not participating were various and included long travel time, lack of perceived benefit, busyness, uncertainty, logistical problems (e.g., coordinating appointments) and communication problems (e.g., unable to contact). One participant did not attend their clinical appointment. Recruited patients in this wave underwent the GA questionnaire in-person and were offered the tablet device to complete this. The mean age was 72 years (range 65-91 years) and the mean time to completion was 35 minutes 10 minutes (range 16-62 minutes), including completion of the survey component. Half of the participants required assistance with using the tablet device and reasons cited included visual problems, difficulty with technology and long fingernails. Results from cognitive screening using the MoCA tool, demonstrated that mean score was 24 (range 18-28), indicating that generally cognition was in the lower limit of normal for older adults in this cohort.

6.3.2 Quantitative survey questions

All recruited patients completed the survey, regardless of their need for assistance. 75% of participants had access to the internet at home and they could access this via their own computer (33%) or tablet device (25%) most commonly. Nearly all participants (92%) could receive help accessing the internet and in 75% this would be from a relative. However, only 17% stated that they would prefer to undertake the assessment at home. Field notes recorded several off-hand comments made supporting this (e.g., "I wouldn't do this at home"). The

summated responses are graphically represented in **Figure 22-Figure 31**. Surveyed participants found the tablet usability and answering questions 'very easy' or 'easy' in 76.7% of cases. For changing questions or moving between questions on the tablet device, 54% and 66% respectively found it 'very easy' or 'easy'. Understandability and readability of the questions was high with 84% and 77% respectively, finding this 'very easy' or 'easy'. Screen size was 'very good' or 'good' in 66% of cases and brightness was 'very bright', 'bright' or 'neutral' in 74%. The length of time to complete was rated favourably as 'quick' (8%) or 'about right' (75%). In 67% of participants, they reported 'strongly disagree' or 'disagree' for their preference to do the assessment on paper, and the remainder were undecided. Most participants (92%) were not educated to degree-level.

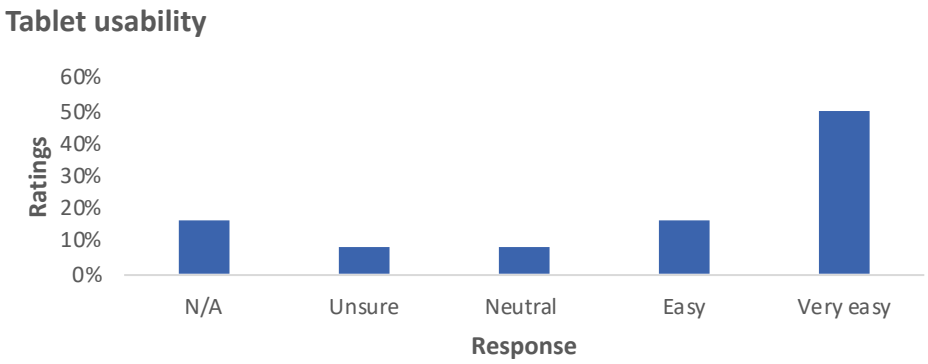


Figure 22 – Survey responses concerning tablet usability.
Mean response ratings to the survey question regarding the usability of the tablet.

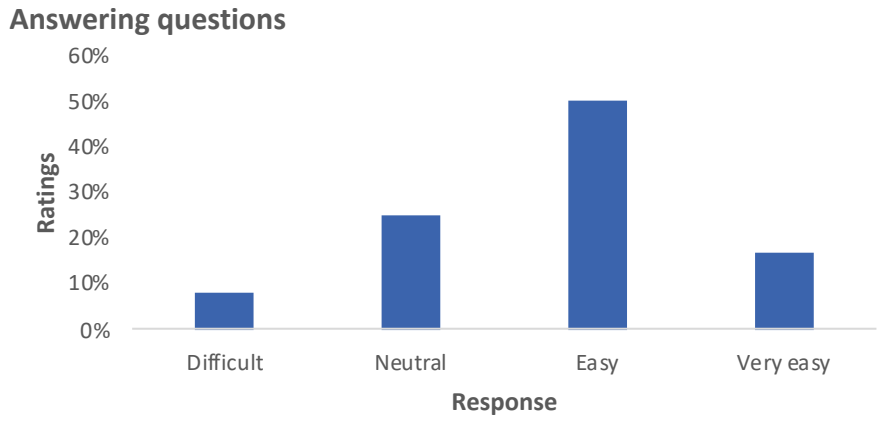


Figure 23 – Survey responses concerning ease of answering questions.
Mean response ratings to survey question regarding the ease of answering questions using the tablet device.

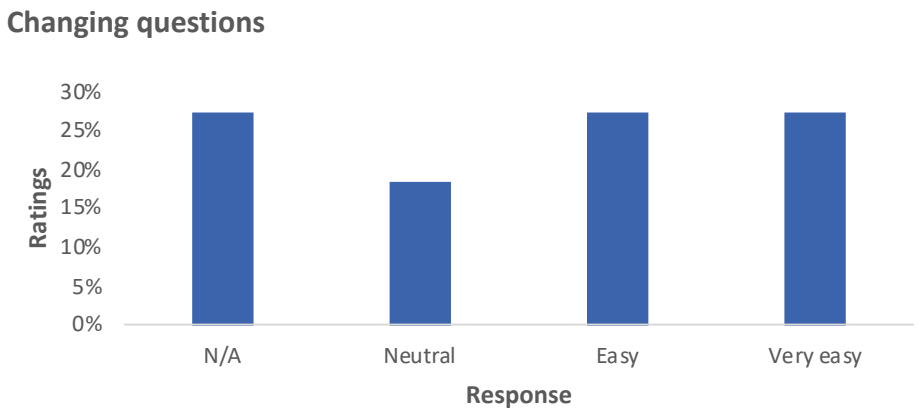


Figure 24 – Survey responses concerning ease of changing questions.
Mean response ratings to survey question regarding the ease of changing questions using the tablet device.

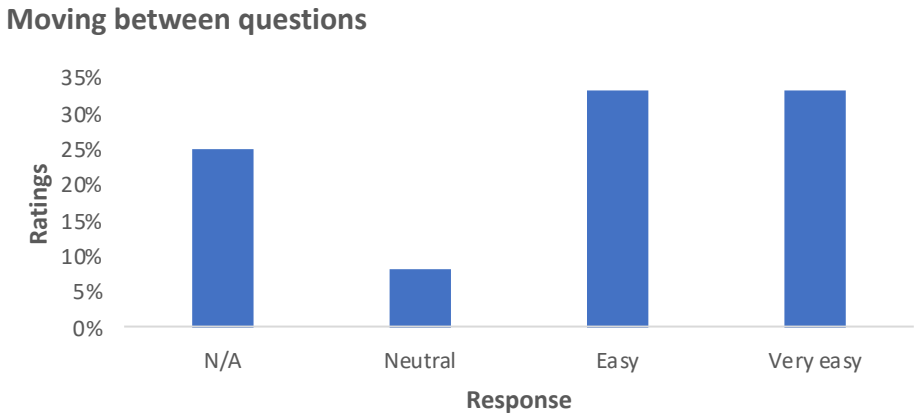


Figure 25 – Survey responses concerning ease of moving between questions.
Mean response ratings to survey question regarding the ease of moving between questions using the tablet device.

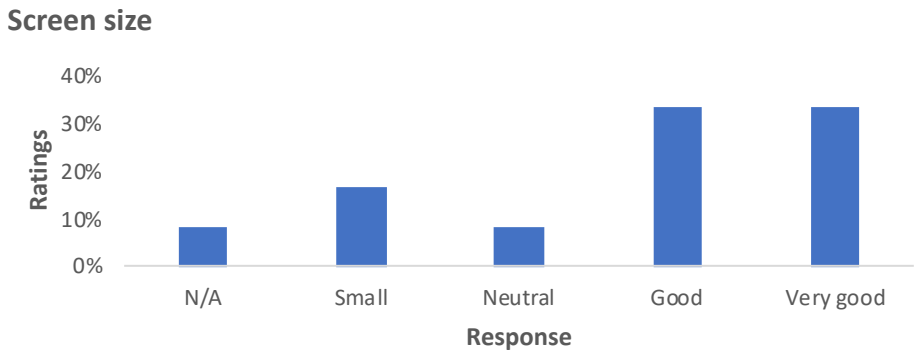


Figure 26 – Survey responses concerning the size of the device screen.
Mean response ratings to survey question regarding the screen size of the device.

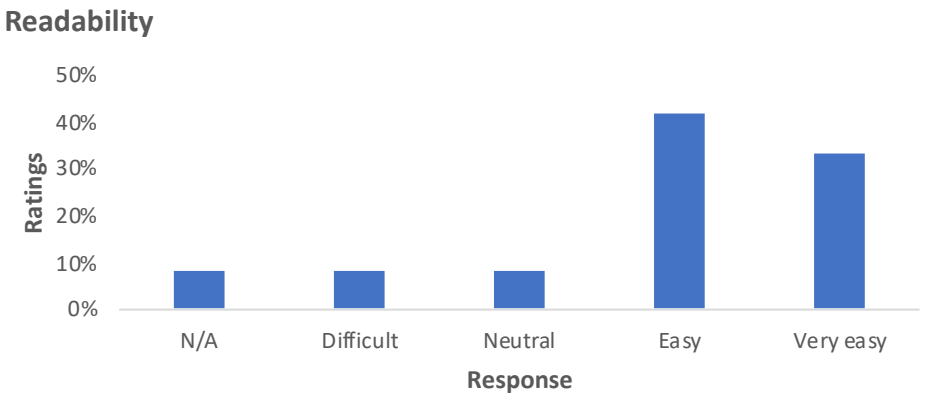


Figure 27 – Survey responses concerning the readability of the questions.
Mean response ratings to survey question regarding the ease of reading the questions on the device screen.

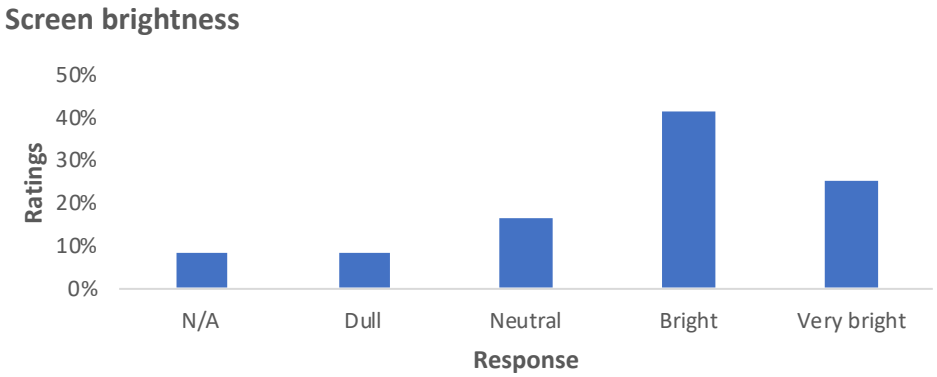


Figure 28 – Survey responses concerning the brightness of the device screen.
Mean response ratings to survey question regarding the brightness of the device screen.

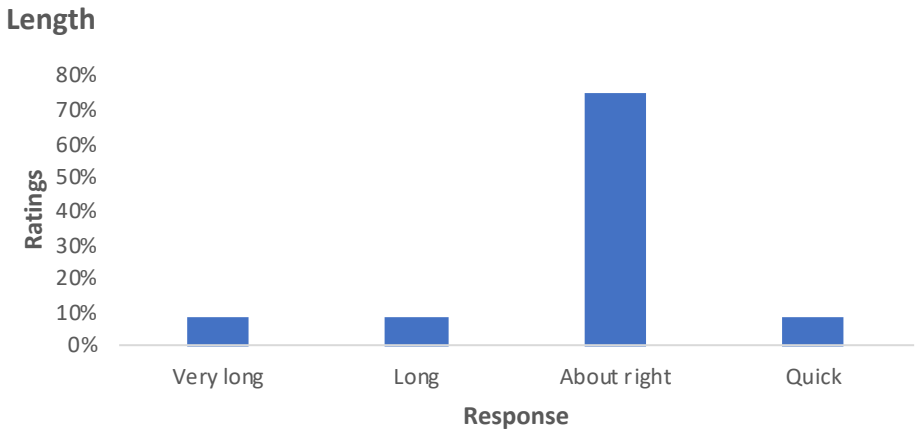


Figure 29 – Survey responses concerning the length of the assessment process.
Mean response ratings to survey question regarding the length of the assessment process.

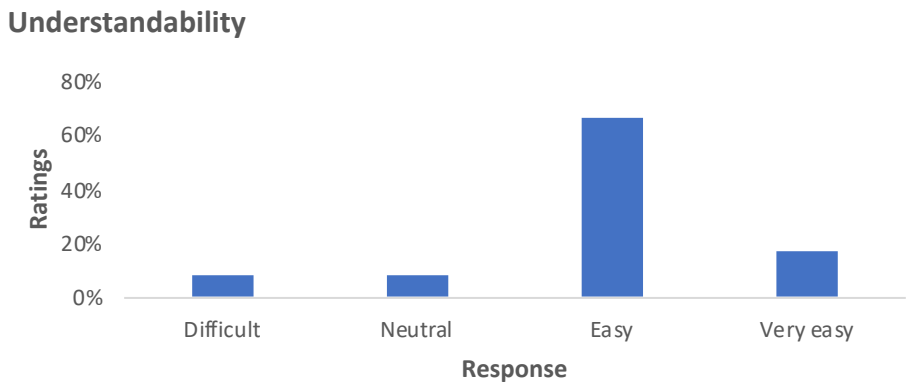


Figure 30 – Survey responses concerning the understandability of the questions.
Mean response ratings to survey question regarding the ease of understanding of the assessment questions.

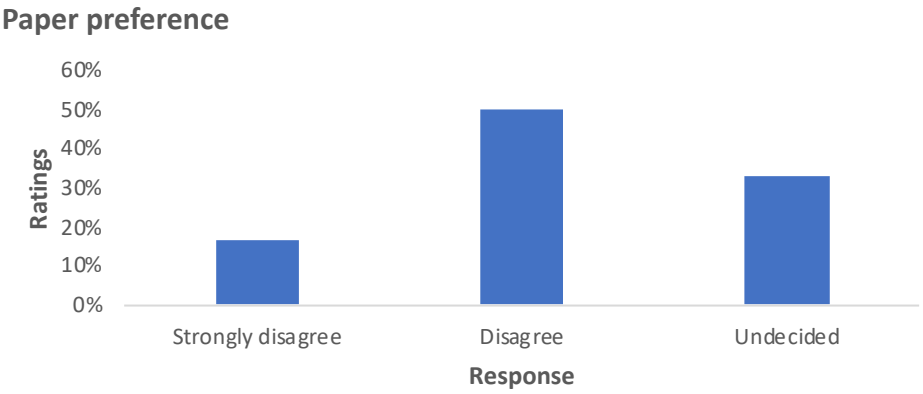


Figure 31 – Survey responses concerning the preference to undertake the assessment on paper.
Mean response ratings to survey question regarding the degree of preference to undertake the assessment in paper form versus the offered digital format.

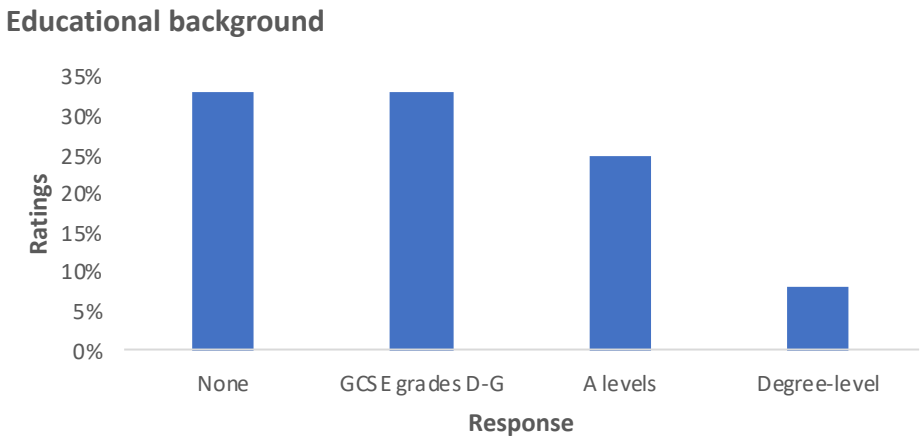


Figure 32 – Survey responses concerning the educational background of participants.
Mean responses to survey question regarding the educational background of participants. None refers to no secondary educational qualifications and qualifications are grouped into modern day equivalent UK examinations.
Abbreviations: GCSE = general certificate of secondary education.

6.3.3 Free text qualitative survey questions

Analysis of free text comments revealed several mentions of ease of use, supporting the high usability ratings. One participant commented positively regarding the informative outcome of the assessment:

"very informative, makes you think about yourself" – **Male, 73 years.**

Another participant ostensibly liked the unidirectional process of the assessment, whereby information was collected, but no immediate feedback was given:

"not trying to tell me anything" – **Male, 65 years.**

Other mentions of being 'fine', 'simple' or 'just right' were also made, although field notes recorded that other participants were slightly frustrated with the length of time taken for the assessment, especially those in the upper time limits. A particular aggravating factor was concern over car parking payment expiration or the length of time already spent waiting in the outpatient department. One participant stated that "some answers missing [sic]" and field notes taken from this interaction supported that this participant felt that they were 'in between' on some responses. There were some responses that included humour, notably one participant with a high MoCA score (28) who was happy to demonstrate this, but felt that questions were 'more relevant' to people older than her:

"*questions right on moca [sic], more relevant to older people*" – **Female, 67 years**.

6.4 Discussion

6.4.1 Summary of main findings

The chapter details the results from the quantitative survey undertaken during the recruitment period of the study prior to the suspension and amendments required during the first UK wave of the COVID-19 pandemic. Despite the low sample size, the survey results were encouraging that a digital patient-led assessment is usable and acceptable for older adults under investigation for cancer.

Despite high internet access and personal usage in this cohort of older adults, few would rather undertake this at home (17%). This likely represents generational differences in the value or convenience of technology in healthcare settings. Furthermore, the disruption to routine that initiation of a cancer investigation pathway, diagnosis or treatment may cause may compound this sentiment. Furthermore, it may also reflect a generational theme that assessment and interaction between patient and healthcare professional should occur in a clinical setting where

possible, as opposed to telehealth. This opinion may change if this survey were to be repeated in the post-COVID-19 setting as some degree of rapid normalisation of telehealth has occurred. There was preference towards undertaking the assessment in a digital format versus a paper-based approach, with the majority (67%) opposed to paper-based formats and the remainder undecided. The mean time to completion of 35 minutes is favourable compared to a traditional clinical-led CGA, with median time of 75 minutes. Even the longest assessment was only 62 minutes, probably because the digital format is quicker to progress, especially when patient reported. The majority (75%) of participants found this time acceptable. The number of patients requiring assistance was quite high at 50%, which is slightly higher than a previous study (258).

Ratings for tablet usability and question understandability and readability were all high indicating that decisions made around question wording and user interface characteristics had resulted in a good user experience. This was probably due to use of previously documented recommendations for digital interfaces used by older adults regarding neutral high contrast colours, clean layout and design and large font size (509). However, 75% were device users (tablet, computer or mobile phone), so familiarity with the use of digital forms meant that interactions with the user interface may have been familiar.

Technical aspects were also favourable, with most participants reporting ease of changing responses and moving between questions and satisfaction with screen size and brightness. Changing responses had a lower majority (54%) and whilst this may reflect the large number of assisted assessments, there may be technical factors to explain this. Within the application there was no feature to review all responses in one view and go back to a previous question. To change questions participants had to sequentially move backwards or forwards through the question set. In a future design, a feature to allow rapid selection of a previous question could be utilised to improve this. However, no specific comments or frustration were noted during the assessments.

6.4.2 Comparison to previous studies

One important finding of this study was that 92% of participants were not educated to degree-level. A concern of previous studies using patient-led digital assessments undertaken within the USA healthcare system was that most participants were educated to degree level (258). Because of the low sample size in the current study, minority groups were undersampled, although similar work in the USA has demonstrated that digital OGA remains feasible for older adults across institutions and racial groups (511). The reasons why some patients could not

self-report was also similar and visual and dexterity problems are a potential risk factor for inability to self-report (511). There is likely to be a minority of patients who prefer a clinician-led approach. Qualitative work by the same research group as (511) using interviews of study providers did highlight some of the disadvantages of digital patient-reporting, including the time burden of overseeing digital self-reporting (512).

6.4.3 Strengths

There are several strengths of the study reported in this chapter. The use of a new format of OGA, including patient-led reporting of geriatric vulnerabilities is a development on previous work in NHS settings, which was largely clinician-led. The use of a bespoke Android application that immediately collected the survey data after a patient-led assessment allowed for rapid feedback, which was largely positive. The all-in-one nature of the study: recruitment, OGA, research survey and in-depth interview all led by a single clinician is also unique and fitted well with themes around continuity of both care and research coordination voiced by the PPI group.

6.4.4 Limitations

Limitations of this study include the low sample size, which precludes any tests of statistical significance and falls well below that of a representative or exploratory sample. This was due to the significant interruption from the COVID-19 pandemic and need to make substantive amendments to the recruitment, operation, and timeline of the study. It is therefore best to view these results as pilot or feasibility study. From this viewpoint, the study has demonstrated both acceptability and usability of a digital patient-led approach to OGA in this cohort, which is encouraging. Other weaknesses include both the management of the study and the participants care being undertaken by myself. This can introduce bias, but as discussed in **Chapter 3**, this has been acknowledged and reflected upon during interpretation. This was not a remote delivery of OGA, therefore the true number able to complete the patient reported component independently at home using their own devices is unknown. However, based on the qualitative comments from the survey, lower data completion may have been observed had a remote-first approach been taken. All the participants recruited spoke native English and professionally translated questions were not available, so this should be considered when applying the results to clinical practice.

6.4.5 Applications for clinical practice

Taken with the service design considerations presented in **Chapter 5**, these findings demonstrate that a digital-first OGA service is feasible and usable by patients and may be acceptable in the NHS. Because the use of technology can facilitate implementation and reduce staff cost inputs as found in **Chapter 2** and **Chapter 4** respectively, new or existing OGA services should strongly consider the use of similar technology in their design. The high level of assistance required by many participants, means that staff must still be available to assist with the patient reported questionnaire when operated in face-to-face setting. This also reinforces the need for a dedicated staff member (e.g., Band 6 nurse) to take responsibility for allocating, coordinating and organising remote patient reported questionnaires, initial telephone assessments and some face-to-face assessments. Digital-first services must always gracefully fallback to low-technology delivery where necessary include full clinician-led services where necessary.

6.4.6 Priorities for future research

Future research should attempt to provide further representative evidence of the acceptability of digital-first OGA services. Studies should also utilise remote delivery of OGA patient reported questionnaires using their own devices or those of someone close to them. Detailed patient's views and opinions are also important and in-depth interviews are being analysed at the time of submission of this thesis, which will be submitted for publication in due course. More complex patient applications involving AI conversational agents and detailed history taking would need for feasibility, usability and acceptability study in this group. The evolving landscape of digital inclusivity and accessibility is also important to understand, as COVID-19 likely increased the number of older adults willing or able to utilise digital services. This picture is likely to increase further over the next 5-10 years as digitally literate adults age.

6.5 Conclusion

The results of this study showed that a digital-first patient reported OGA was feasible and usable in NHS settings and may be acceptable for older adults with confirmed or suspected cancer. Further insight from in-depth interviews regarding the views and opinions of this patient group in the use of an OGA service are awaited.

Chapter 7 – Complex modelling of an oncogeriatric population

7.1 Introduction

Due to the extensive disruption to research during the COVID-19 pandemic, the secondary data analysis of prospectively collected OGA data were not possible. The originally planned research questions concerned were: i) the utility of eFI to predict adverse outcomes following cancer treatment; ii) the prospective validation of a three-question decision tree to predict the TUG test result; and iii) identifying specific predictors to classify oncogeriatric patients into high- or low-risk categories for adverse post-treatment outcomes. To circumvent the need for real world data (RWD) and progress the original quantitative aspect of this thesis, this chapter represents the work undertaken using synthetic individual patient data (IPD) and modelling.

Reported analyses of OGA often derive from relatively small research datasets, which are siloed within research groups and institutions. Furthermore, there is no national oncogeriatric database to utilise for analysis. Synthetic IPD research has been used in various healthcare domains, from generating synthetic radiological imaging data (513) to whole EHRs (514). Various approaches to synthetic IPD generation exist using combinations of epidemiology, simulation, curation of research data and expert consensus (515). Manual curation generally reduces the transferability of a synthetic dataset to another patient cohort or disease. However, it was not a requirement of this chapter to develop a transferable model, because of the sub-specialist nature and unique combination of oncology and geriatric cohorts. In other circumstances, it may have been important to derive synthetic IPD purely from real data to preserve privacy, by capturing the statistical relationships but obfuscating the demographic or other potentially identifying information. This requires a different approach, leveraging AI such as generative adversarial networks and an underlying training dataset (516).

Alongside the lack of RWD, approaches using modelling and state-of-the-art technologies, including AI, are lacking in oncogeriatrics and often limited to prediction of isolated or extreme outcomes, such as mortality (517). AI-assisted modelling may be a solution to manage the complex decision-making in oncogeriatric populations. Modelling in this case refers to that of complex systems, due to the human body behaving as a CAS and the potential granularity of modelling possible. There are various methods of modelling individuals and populations, including finite element analysis, agent-based modelling, discrete event simulation, lumped parameter modelling and probability-based models. Since clinical-clinical interactions are the predominant level of data within oncogeriatrics, this immediately excludes some types of

modelling. Finite element analysis involves modelling individual elements (e.g., cells and/or fibres) under conditions of stress or strain (518), which would be too granular for this case. Lumped parameter models are useful for individual organ physiology such as cardiac modelling (519), but many of the parameters are known precisely in clinical-clinical interactions making this unnecessary. Agent-based modelling would be better suited to modelling interactions within the cancer MDT, but could also be used to model the interactions between a tumour and patient (520). However, this would require a dedicated tumour model which would mean modelling tumour dynamics and computational biology is outside the remit of this thesis. Discrete event simulation is often used for simulating future events where resource constraints create queues in networked inhomogeneous individuals (521). Although there are advantages over cohort methods such as decision trees and Markov chains, this method may be better served when simulating transitions in health states in economic models. If a model can be developed to represent an older adult with cancer and dynamically updated with RWD, this represents a digital twin. Originally developed within manufacturing, a digital twin is conceptualised in healthcare as a digital model of a patient, process or even population (522). A digital twin may include existing RWD or synthetic IPD, algorithms (including AI) and a bidirectional connection to new RWD (522). This could serve multiple use cases from the development of clinical decision support systems (CDSS) to support cancer MDTs through to business intelligence of healthcare systems. Following GA, an individual patient could be modelled, tested virtually against different treatment strategies, and iteratively optimised to provide the best available summarised information to empower shared decision-making.

Given the low sample size of the quantitative data available from prospective recruitment and the lack of suitable raw data from local EHRs, new synthetic IPD was required entirely *de novo*. This is termed a generative model and utilises hard-coded rules based on curation of existing high-level research/population data and expert opinion. Although this approach is time consuming and at risk of selection and internal bias from the existing data and assumptions used, there are several advantages to this approach: i) avoidance of imbalance in the data (e.g., in RWD there may be low numbers of frail patients with complete datasets, due to early decision-making by the MDT for best supported care); ii) elimination of the black box problem (e.g., the hard-coded rules are transparent and not inferred by a deep neural network); iii) elimination of the need to impute or exclude missing IPD; iv) lack of unmeasured effects (e.g., changes during the process of RWD acquisition); and v) data is clean on generation, eliminating lengthy processes of data sanitisation (523).

To the best of my knowledge, the use of synthetic IPD and complex modelling in oncogeriatrics has not been published in the world literature. The aim of this chapter was therefore to generate a complex model of an oncogeriatric population using synthetic IPD, working towards the concept of a digital twin.

7.2 Methods

7.2.1 Data sources

7.2.1.1 Literature review

Non-systematic searches were undertaken using PubMed and Google Scholar for peer-reviewed publications that could be used for modelling. Relevant meta-analyses, large population studies, large single institutional studies or smaller studies were used in order of preference. As a last resort, prevalence was obtained from studies deriving indices or models, or large sample size retrospective studies. Summary statistics including disease prevalence data, odds ratios (ORs), relative risk (RR), hazard ratios (HRs) and other relevant data were extracted and used to create the data model of the digital twin.

7.2.1.2 English Longitudinal Study of Ageing

Raw RWD from the English Longitudinal Study of Ageing (ELSA) was retrieved from the UK Data Service (524) using the University of York's access rights. Data were sanitised and processed using Python programming and the *Pandas* and *NumPy* libraries to extract and analyse statistical associations between age, gender and i) temporal orientation (correctly reporting the individual components of the date at the time of assessment); ii) self-reported health; iii) height; and iv) weight. Data were categorised into bins using age bands 65-69, 70-74, 75-79, 80-84, 85-89, 90-94, 95-99, 100+ and the mean and standard deviation was calculated. This data were used to generate probability distributions for random sampling during synthetic IPD generation.

7.2.1.3 Simulacrum

The *Simulacrum* database is a synthetic cancer dataset generated from RWD held by the National Cancer Registration and Analysis Service, including the systemic anti-cancer therapy data within Public Health England (525). The data model has been preserved from the RWD, allowing for a high degree of accuracy of the synthetic IPD, especially for simple queries. The data were downloaded from the Simulacrum website and the individual tables were joined using Python programming and the *vaex* library. Data were sanitised to include only synthetic IPD where age was ≥ 65 years and sex, ethnicity, deprivation quintile, cancer type, cancer

stage, date of first surgery (as a proxy for surgical treatment), chemotherapy and chemoradiotherapy administration were available. International classification of disease 10 (ICD-10) codes were converted to simple cancer types and mapped to cancer-specific MDTs for ease of later processing. The resulting dataset of 239,480 rows of synthetic cancer IPD was used for random sampling in generation of the digital twin.

7.2.1.4 Expert opinion and assumptions

Expert opinion was used where data were unavailable for the specific data query and supported by evidence from the literature. Clinical academic members of the TRANSFORM outcomes team offer several decades of senior experience of oncology, palliative care and oncogeriatrics. Some clinical assumptions were made to preserve the spectrum of ageing observed and model the population based on the widely used Clinical Frailty Scale (CFS). Where data were unavailable for a particular age group either the overall prevalence for a subgroup (e.g., '80+') or the nearest age grouping was chosen to represent this group. This does risk making the incorrect assumption that the prevalence within oldest old age groups mirrors that of older adults who are younger. Whilst it may capture some rare real-life anomalies, for example very fit and athletic octogenarians and nonagenarians, I accept that it is likely an under-estimation of risk or protective factors. For some prevalence statistics, an accurate breakdown of prevalence by gender was not available. In this situation, males and females were assumed to have similar prevalence. Given the fact that for many major and common medical co-morbidities, there may only be modest gender differences, this assumption probably has little consequence in modelling a population such as this.

One challenge of modelling older adult populations is determining an appropriate set of starting parameters. Birth-to-death synthetic IPD models such as Synthea, simulate the ageing process considering as many possible events throughout life as possible. Many genetic influences on disease and environmental exposures are mature in older adults, so previous states are less relevant, and a birth-to-death model may add unnecessary complexity. A decision was made to develop a cross-sectional representation of biopsychosocial health status, with reference to clinically universal conceptions of health in older age, such as frailty. As discussed in **Chapter 5**, the CFS offers an easy-to-understand tool to describe frailty. One reason that the CFS has been used extensively during the COVID-19 pandemic is because it provides an easy way for different clinicians to understand the spectrum of frailty in older adults from very fit to terminally ill. The top two categories in the CFS (very fit and fit) are characterised by active adults with no limiting symptoms of disease. In the model of frailty proposed by Fried *et*

al.(526), a diagnosis of frailty requires the presence of three or more of the following criteria: unintentional weight loss, self-reported exhaustion, weakness (as measured by grip strength), slow walking speed and low physical activity.

Physical activity confers well-documented protective effects against cardiovascular disease, dementia, type 2 diabetes mellitus and mortality and is associated with improved mental health and wellbeing (527, 528). In a recent systematic review by Oliveira *et al*. (529), physical activity was found to probably prevent frailty among older adults. Physical activity of an intensity and duration generally in line with UK recommendations was found to be predictive of the absence of frailty in a study of 622 older adults (530). The Suemoto index includes a single question regarding the undertaking of physical activity once or more a week (71). Conversely, a systematic review found nine studies supporting the finding that low levels of physical activity/exercise were predictive of ADL disability (531). An adult who undertakes regular exercise will not only score lower on mortality indices, but it is a well-utilised clinical heuristic that aerobic activity in an older adult virtually negates the presence of frailty (**Figure 33**). This is apparent within the CFS categories very fit and fit, and by the observation that many of the indicators of frailty (e.g., self-reported exhaustion or sedentary lifestyle) are contradictory in the context of aerobic physical activity (321). For these reasons, the presence or absence of the recommended amount of moderate-to-vigorous physical activity was utilised as an initial way to simulate adverse ageing (532). An older adult who is aerobically physically active is unlikely to have major medical co-morbidities, especially those associated with limiting symptoms (e.g., heart failure) or disability (e.g., stroke). This premise can be made both from an aetiological (533) and participatory perspective (534). As a general assumption, and for the purpose of simulation, using aerobic physical activity as a proxy for fitness is pragmatically aligned with observed clinical heuristics and frailty phenotypes.

Figure 33 – The network effect of moderate-vigorous physical activity on other variables.
The presence of moderate-vigorous physical activity is known or assumed to negate (thick red line) or have an association with other variables (dashed red line).

7.2.2 Model architecture

The overall design of the model is illustrated in **Figure 34** with reference to the future development of a digital twin. The flow of data and processing in **Figure 35** represents the core model used for analysis in this chapter. Modular additions were experimentally made using this core model and are reported separately for clarity. Synthetic IPD was generated incrementally starting with demographics and relevant genetic risk and progressing through disease and clinical outcome states. Probability theory; published and custom algorithms; and supervised machine learning algorithms are then introduced until synthetic IPD is generated for each patient.

7.2.3 Feature and label selection

In machine learning terminology, input variables are often termed features, which in this case represent disease states (see **Appendix Table 35**). Feature selection was driven primarily by those required for important outcome measures in (onco-)geriatrics (e.g., mortality). Backward

selection was undertaken for the risk factors determining these outcomes. For example, the risk factors for chemotherapy toxicity in the CARG model are important features. The clinical outcomes represent labels for machine learning. Label inclusion was not exhaustive to RWD, and preference was given to those features that are clinically relevant and easily obtainable from EHRs or direct patient questioning.

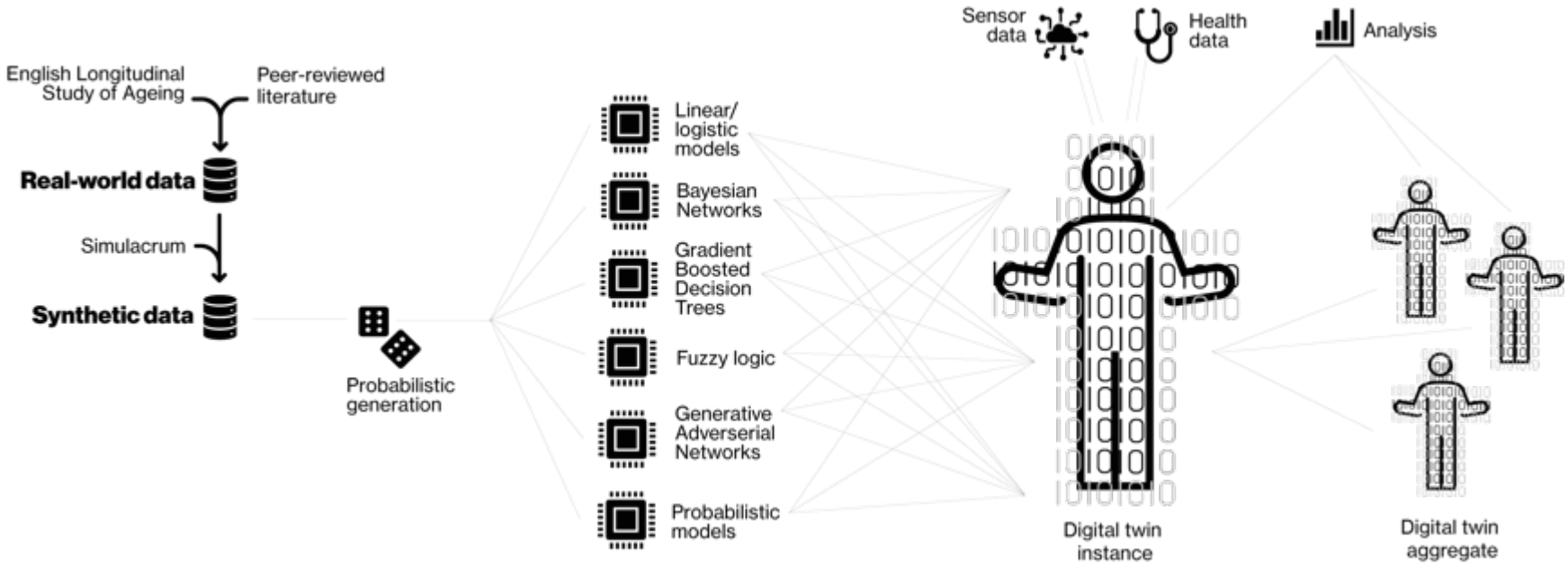


Figure 34 – Digital twin technology architecture.
Raw (English Longitudinal Study of Ageing) and synthetic (e.g., Simulacrum) data are filtered, cleaned and integrated. Stochastic processes enable probabilistic generation of further synthetic data that is enhanced using machine learning, including Bayesian networks, gradient-boosted decision trees, fuzzy logic, generative adversarial networks. Each iteration generates a single digital twin instance, where additional data from health records or internet of things sensors can be integrated to personalise the model. Digital twin instances create an aggregate population where analysis on the individual digital twin or aggregate population can be used for clinical decision support systems, economic modelling, population health, training and education

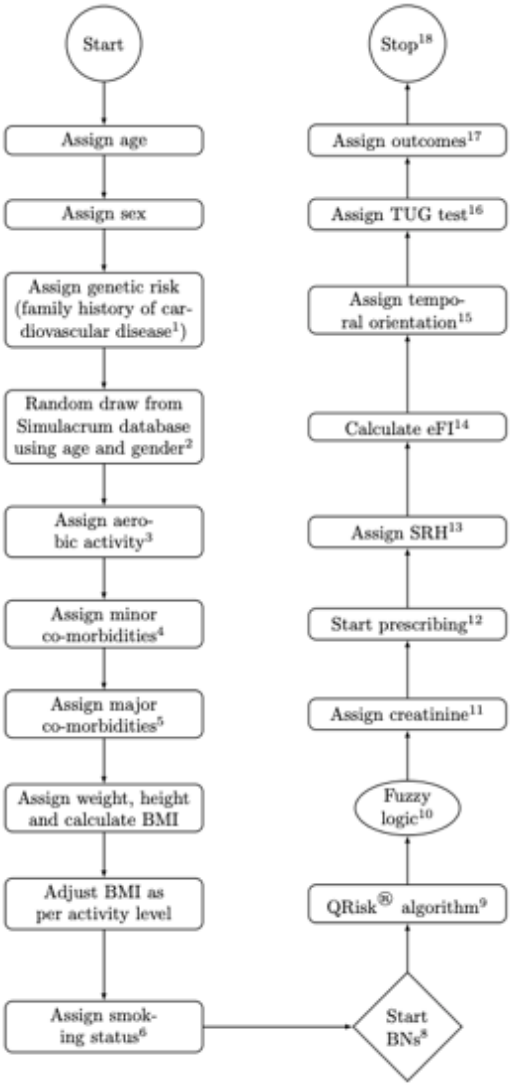


Figure 35 – Flow diagram representing model architecture.
This is a simplified representation of the architecture of the model, demonstrating data flow within program. A configuration file containing the epidemiological statistics is loaded and iterated over where age is binned into groups 65-69, 70-74, 75-79, 80-84, 85-89, 90-94 and 95-99 and 100-105. Sex is assigned as per the overall UK population ratio.[1]Genetic risk is assigned as the estimated population risk of having a family history of a first degree relative with cardiovascular disease diagnosed under 55 for a male and under 65 for a female. [2]Using the assigned age and sex, the modified Simulacrum database is queried. [3]Aerobic activity is assigned early to ensure that there is a significant prevalence of fit frailty status in synthetic individual patient data (IPD). [4]Minor co-morbidities are those that are common and are not strongly associated with activity of daily living (ADL) disability. [5]Major co-morbidities are those that may be severe or accrue and associate strongly with ADL disability and/or frailty.[6]Smoking status is adjusted where lung cancer is the cancer type. [8]Baysian network (BN) sequence may be interrupted to await state decisions from other algorithms (e.g., QRisk®) or fuzzy logic and then continued when this is available. [9]The QRisk algorithm is used to generate the probability of a cardiovascular event. [10]Fuzzy logic is used for fuzzy disease states. [11]Creatine level is randomly sampled according to chronic kidney disease status. [12]A prescribing algorithm makes stochastic prescribing decisions according to published prescribing patterns. [13]Self-rated health is assigned according to aerobic activity, stroke and ADL status. [14]Electronic frailty index (eFI) is calculated according to its published algorithm. [15]Temporal orientation (the ability to correctly report the date when asked) is assigned according to cognitive disease, depression and Parkinson's disease status. [16]The Timed-up-and-Go (TUG) test result is assigned according to its published diagnostic accuracy for frailty.[17]Outcomes are assigned stochastically using the state of each synthetic IPD. [18]The synthetic IPD is passed to the analysis class.

7.2.4 Software architecture

The Python programming language (v3.7.3, Python Software Foundation) and numerous third-party libraries (see **Appendix Table 36** for full details) were utilised to engineer a program capable of generating synthetic IPD using conventional object orientated programming supported by probability theory, linear models, fuzzy logic and probabilistic graphical modelling (PGM). Modular extensions to experimentally improve the granularity of synthetic IPD included the use of gradient boosted decision trees; linear and logistic models and generative adversarial networks (GANs). Extensive unit and integration testing, version control using *git* and GitHub and automated data analysis pipelines were engineered to facilitate continuous deployment to a high-performance computing network. Using parallelism across multiple compute nodes (each with two 14-core Intel® Broadwell E5-2680v4 processors, 2.4–3.3 GHz, and 128 gigabytes of random access memory), supported by the *Open Run-Time Environment* software (v1.8.8, (535)), synthetic IPD generation scaled to thousands of unique data points and rapid experimental manipulation of model parameters was possible. When run locally a 2.3 GHz dual-core Intel® Core i5 processor with 16 gigabytes of random-access memory was used.

7.2.5 Probability theory

A Bayesian perspective was assumed in the generation of the synthetic IPD. Prevalence data for various conditions ($X_i \ldots X_n$) derived from the literature and existing datasets were assumed to represent a prior (or baseline) risk of condition X_i (**Appendix Table 37-Table 44**). The true baseline risk, as would be observed without *any* risk factors, is usually unknown, therefore the prevalence serves as the best available representation of the prior. Covariates ($\theta_i \ldots \theta_n$) interact with X_i to alter its likelihood, $p(X_i|\theta)$. Using the *NumPy* random number generator (RNG) and the likelihood, the final observation (0 or 1) of X_i is determined stochastically. Due to the law of large numbers, mean prevalence in the synthetic IPD should approximate that expected from the prior. Probability distributions were created for certain parameters to enable random draws and resampling to adjust for certain disease states (**Appendix Table 45**). Normal distributions were selected for continuous features (e.g., height) and truncated normal distributions for continuous or ordinal features (e.g., self-reported health), which could not exhibit zero or negative values. A multinomial distribution was selected for smoking status with three categories (current, former and never). All other stochastically generated features used a Bernoulli distribution.

7.2.6 Probabilistic graphical models

Probabilistic graphical modelling, specifically Bayesian networks (BNs), were selected as the primary algorithm to generate synthetic IPD through risk prediction of other features. BNs were used as the 'glue' to create inter-relationships between features. BNs are well suited to reasoning under conditions of uncertainty and can handle non-fixed relationships between independent and dependent variables (536). BNs have a directed acyclic graph (DAG) consisting of nodes and edges representing the random variables (in this case diseases, symptoms or outcomes) and their direct probabilistic interactions respectively. The relationships can be modelled using a conditional probability distribution (CPD) for each node (536). The DAG and CPD are constructed for X_i using data sourced from the literature, including the prior probability of X_i where $\theta_i \ldots \theta_n$ are zero.

The Python library *pgmpy* was used to construct BNs. An automated script was developed to generate the code required to represent the DAG and CPD for $X_i \ldots X_n$ and its covariates using the *pgmpy* classes and methods. Briefly, an object containing the relevant summary statistics (OR, RR, HR) for each covariate of X_i was hard coded. Summary statistics were converted to RR (**Equation 1** and **Equation 2**) (537, 538), before creating the CPD matrix, which was embedded within the auto-generated *pgmpy* boilerplate code and appended to a class containing all PGMs.

$$RR = \frac{OR}{(1 - P_0) + (P_0 \times OR)}$$

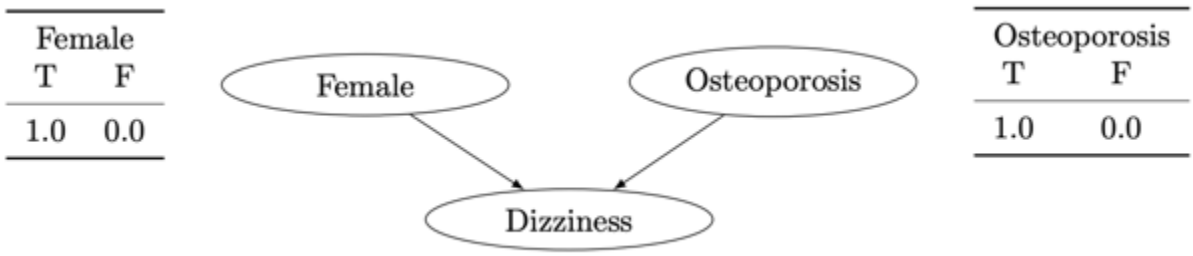
Equation 1 – Conversion of odds ratio to relative risk.
The odds ratio (*OR*) can be converted to relative risk (*RR*) where P_0 is the baseline risk.

$$RR = \frac{1 - e^{HR \times \ln(1 - r)}}{r}$$

Equation 2 – Conversion of hazard ratio to relative risk.
The hazard ratio (*HR*) can be converted to relative risk (*RR*) where *r* is the baseline rate of the event.

This avoided the error-prone process of hand coding each PGM. Each BN for X_i uses variable elimination for exact inference and the resulting probability is used with the RNG to determine the state of X_i. A single instance of the RNG is injected as a dependency throughout the model.

For each condition X_i, BNs were chained in a hard-coded specific order so that once a BN has inferred the risk of X_i, its stochastically determined state was available for another BN. This created a DAG of BNs and avoided the computational complexity of one large BN and large CPDs for each node. By separating the concern of each BN, it was not necessary for a single BN to compute probabilities for nodes without parents. A simple BN is exemplified in **Figure 36**, where each node is associated with its CPD table. The overall DAG of features are represented in **Figure 37** and the studies utilised are listed in **Appendix Table 46**. As an example, frailty was derived from the presence or absence of hearing loss (539), diabetes (540), visual impairment (541), three or more comorbidities (542), cardiovascular disease (543) and COPD (544).



Female	
T	F
1.0	0.0

Osteoporosis	
T	F
1.0	0.0

Female	Osteoporosis	Dizziness	
		T	F
F	F	0.11	0.89
F	T	0.263	0.737
T	F	0.155	0.845
T	T	0.37	0.63

Figure 36 – A simple Bayesian network for dizziness and its risk factors.
A simple Bayesian network for dizziness and its risk factors. Here two risk factors (female sex and osteoporosis) contribute to the risk of dizziness. The prevalence of dizziness in adults 65 years and above is 11%. The conditional probability distribution (CPD) table for dizziness shows that the prior risk of dizziness before observing female sex or osteoporosis is the symptom prevalence. When osteoporosis is observed the probability of having dizziness doubles, and when female sex is also observed the probability trebles. Osteoporosis is already more common in females than males, so females are more likely to be diagnosed with osteoporosis. This highlights an important aspect of this model, where each Bayesian network does not need to be concerned with the probability of nodes without parents. Parentless nodes simply provide common evidence for an outcome (e.g., dizziness).

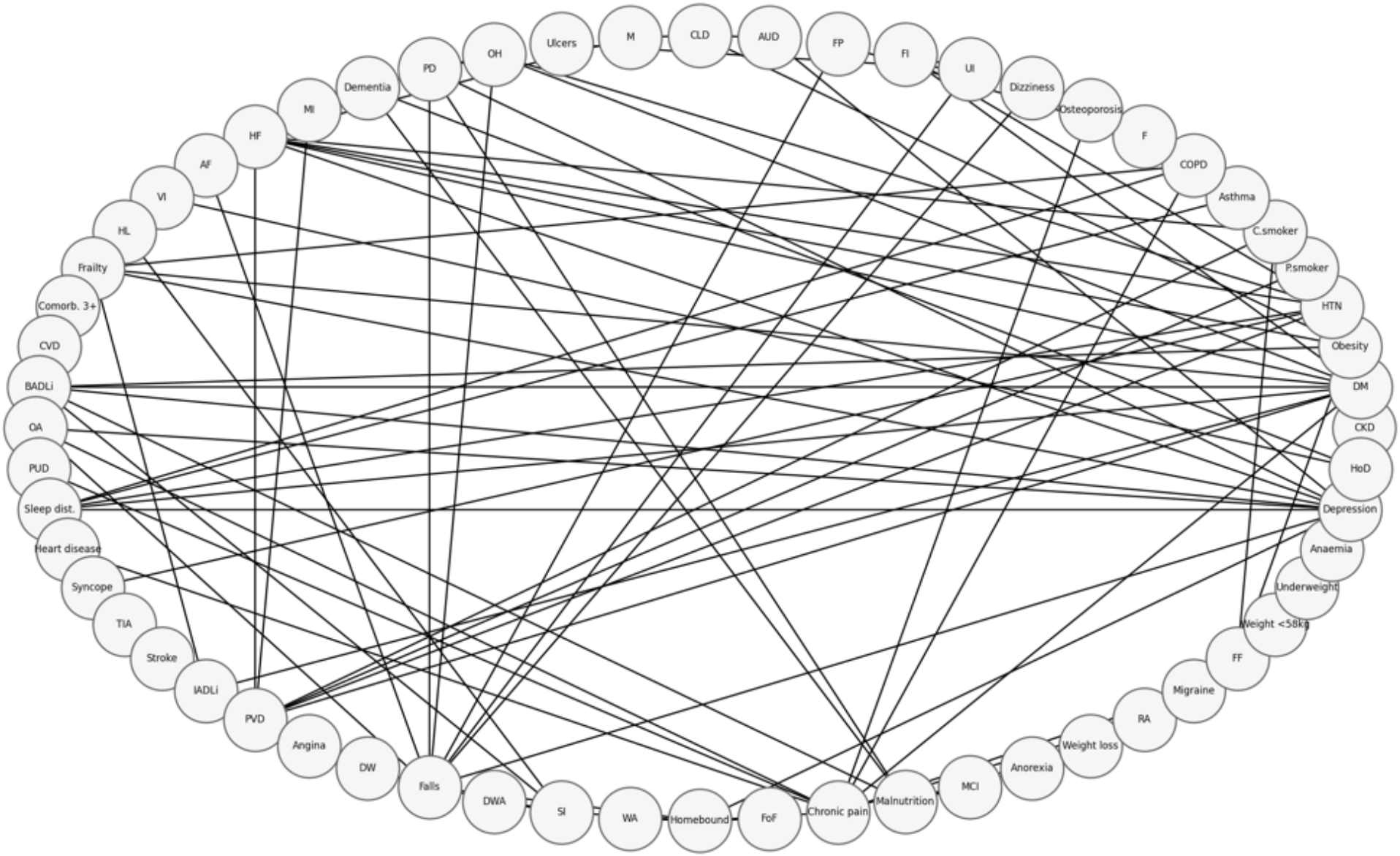

Ulcers
M
CLD
AUD
FP
FI
UI
Dizziness
Osteoporosis
F
COPD
Asthma
C.smoker
P.smoker
HTN
Obesity
DM
CKD
HoD
Depression
Anaemia
Underweight
Weight <58kg
FF
Migraine
RA
Weight loss
Anorexia
MCI
Malnutrition
Chronic pain
FoF
Homebound
WA
SI
DWA
Falls
DW
Angina
PVD
IADLi
Stroke
TIA
Syncope
Heart disease
Sleep dist.
PUD
OA
BADLi
CVD
Comorb. 3+
Frailty
HL
VI
AF
HF
MI
Dementia
PD
OH

Figure 37 – Directed acyclic graph of features network.
The features are interconnected using Bayesian networks to create a directed acyclic graph. Each node has a conditional probability distribution table associated with it. *Abbreviations (from top centre clockwise): M = male, CLD = chronic liver disease; AUD = alcoholic liver disease; FP = foot problems; FI = faecal incontinence; UI = urinary incontinence; F = female; COPD = chronic obstructive pulmonary disease; C.smoker = current smoker; P.smoker = past smoker; HTN = hypertension; DM = diabetes mellitus; CKD = chronic kidney disease; HoD = history of delirium; FF = fragility fracture; RA = rheumatoid arthritis; MCI = mild cognitive impairment; FoF = fear of falling; WA = walking aid; SI = social isolation; DWO = difficulty walking outside; DW = difficulty walking; PVD = peripheral vascular disease; IADLi = instrumental activities of daily living impairment; TIA = transient ischaemic attack; Sleep dist. = sleep disturbance; PUD = peptic ulcer disease; BADLi = basic activities of daily living impairment; OA = osteoarthritis; CVD = cardiovascular disease; HL = hearing loss; VI = visual impairment; AF = atrial fibrillation; HF = heart failure; MI = myocardial infarction; PD = Parkinson's disease; OH = orthostatic hypotension;*

This approach to generating interactions between variables was selected for several reasons. Firstly, most diseases do not have an established/validated predictive model (and where available this could be used alternatively). The actual summary statistic has little relevance, as the relative magnitudes of the interactions are most important. Finally, first principles dictate that the presence of multiple risk factors will have an augmenting effect and increase the likelihood of X_i, which may get close to, but never reaches, certainty.

7.2.7 Fuzzy logic

Fuzzy logic (FL) was first conceptualised by Zadeh in 1965 (545) to extend classic set theory and Boolean logic. Traditional Boolean logic deals with crisp sets, where members are either true (= 1), and completely belong in a set, or false (= 0), and are completely absent from the set. In a fuzzy set, members have a degree of membership, quantified as $x \in (0,1) \subset \mathbb{R}$. The degree of membership is expressed as a membership function where fuzzy set X has a universe of discourse (i.e., range between two extremes) U defined as $\mu_X: U \rightarrow [0,1]$. The resultant fuzzy inference system (FIS) helps deal with imprecision, which is common in medicine.

FL was used where modelling disease risk prediction with BNs using quantitative data were difficult. This could be due to the fuzzy nature of the condition itself (e.g., difficulty walking) or a lack of well-defined risk factors from meta-analyses or other large studies. Data from disparate studies was used to qualitatively generate combinations of fuzzy sets using both crisp and triangular membership functions. The latter is defined by lower limit a, upper limit b and value m, where $a < m < b$ and its membership function can be expressed as **Equation 3**.

$$\mu_X(x) = \begin{cases} 0, & x \leq a \\ \dfrac{x-a}{m-a}, & a < x \leq m \\ \dfrac{b-x}{b-m}, & m < x < b \\ 0, & x \geq b \end{cases}$$

Equation 3 – Triangular membership function. A triangular membership function is defined by lower limit $\boldsymbol{a}$, upper limit $\boldsymbol{b}$ and value $\boldsymbol{m}$, where $\boldsymbol{a < m < b}$.

This allows states of precision to be combined with states of imprecision in a process known as fuzzification, where crisp values are transformed into fuzzy sets. The fuzzification module is the first step in generating a FIS, which also consists of i) a knowledge base to store IF-THEN rules, either developed by experts or machine learning (e.g., fuzzy neural networks); ii) an inference engine that reasons via a fuzzy inference process using the inputs and knowledge base; and iii) an optional defuzzification module to output crisp values from the fuzzy set generated from the inference engine. The open source Python library *Simpful* (546) was used to generate the FIS as it offers boilerplate code for FIS development, including helpful utility classes and the ability to code rules in natural language. The knowledge base was constructed using expert opinion of how disparate risk factors likely interact to increase the risk of condition X_i. Fuzzy reasoning occurs in the inference engine and either Sugeno's or Mamdani's method could be used, which are both supported by *Simpful*. Sugeno's method was selected for this model for two main reasons: i) at runtime this is a mathematical analysis, which is better suited towards Sugeno's method; and ii) all systems are Multiple Input Single Output, making the computational burden of Mamdani's method unnecessary. It should be noted that Sugeno's method does not require defuzzification, as the crisp output uses the weighted average of the output from the rules.

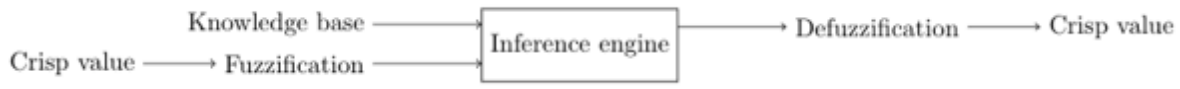


Figure 38 – Fuzzy inference system.
Crisp input values undergo fuzzification and are combined with the IF-THEN statements from the knowledge base in the inference engine. A process of defuzzification converts the fuzzy inference set into a crisp value.

7.2.8 Existing models

There are several existing models that could be used to predict disease states and outcomes, including the: i) QRisk® algorithm for 10-year risk of cardiovascular disease (angina,

myocardial infarction, stroke and transient ischaemic attack) (547); ii) Suemoto Index for predicting 10-year mortality (71); iii) CARG chemotoxicity risk prediction score (7); iv) National Confidential Enquiry into Patient Outcome and Death Surgical Outcomes Risk Tool for 30-day postoperative mortality (455).

7.2.9 Custom algorithms

7.2.9.1 Prescribing and polypharmacy

Study of the risk factors of polypharmacy is limited to several studies using linear/logistic regression that identified disparate upstream factors (see review by Khezrian *et al*. (548)), which were difficult to model and impossible to meta-analyse. Given that polypharmacy is a function of prescribing for disease or symptoms states, a custom prescribing algorithm was developed. An advantage of this approach also enables the generation of synthetic prescribing data, potentially useful for health economic modelling, clinical training or semi-supervised training of reinforcement learning algorithms to optimise oncogeriatric prescribing. Synthetic IPD was iteratively searched for disease states that have a high likelihood of association with a prescribable medication. Prescribing data were obtained from existing publications reporting patterns or prevalence data on prescribing. This data were used to develop probability distributions for individual disease-based prescribing. A prescribing class was programmed using the *Python* programming language and synthetic IPD generated for testing was used for development. Structured query language (SQL) was used with an SQLite database to store and query prescribing data, linked to synthetic IPD by a unique identifier. Extensive integration testing was undertaken to eliminate duplication of the same agent and class. The prescribing data were programmatically audited against the Screening Tool to Alert to Right Treatment (START) and Screening Tool of Older Persons' Prescriptions (STOPP) criteria (416). A decision was made to allow imperfect synthetic prescribing, where some important patterns observed clinically and in published articles are preserved.

7.2.10 Gradient-boosted decision trees

For the development of predictive algorithms using the synthetic IPD, gradient-boosted decision trees (DTs) were selected as the primary method of analysis due to their high accuracy, ease of training and explainability. DTs are supervised machine learning algorithms used for solving classification problems (549). By iterating over the data, simple if-then-else decision rules can be generated from the data features to produce a tree-like representation of the predictive model. This enables the model to predict a label (e.g., adverse outcome), given certain features and conditions, with a certain degree of accuracy (549). DTs have many

advantages for clinical predictive models, including an intuitive basis (i.e., clinical decision-making follows certain if-then-else rules) and the visualisation element is identical to flowcharts within protocols. DTs are a white-box model and are clearly explainable using logic and can be validated using statistical tests to establish both reliability and accuracy. There are some important disadvantages of DTs to consider, including i) overfitting, where overly complex trees can be developed with poor generalisation; and ii) instability, where small data variations can lead to very different trees being developed (549). The specific DT algorithm selected was *CatBoost* (v0.26, Yandex LLC) (550). *CatBoost* is an open-source Python library for gradient-boosted DTs with several advantages: i) the default parameters used for tuning are optimised to produce high quality results; ii) gradient-boosting helps to reduce overfitting; and iii) the option to use categorical features without further data processing (550). The *CatBoost* library was utilised in accordance with the developer's instructions. A grid search for hyperparameters using the in-built grid search function within *CatBoost*. The hyperparameter search space included iterations (100, 1000), tree depth (4, 6, 8, 10), learning rate (0.03, 0.1, 1) and L2 leaf regularisation (1, 3, 5, 7, 9). The *CatBoost* developers recommend iterations above 100 and depth between 4-10 with optimum depth usually 6-10. Lower depth levels are preferable from a clinical implementation perspective. The in-built overfitting detector was applied and set to the *Iter* function with a *Logloss* function.

7.2.11 Data pre-processing

Data were split into training, validation and testing sets as required using the *Scikit-learn* package and train_test_split function. Where only training and testing sets were required, the ratio was 4:1 respectively. If a validation set was also required, the ratio was 3:1:1 for training, validation and testing respectively.

All classes were binary and class balancing was undertaken where the proportion of each class (e.g., absent versus present) for a label was significantly unmatched. Synthetic minority oversampling technique (SMOTE) was used via the *Imbalanced-learn* package for Python (551). Depending on the need to attempt to improve upon the AUROC, different strategies were utilised for class balancing, starting with a 1:1 balance (the package default) or oversampling the minority class and under sampling the majority class. The latter was proposed in the original development of SMOTE (552) and is thought to perform better.

To capture the prevalence of outcomes, the RNG was used to stochastically generate these outcomes, which also served as an integration test of BN function and the overall DAG.

However, initial analysis revealed that this method perturbated significant stochastic effects throughout the model. This led to almost all predictive models performing only slightly better than chance, with AUROC of approximately 0.5. This was often due to poor specificity in labels with balanced classes. In the absence of reference RWD on the outcomes simulated, and to enable the modelling of unknown outcomes based on their probabilities, pseudo classes were used for labels. Pseudo classes were generated by tuning the thresholds used for unbalanced classes against the F1 score, or assuming a threshold of 0.5 for balanced classes. For unbalanced classes, the probabilities predicted by the DTs trained against the stochastically generated labels were systematically revaluated using the F-Measure and thresholds between 0.0 and 1.0 with a step size of 0.001. The threshold exhibiting the highest F-Measure was selected.

7.2.12 Statistical analysis

All statistical analysis was undertaken using the Python programming language, assisted by numerous open-source packages (see **Appendix Table 36**). Accuracy was reported using area under the receiver operating characteristic (AUROC) curve for outcomes with balanced classes and area under the precision-recall (AUPR) curve for unbalanced classes, sensitivity and specificity. Data splitting, model fitting and evaluation was repeated 100 times using Monte Carlo simulations to achieve a mean accuracy metric with a 95% confidence interval.

A core motivation for undertaking complex modelling was to conceptualise a predictive algorithm for general adverse outcomes which could enable cancer MDTs to risk stratify patients. To model this, composite endpoints (CEs) were formulated as shown in **Table 10**. These CEs were adjusted to strike a balance between the sensitivity of the CE and its completeness. For example, the addition of chemotherapy toxicity to the CE for oncogeriatric input being desirable increased the sensitivity dramatically, with an unacceptably high prevalence (>90%) from a clinical perspective.

Composite endpoint	Components
Adverse surgical outcomes	30-day post-operative mortality (minor procedure) 30-day post-operative mortality (major procedure) Postoperative major adverse cardiac event Postoperative intensive therapy unit admission Postoperative neurological complications Postoperative pulmonary complications Postoperative sepsis Increased length of stay
Adverse chemotherapy outcomes	Neutropaenic events Chemotherapy toxicity present
Adverse general outcomes	30-day post-operative mortality (minor procedure) 30-day post-operative mortality (major procedure) Postoperative major adverse cardiac event Postoperative intensive therapy unit admission Postoperative neurological complications Chemotherapy toxicity present
Oncogeriatric input desirable	Functional decline Postoperative major adverse cardiac event Postoperative intensive therapy unit admission Postoperative neurological complications Postoperative delirium Increased length of stay

Table 10 – Composite endpoints
Composite endpoints and their components

7.3 Results

7.3.1 Synthetic individual patient data

7.3.1.1 Demographics and basic characteristics

The core dataset used in this chapter was run on the 29th of November, 2021 and generated 243,541 synthetic IPD samples. The demographic and other basic characteristics of the synthetic IPD are shown in **Table 11**, the prevalence of features compared to expected prevalence is illustrated in **Figure 39**. Most features mirrored the expected prevalence, except for polypharmacy, weight loss, COPD and CKD. Statistical tests are not possible when comparing the expected versus the simulated prevalence of features, as the expected prevalence is not derived from another sample.

Age*, years (range)	76 (65-104)
Gender, % female	51
Anthropometrics	
Height*, cm (SD)	163.6 (5.2)
Weight*, kg (SD)	72.0 (5.2)
Body mass index* (SD)	27 (5)
Other	
Creatinine*, µmol/L (95% CI)	118 (118-119)
Self-reported health* (95% CI)	2.6 (2.6-2.6)
Timed-up-and-Go test*, s (95% CI)	10.1 (10.1-10.1)
Frailty*, % (95% CI)	35.3 (35.1-35.5)
Electronic frailty index	
Moderate frailty, %	38.5
Mild frailty, %	31.3
Severe frailty, %	26.9
Fit, %	3.3

Table 11 – Demographic and basic characteristics of synthetic individual patient data.
*Arithmetic mean. *Abbreviations: SD = standard deviations; CI = confidence interval*.

7.3.1.2 Cancer epidemiology

The prevalence of each cancer type is illustrated in **Figure 40**. Lung cancer was the most common cancer type (14.9%), followed by breast cancer (13.8%), colon cancer (11.1%), non-Hodgkin's lymphoma (7.3%) and prostate (5%).

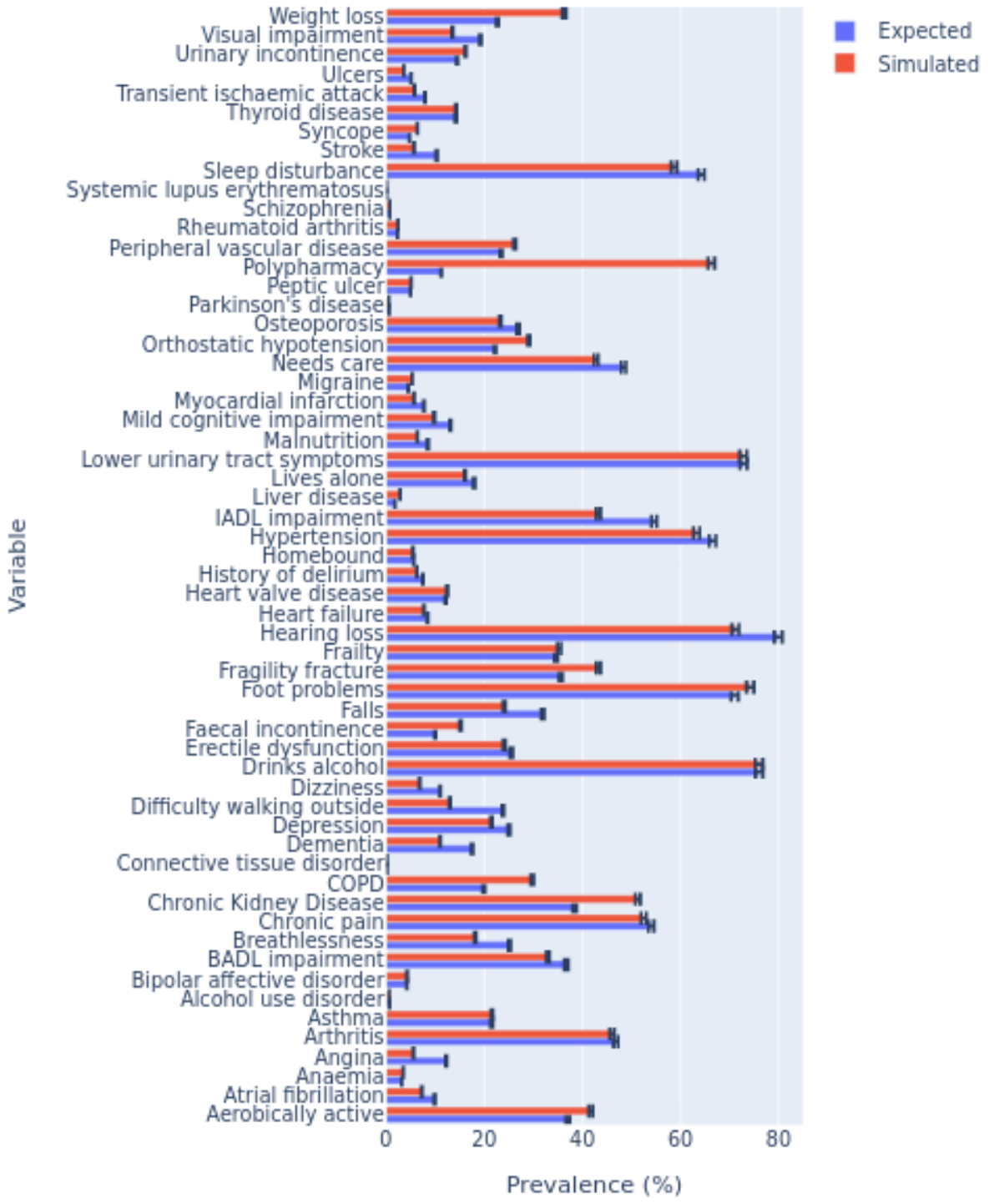


Figure 39 – Horizontal bar chart representing the expected prevalence of each feature compared to the simulated prevalence of the synthetic population.
Abbreviations: BADL = basic activities of daily living; COPD = chronic obstructive pulmonary disorder; IADL = instrumental activities of daily living.

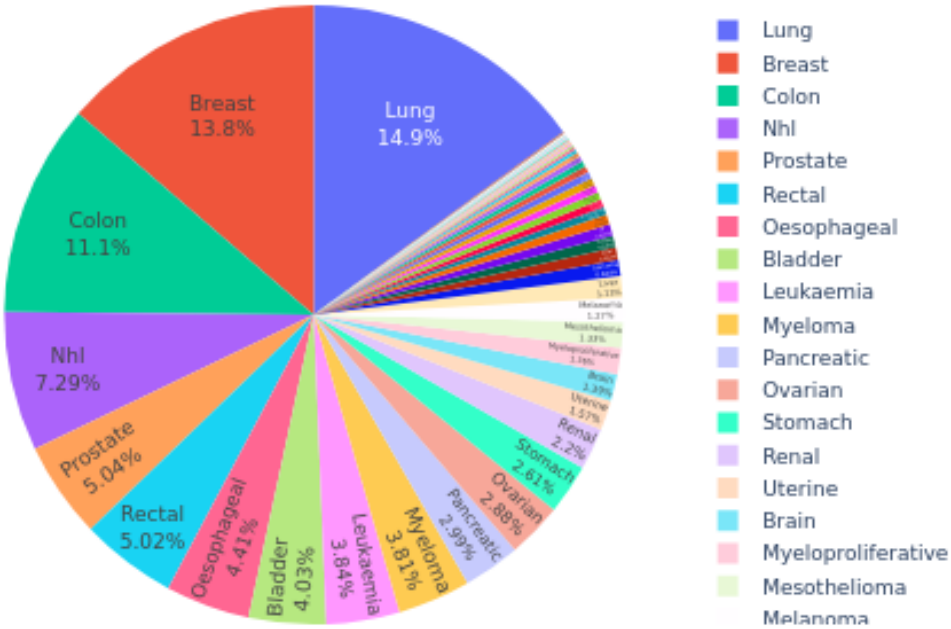


Figure 40 – Pie chart of prevalence of cancer types in synthetic individual patient data.

7.3.1.3 Spectrum of frailty, disability and multimorbidity

The prevalence of frailty, disability and multimorbidity was 35.3%, 33% and 88.4% respectively (**Figure 41**) and the most significant overlap was between frailty and multimorbidity (18.9%), followed by disability and multimorbidity (14.9%). The triad of frailty, disability and multimorbidity was observed in 14.9% of the synthetic population. Only 0.9% of synthetic patients exhibited isolated frailty, whereas isolated multimorbidity was observed in 39.7% of cases. Less than 1% of synthetic patients exhibited frailty and disability without multimorbidity.

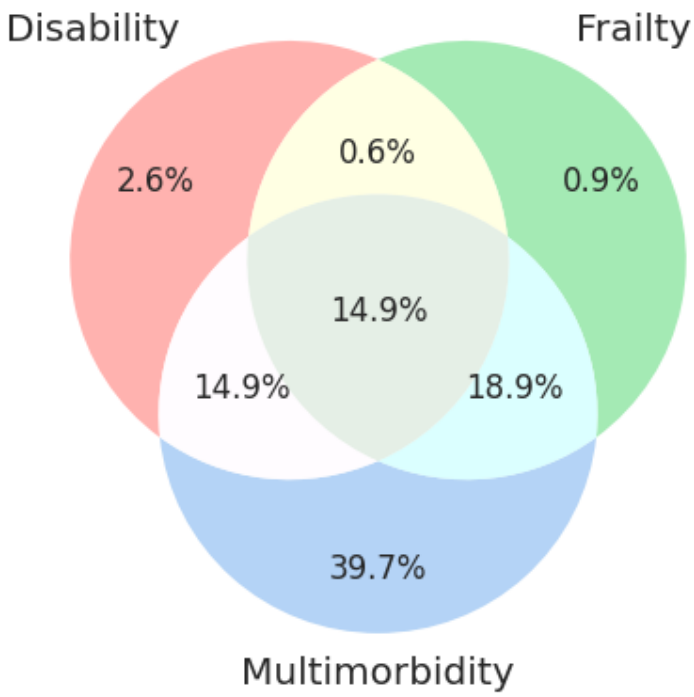


Figure 41 – Venn diagram illustrating the overlap between frailty, disability and multimorbidity.

7.3.1.4 Relationship between features

The relationship between activity levels and body mass index (BMI) is illustrated in **Figure 42**. The population was overweight (BMI 25-29.9) or obese (BMI ≥ 30) in 59% of cases and the highest levels of activity (17%) were seen in the normal weight (BMI 18.5-24.9) group. The relationship between other variables is demonstrated in **Figure 43** using Spearman's corelation coefficient and **Figure 44** using hierarchical clustering (unsupervised machine learning) and a *Python* programming language port of the *R* programming language package *hclustvar*. Hard-coded relationships tend to exhibit stronger correlations than BN derived relationships, which are more subtle.

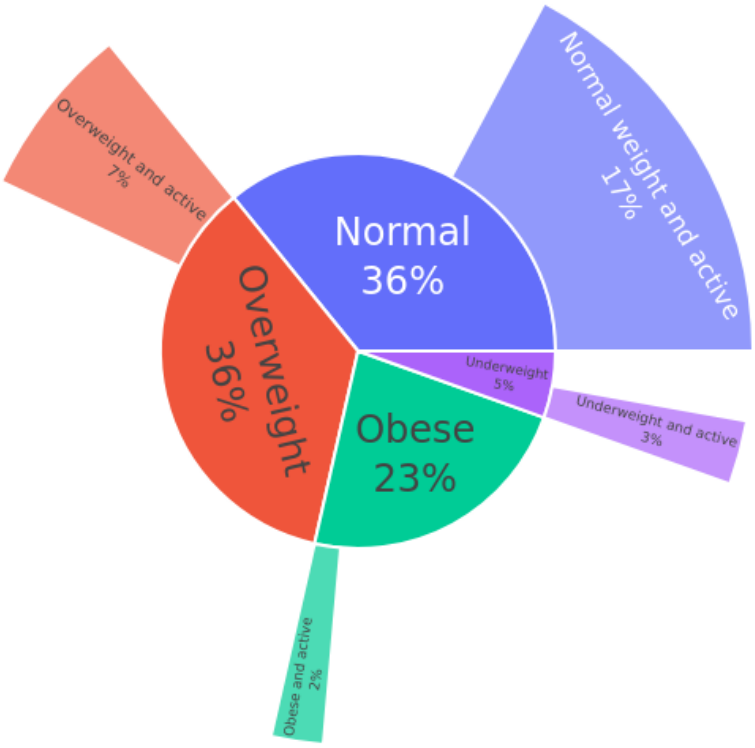


Figure 42 – Multilevel pie chart illustrating the relationship between body mass index categories and activity levels.
BMI categories: underweight (BMI < 18.5); normal (BMI 18.5-24.9); overweight (BMI 25-29.9); obese (BMI ≥ 30).

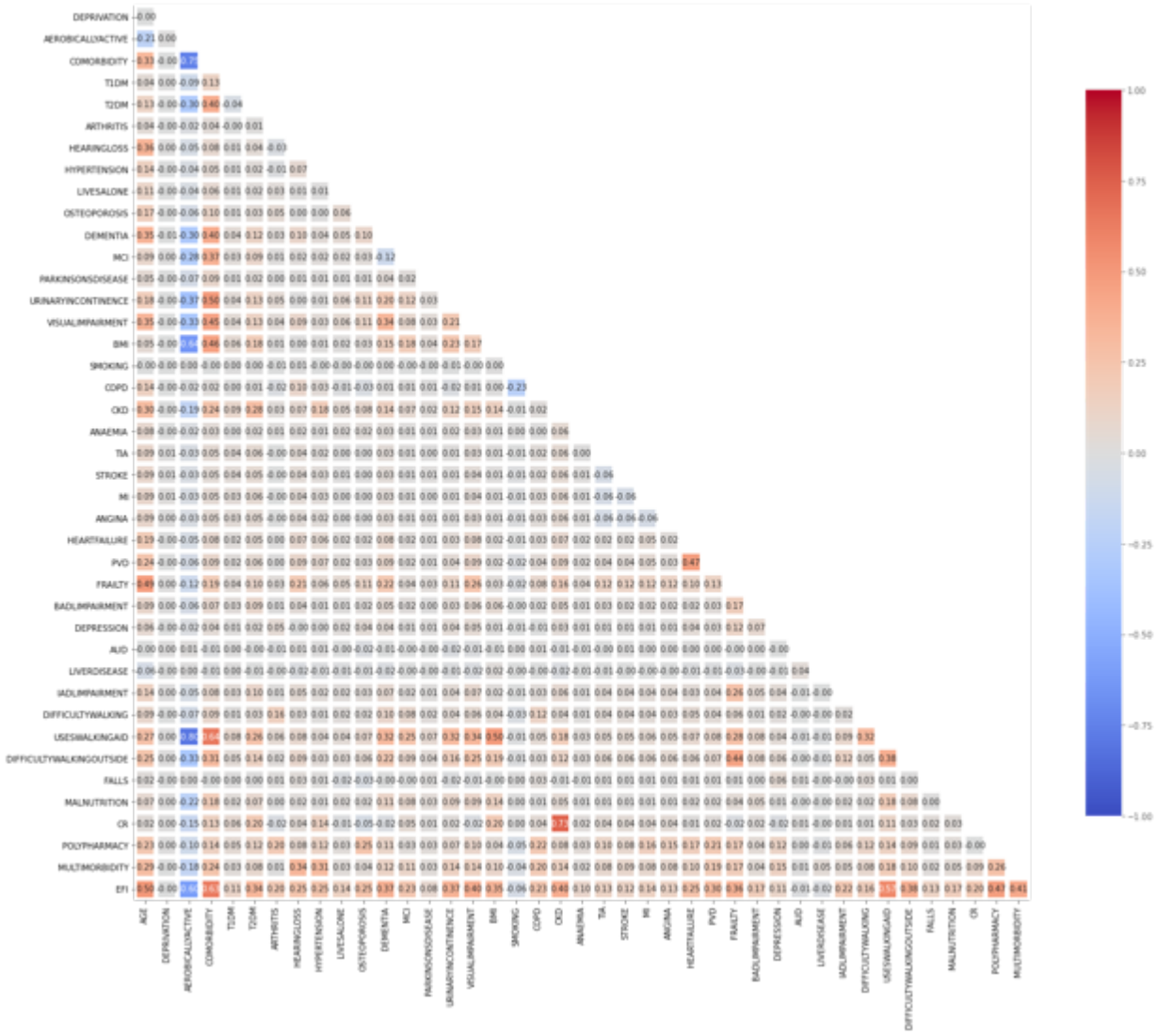


Figure 43 – Correlation heatmap between key features.
Spearman's correlation coefficient was used to generate a heatmap of relationships between variables. *Abbreviations: T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; MCI = mild cognitive impairment; BMI = body mass index; COPD = chronic obstructive pulmonary disease; CKD = chronic kidney disease; TIA = transient ischaemic attack; MI = myocardial infarction; PVD = peripheral vascular disease; BADL = basic activities of daily living; IADL = independent activities of daily living.*

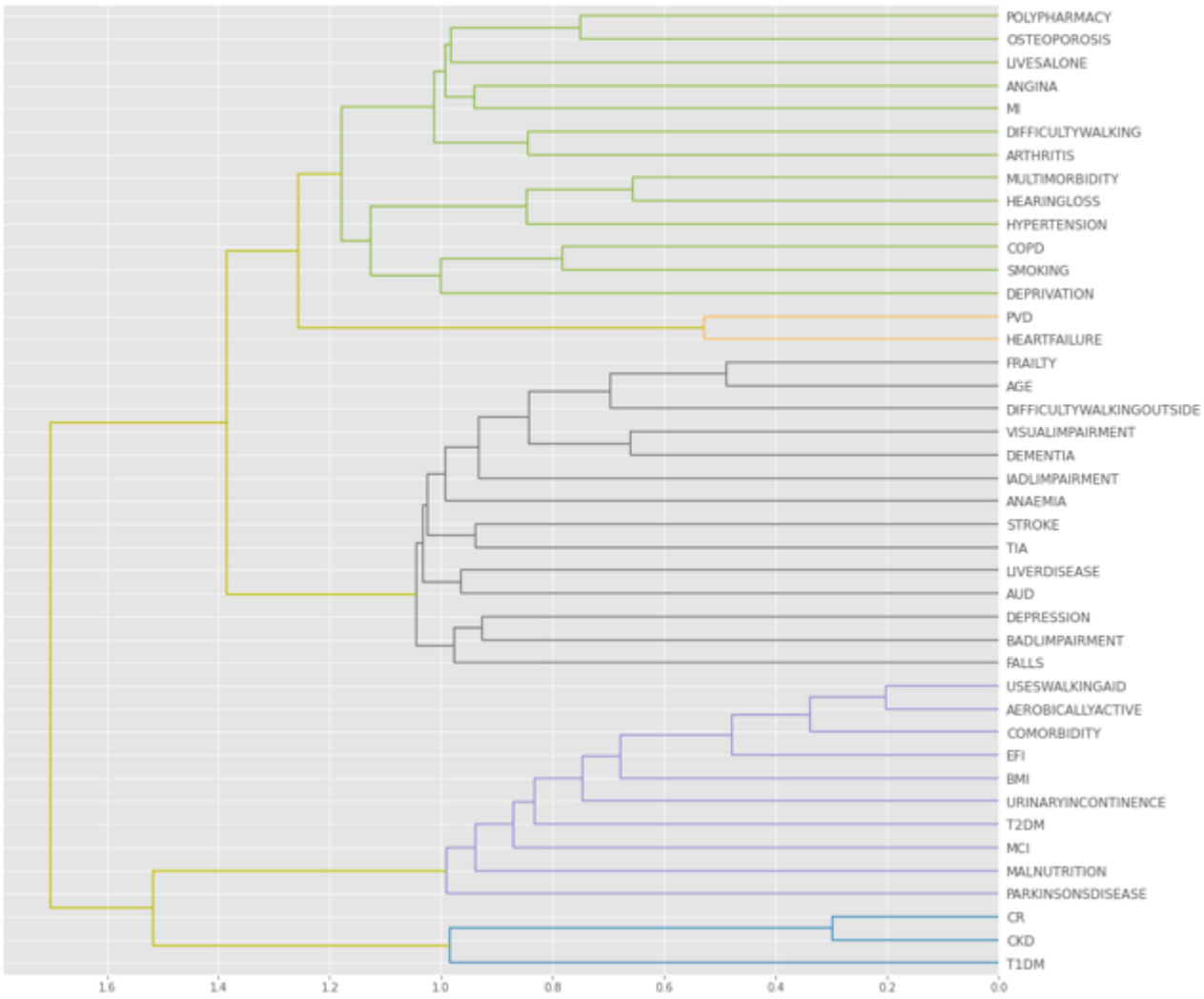


Figure 44 – Dendrogram representing the hierarchical clustering of variables.
There were strong relationships between all variables, except renal disease, creatinine and alcohol use disorder. There were complex sub-hierarchies that broadly were related to eFI and multimorbidity. Abbreviations: MI = myocardial infarction; COPD = chronic obstructive pulmonary disease; PVD = peripheral vascular disease; TIA = transient ischaemic attack; AUD = alcohol use disorder; EFI = electronic frailty index; BMI = body mass index; T2DM = type 2 diabetes mellitus; MCI = mild cognitive impairment; CR = creatinine; CKD = chronic kidney disease; T1DM = type 1 diabetes mellitus; BADL = basic activities of daily living; IADL = instrumental activities of daily living.

7.3.1.5 Electronic frailty index

The diagnostic accuracy of eFI for frailty was calculated with sensitivity 99.4%, specificity 4.4%, negative predictive value 90.5% and positive predictive value 44.5%. Given the interest in the use of eFI as a single measure for the prediction of oncogeriatric outcomes, its diagnostic accuracy within the model was evaluated (**Table 12**).

Composite endpoint	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Adverse general outcomes	97.4	26.9	99.5	26.9
Adverse chemotherapy outcomes	98.4	9.3	86.0	50.5
Adverse surgical outcomes	97.5	16.9	100	9.5
Oncogeriatric input desirable	97.4	14.8	98.8	7.6

Table 12 – Electronic frailty index and diagnostic accuracy of composite endpoints
The electronic frailty index as a single feature was evaluated against the four composite endpoints. *Abbreviations: PPV = positive predictive value; NPV = negative predictive value.*

7.3.1.6 Outcome data

The prevalence of important individual and CE outcomes is detailed in **Table 13**.

Outcome	Prevalence, % (95% CI)
Postoperative delirium	28.6 (27.2-30.1)
Postoperative complication (any)	41.7 (40.2-43.3)
Postoperative wound complications	7.7 (6.9-8.5)
Postoperative sepsis	2.7 (2.2-3.3)
Postoperative pulmonary complications	21.8 (20.5-23.1)
Postoperative neurological complications	0.7 (0.4-1.0)
Postoperative ITU admission	0.8 (0.5-1.1)
Postoperative increased length of stay	52.2 (50.6-53.8)
Functional decline	31.5 (30.1-33.0)
Postchemotherapy neutropaenic events	15.9 (14.7-17.1)
Dependent care setting	9.8 (8.9-10.7)
Chemotherapy toxicity (Grade 2-4)	46.5 (44.9-48.1)
Postoperative major adverse cardiac event	1.3 (1.0-1.7)
Postoperative 30-day mortality (major procedure)	7.9 (7.1-8.8)
Postoperative 30-day mortality (non-major procedure)	6.1 (5.4-6.9)
Excess 10-year non-cancer mortality[1]	51.2 (49.6-52.8)
Composite endpoint (adverse events – surgery)	70.1 (68.6-71.5)
Composite endpoint (adverse events – chemotherapy)	54.7 (53.2-56.3)
Composite endpoint (adverse events – general MDT level concerns)	55.0 (53.4-56.5)
Composite endpoint (may benefit from oncogeriatric input)	77.1 (75.7-78.4)

Table 13 – Prevalence of individual and composite endpoint outcomes generated through modelling.
[1]Above median cancer survival for all cancers. *Abbreviations: CI = confidence interval.*

7.3.2 Predictive algorithms

7.3.2.1 Predicting a composite general adverse outcome

A DT for the CE for general adverse outcomes was generated. The mean AUROC was 0.996 (95% CI, 0.996-0.997) after 100 Monte Carlo simulations.

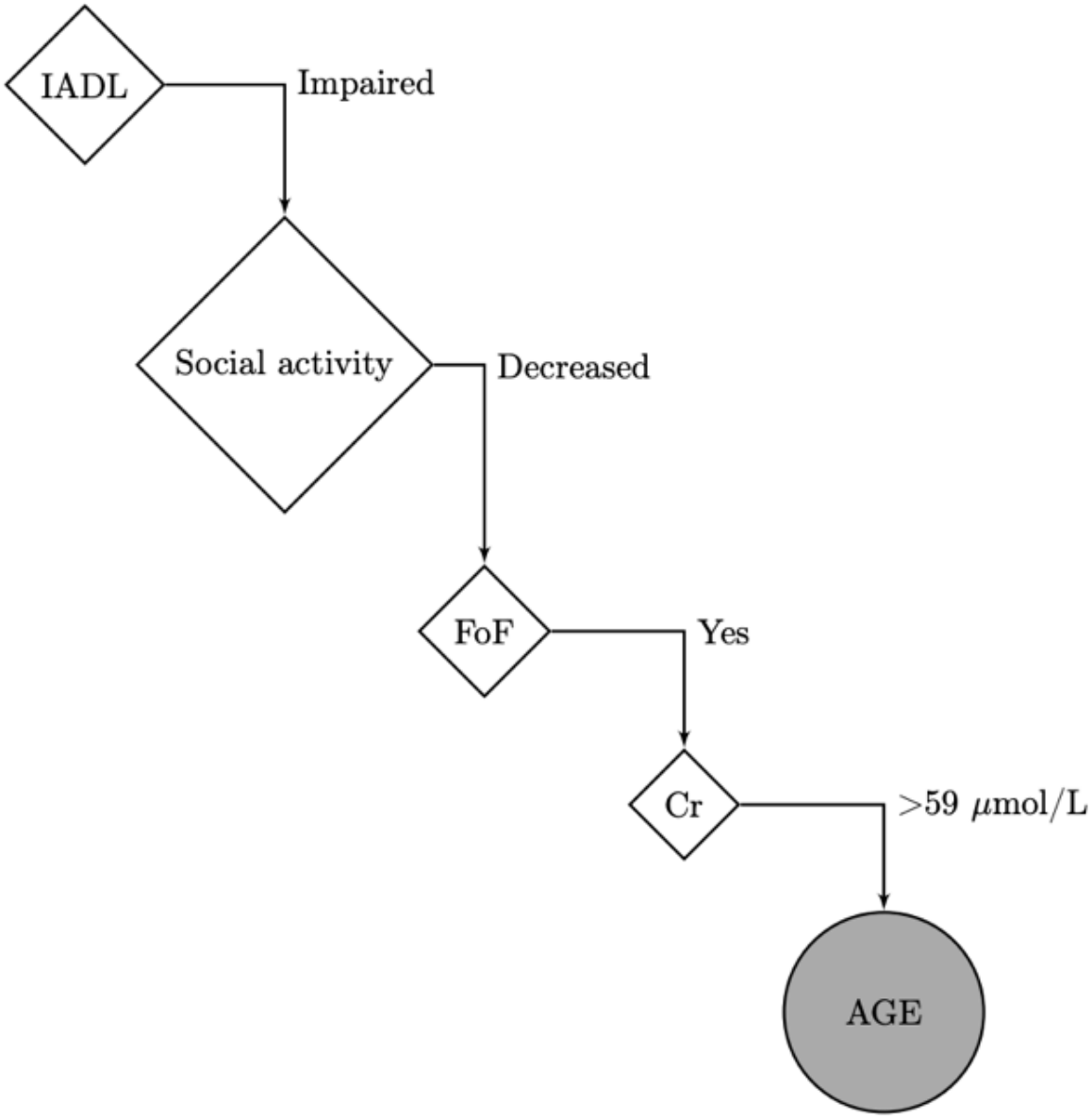


Figure 45 – Decision tree for adverse general events
Abbreviated representation of gradient-boosted decision-tree plot for an adverse general event (AGE), which is a composite endpoint for multiple outcomes across surgery and chemotherapy treatments. The alternative nodes and edges of the tree are not illustrated for brevity. Hyperparameters: depth=4, l2_leaf_reg=1, iterations=1000, learning_rate=0.03. *Abbreviations: IADL = instrumental activities of daily living, FoF = fear of falling; and Cr = creatinine.*

7.3.2.2 Predicting the need for oncogeriatric assessment

A DT for the CE for oncogeriatric input being desirable was generated. Age and TIA appeared to be resulting in overfitting therefore these features were excluded and fitting revaluated. The mean AUROC was 0.994 (95% CI, 0.993-0.994) after 100 Monte Carlo simulations.

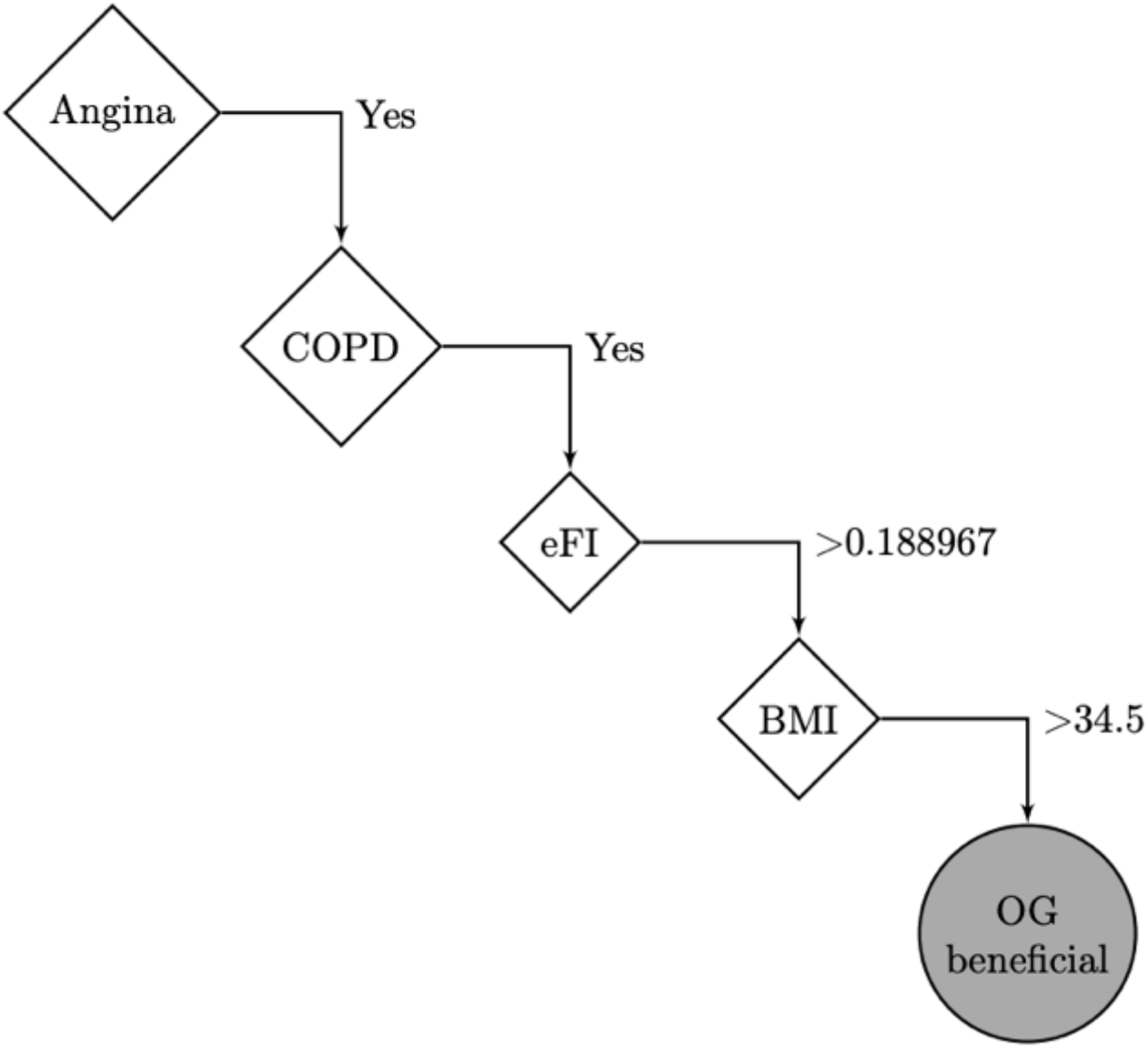


Figure 46 – Decision-tree for predicting whether oncogeriatric input may be beneficial
Abbreviated representation of gradient-boosted decision-tree plot for oncogeriatric (OG) input being beneficial. Hyperparameters: depth=4, l2_leaf_reg=1, iterations=1000, learning_rate=0.03. *Abbreviations: COPD = chronic obstructive pulmonary disease; eFI = electronic frailty index; BMI = body mass index.*

7.3.2.3 Predicting adverse surgical event

A DT for the CE for adverse surgical events being desirable was generated. The mean AUROC was 0.996 (95% CI, 0.996-0.996) after 100 Monte Carlo simulations.

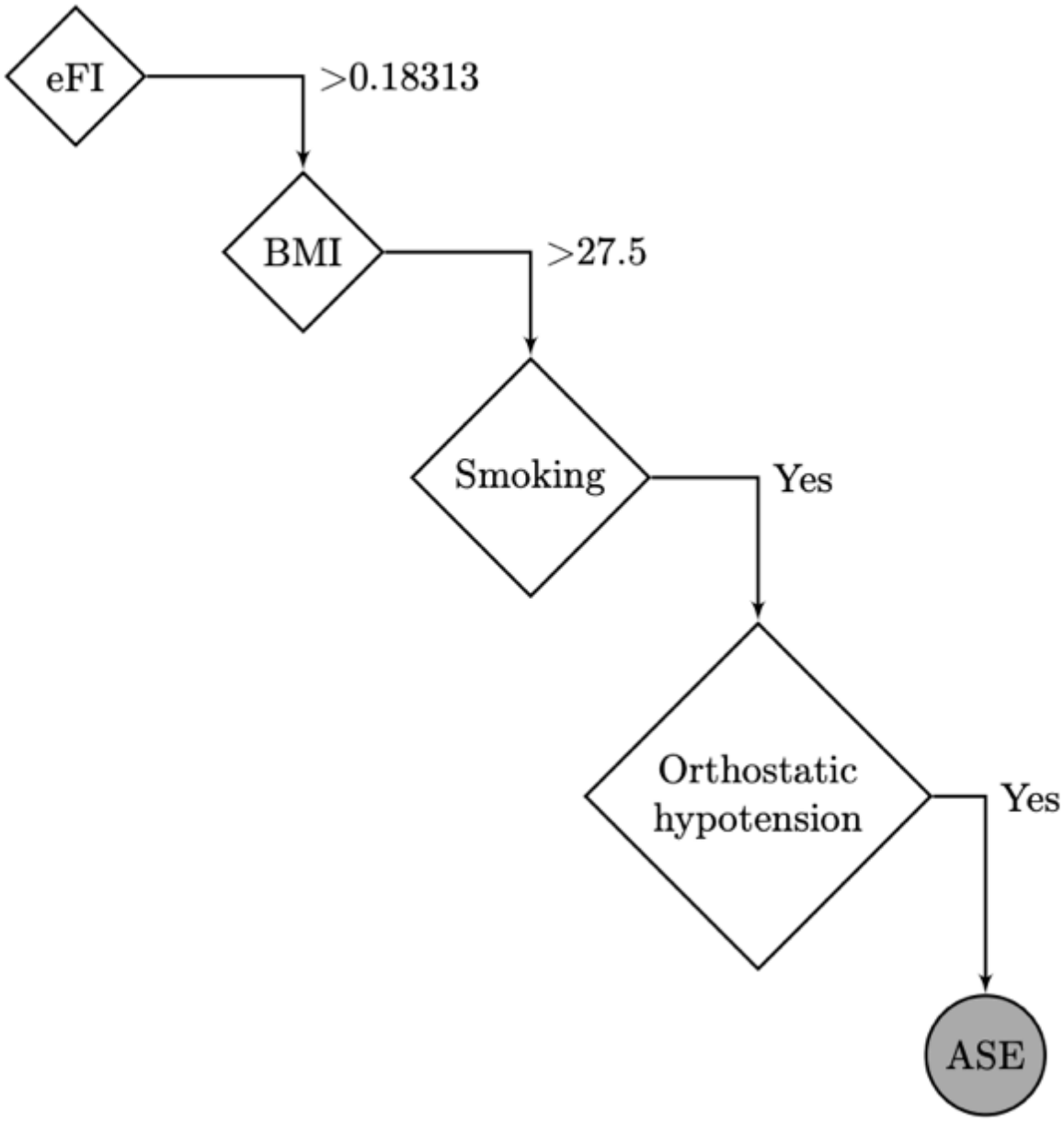


Figure 47 – Decision tree for adverse surgical events
Abbreviated representation of gradient-boosted decision-tree plot for an adverse surgical event (ASE), The alternative nodes and edges of the tree are not illustrated for brevity. Hyperparameters: depth=4, l2_leaf_reg=3, iterations=1000, learning_rate=0.03. *Abbreviations: eFI = electronic frailty index; BMI = body mass index.*

7.3.2.4 Predicting adverse chemotherapy events

A DT for the CE for adverse chemotherapy events was generated **Figure 48**. The mean AUROC was 0.954 (95% CI, 0.953-0.955) after 100 Monte Carlo simulations.

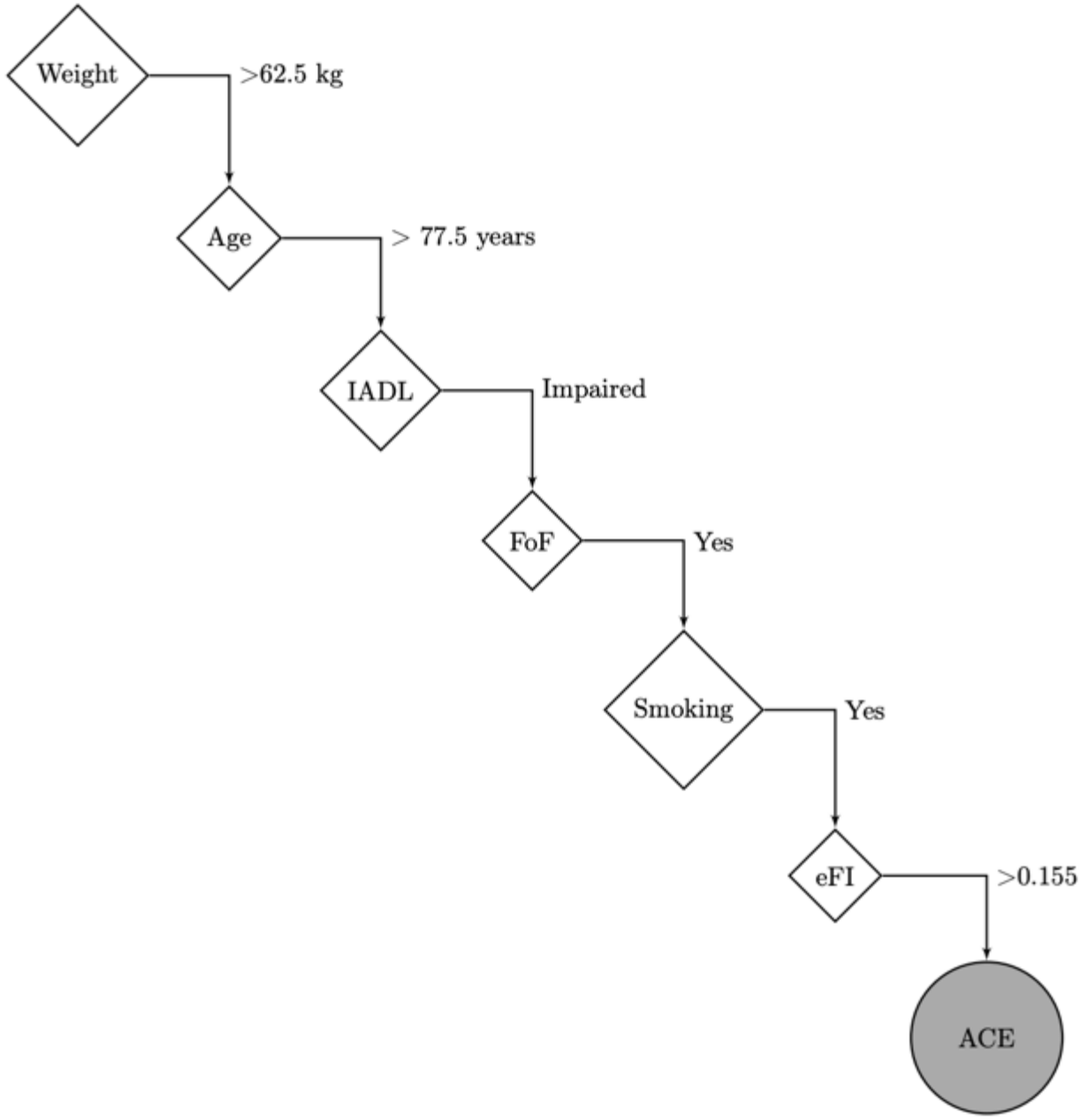


Figure 48 – Decision tree for adverse chemotherapy events
Abbreviated representation of gradient-boosted decision-tree plot for an adverse chemotherapy event (ACE), which is a composite endpoint for grade 3-5 chemotherapy toxicity and neutropaenic events. The alternative nodes and edges of the tree are not illustrated for brevity. Hyperparameters: depth=6, l2_leaf_reg=3, iterations=1000, learning_rate=0.03. *Abbreviations: IADL = instrumental activities of daily living, FoF = fear of falling; and eFI = electronic frailty index.*

7.4 Discussion

7.4.1 Summary of study and main findings

A plethora of data were identified, extracted, sanitised and analysed from the peer-reviewed literature, the English Longitudinal Study of Ageing and synthetically derived RWD from the *Simulacrum* database. An expert-curated, complex model was developed and analysed through software engineering using synthetic IPD generated by probability theory, custom and existing algorithms and supervised machine learning. Synthetic IPD exhibited high fidelity to RWD with preservation of important statistical and clinically relevant inter-relationships between features. The model analysis using supervised machine learning generated interesting and explainable predictive algorithms for a range of clinically important composite endpoints. The model developed is a sandbox environment that can be expanded, contracted and updated in a modular fashion.

7.4.2 Comparisons to previous studies

The known overestimation of frailty by the eFI due to high sensitivity and low specificity, was preserved by the model. For example, this could mean that a fit older adult with several minor conditions that were non-limiting could be scored as mildly frail. Broad *et al.* (553) undertook a cross-sectional study of 2,655 patients comparing the CFS to the eFI and found that the odds of overestimation of frailty by eFI was 5.43. No attempt was made to engineer this into the synthetic model, instead the preservation of these observations probably relates to the high prevalence of some of the deficits included in the eFI, such as hearing and visual impairment.

This study draws parallels with several other research themes. Precision oncology has principally focussed on somatic tumour mutations to aid diagnosis (e.g., the *BCR-ABL* fusion gene in chronic myeloid leukaemia), guide the selection/avoidance of systematically administered anti-cancer therapies (SACT; e.g., *EGFR* in non-small cell lung cancer) and avoiding treatment toxicity (e.g., *UGT1A1* genotyping before irinotecan prescription) (554). Germline genomics has received less attention, although some evidence suggests certain non-oncogenic germline mutations may have relevance for certain outcomes (554). GA should be considered a component of precision oncology as the data enhances the selection of the treatment *strategy* (e.g., surgery, systemically administered cancer treatments, radiotherapy or best supportive care) and *intensity* (e.g., dose reduction) towards utilitarianism (i.e., the greatest good for the greatest number). For example, a systematic review showed that GA changes management in around 28% of cases at the MDT (tumour board) level, frequently to lower

intensity (73). Modelling in oncogeriatrics must therefore take a different approach focussing on clinical-clinical interactions initially, before introducing additional layers of complexity.

Digital twins have focussed on single organs, including pancreatic, paediatric cardiology and diabetes models (555). Barbiero *et al*. (555) took a more general approach utilising graphical representations of transcriptomic, cellular, organ and tissue dynamics by employing ordinary differential equations and synthetic data, graph neural networks and GANs. Modelling at omic levels has less relevance in older adults, since health, disease and environmental exposure states have already become well established. This chapter focussed on clinical-clinical interactions since they map directly to important clinical endpoints. Cancer MDTs see a wide distribution of health states of older adults and computational regression to previous states may have less relevance when making a future decision. The largest known other synthetic IPD source is Synthea (514), which models US primary care data from birth to death. Synthea is based on basic epidemiological and probabilistic methods that form the first layer of the work in this chapter. More complex approaches using machine learning are not currently employed by Synthea. The underlying rationale behind data synthesis also differs with this study. Synthetic IPD is derived from RWD and empirical data to bootstrap the training of the model. Further aggregate or individual RWD may be used to refine the underlying data model in a bidirectional manner, therefore creating a digital twin.

7.4.3 Strengths

The strengths of this study include the novel generation of thousands of synthetic IPD for this population using robust software engineering and data science practices. The large amount of data utilised meant that high fidelity to RWD was possible. High performance computing was employed to scale the model and data were analysed using machine learning, generating interesting and explainable predictive algorithms. The adoption of complex modelling played an important role in this thesis that enabled further exploration of the findings in **Chapter 5** in a sandboxed environment. Although a digital twin was not created in the strictest sense, the model generated here and many of the techniques employed, including Bayesian inference, FL, high performance computing and Monte Carlo simulations would formulate part of a digital twin. The data collection application developed in **Chapter 6** could easily create a data feed to the algorithms in this chapter, thereby creating a bidirectional connection to RWD and a digital twin.

7.4.4 Limitations

The limitations of this study include the principal fact that this is a model and not derived solely from RWD. Some features that may be relevant were not included in the data model and inter-relationships between features are not exhaustive. However, the preferred use of meta-analyses as a data source means that most major associations should be captured where available. The AUROC values derived in the predictive models are abnormally high. This is due to the threshold tuning process used to generate the pseudo classes. When the RNG was used to generate classes, excessive randomness propagated throughout the system, whereas the pseudo classes are artificially accurate. Future work could seek unique methods to find a median to these phenomena. One possibility is to integrate fuzzy cognitive maps to handle the calculated risks of post-treatment outcomes and use them with expert curate weights to derive CEs. Fuzzy cognitive maps use FL and graphical structures with expert or (AI-derived) weighting to nodes to reason over decisions and have been used CDSSs previously (556). There is a new *Python* programming language module called FCMpy to help construct fuzzy cognitive maps (557), which could be leveraged, Deeper relationships observed in RWD will be lost as queries of the model become more granular or complex. This is expected and is a key limitation of synthetic data and complex models in general. The software pipeline was developed with extensive use of version control, testing and continuous delivery to a high-performance computing network so that future extensibility is easy. Neither the clinical utilisation of this model, nor the predictive algorithms generated can be clinically utilised, because they have not been validated on RWD. However, this was a first proof-of-concept study, and the insights are useful for hypothesis generation, testing and further study.

7.4.5 Clinical relevance

The concept of digital twin technology in shared decision-making in cancer care is promising. The ability to utilise increasingly complex and large RWD in a bidirectional manner with powerful algorithms and existing data means that objective CDSSs can be developed to support clinicians and patients. The use of chronological age as a proxy of biological ageing and a clinical heuristic to offer or deny treatment must end. This represents the frenetic nature of cancer MDTs, often run between clinical commitments with little time for adequate discussion and missing or incomplete data. Decision-makers naturally resort to system 1 thinking (i.e., fast but shallow and based on heuristics) to avoid the increasing complexity of oncogeriatric populations. There may be a lack of time for system 2 thinking (i.e., slow but deep and based on extensive cognitive processing) (558) in the current MDT setup. The latter is a prime

candidate for outsourcing to computational models that can analyse multiple inter-related data points much faster and with higher accuracy than human decision-makers. However, it is important that future CDSSs are fully transparent, unbiased, explainable, auditable and overridable.

7.4.6 Priorities for further research

Aside from advancing the current work, for example by improving granularity, adding additional features, outcomes and data points and bidirectional integration with RWD, there are many other research avenues to address in parallel. One critical aspect is the implementation science around embedding CDSSs developed using digital twin technology into clinical practice. Implementation science is a rapidly growing and diverse discipline that seeks to address the 'know-do gap' between utilising evidence-based practices in clinical workflows. An early understanding of the barriers and facilitators of utilising digital twin technology from a range of stakeholders is required. Understanding what contexts and their mechanisms would lead to successful outcomes, in terms of implementation, would be important. Much recent work has been undertaken regarding the ethics of digital twin technology. Of profound importance is the issue of bias in the underlying technology. A discriminative system, or one that simply echoes existing clinical biases, such as ageism, needs to be avoided at all costs.

Digital twin technology in cancer MDTs will come at an opportunity cost, as commercial enterprises develop CDSSs and sell software-as-a-service products to healthcare organisations. The cost-effectiveness of using this technology needs formal health economic evaluation and interestingly aggregate digital twin populations, such as that developed in this study could provide useful data for micro- or macrosimulations. In **Chapter 4**, I questioned the appropriateness of evaluating the cost-effectiveness of practices, such as undertaking GA in cancer care, that tend towards utilitarianism in clinical decision-making. The best clinical decisions in cancer care are not necessarily the most cost-effective. Thus, key stakeholders must decide the value of the extra information generated from processes and technologies such as CDSSs. Cost-consequence analyses may therefore be more appropriate.

7.4.7 Conclusions

The proof of concept of a complex model of an oncogeriatric population demonstrates the possibility of creating a digital twin instance of an oncogeriatric patient. The use of synthetic IPD can be used to generate a sandbox environment to experiment with predictive modelling

in oncogeriatrics. Future research can utilise different modelling and simulation techniques, including at lower levels (e.g., genomic and physiological) to increase fidelity to RWD.

Chapter 8 – Discussion and conclusions

8.1 Summary of main findings

This thesis began by introducing the problem area, which firstly concerns the projected demographics of an ageing and growing population. As cancer is primarily a disease of ageing, considerably more older adults with cancer will require cancer treatment over time. There is significant disparity in cancer treatment outcomes between older adults and their younger counterparts, with higher levels of postoperative complications, chemotherapy toxicity, mortality and decision-making towards best supportive care. The spectrum of biological ageing is vast, from athletic octogenarians through to 65-year-old patients with the triad of frailty, multimorbidity and disability. Chronological age does not adequately capture biological age and ageism is still a problem in cancer decision-making. Furthermore, the current organisational features of cancer MDTs are not conducive to embedding principles from geriatric medicine that could enhance shared decision-making.

GA has been proposed to improve decision-making by offering both predictive assessment capabilities and optimisation prior to cancer treatment. The former component facilitates the realisation of unmet needs (e.g., previously undiagnosed depression and a history of recent falls) and collecting the data necessary to use validated predictive models (e.g., CARG chemotoxicity score). The later component consists of arranging appropriate investigations and instituting management of holistic health needs. Even though robust evidence of improved cancer outcomes from optimisation is limited, the clinician is compelled to act on the new information, from a purely compassionate basis, especially if evidence-based treatment options exist (e.g., arranging psychological therapy and a falls clinic review). Because GA is notoriously difficult to implement and the implementation factors have not been comprehensively explored, the first research question concerned the implementation science of GA in cancer care.

Through undertaking a systematic realist review, a whole system approach including four major programme theories were developed, based on the most frequently cited implementation barriers: i) limited workload capacity; ii) absence of funding; iii) uncertain practicalities; and iv) limited resources. Enablers include protocolising OGA towards OGA-guided interventions, formulated as referrals to other services made by clinically autonomous non-specialists. The consensus of individual MDTs helps to view OGA as a predictive optimisation tool. A single proponent within the MDT can help drive adoption of OGA. Although a GOP is viewed as the

gold-standard, it requires robust clinical governance and training, research and health economic impact to promote sustainability. Where a GOP is not possible, referring to existing geriatrician-led services can promote inter-professional network formation. Technology can be utilised to address workload, health economic and resource barriers. Recognition of the cost consequences of OGA, such as medicolegal mitigation, research opportunities and data generation for service improvement provide top-down incentives for GA. The programme theory of developing favourable health economics was inadequately addressed in the world literature and therefore warranted further exploration. This motivated the second research question of this thesis, which concerned modelling the health economics of undertaking OGA before cancer treatment.

A model-based synthetic health economics evaluation of undertaking OGA before cancer treatment was completed. OGA was found to have additional costs over standard care alone of between £390 and £576, dependent upon the implementation configuration selected. The potential effect of a reduction in postoperative complications from OGA was significant in modelling, due to its potential mortality reduction and consequent improvement in QALYs. However, there are intensely competing causes of mortality in older adults with cancer and meta-analyses have not demonstrated that the effect of perioperative outcomes from CGA is consistent between studies. It appears centres of excellence for perioperative geriatrics, such as the POPS model at Guy's and St Thomas' NHS Foundation Trust, can demonstrate this effect. When major assumptions about the effectiveness of OGA were modelled, the INHB was marginally positive representing borderline cost-effectiveness. When the effect of a reduction in postoperative complications was neutralised, the cost-effectiveness of OGA is lost. When the implementation configuration was changed, so that OGA was used solely before chemotherapy, with minimal healthcare staffing inputs and technological assistance, OGA is cost-effective. It may be more prudent for stakeholders to take a pragmatic approach towards OGA introduction and evaluate locally rather than strive for generalisable research. From an ethical perspective GA tends towards utilitarianism by generating the information required to make the most appropriate decision for a given patient. OGA has no safety issues and is therefore a suitable intervention for more widespread implementation. Both the findings from the realist review and the health economics evaluation highlighted the role technology can play in enabling the implementation of GA and improving the cost-effectiveness. The third research question answered in this thesis, concerned developing both the technology and sociotechnical system to facilitate the GA data collection within an NHS setting.

A new digital-first NHS service was developed and operationalised to assess older adults with confirmed or suspected cancer. This was made possible using appropriate theories, high level literature review, implementation science principles, the findings from **Chapter 2**, key stakeholder consultations and the use of technology. The power of a single intrapreneur to make a change within a healthcare organisation was also significant. There was also a strong possibility that implementation could have failed, like the situation experienced by Kocman *et al*. (92) The OGA service was consequently merged into a consultant-led oncogeriatric liaison service for oncology inpatients with plans to scale to outpatients soon. The COVID-19 pandemic heavily disrupted the OGA service, suspending research recruitment and changing its delivery. Whether the initial introduction of the digital-first OGA service inspired the consultant-led service is unclear, but it certainly helped keep the conversation alive and showed proof-of-concept. This demonstrates the blurred line between QI initiatives, innovation and implementation science.

The OGA service included a digitalised patient reported questionnaire, administered using a tablet device through a bespoke Android application that I developed. This was evaluated using a quantitative survey and in-depth interviews. The latter are not reported in this thesis but will be published separately, soon after submission. This study was significantly interrupted by the COVID-19 pandemic and recruitment continuation was no longer possible. Unfortunately, the sample size was too small to be representative or exploratory of the population and fulfil the primary outcome of assessing the acceptability of the questionnaire. The results were encouraging that a digital-first OGA is feasible and usable by patients, if assistance is available, and it can fallback to a clinician-led service where necessary. Most patients surveyed were able to access the internet directly, or via someone close to them, so an option to remotely deliver the OGA questionnaire is possible. Despite this chapter proving the concept of digital-first OGA, the utility of OGA derived data has not been fully realised. Although the currently recommended predictive models provide clinically useful insight, state-of-the-art technology, including artificial intelligence is nascent within oncogeriatrics. The data from individual OGA and other sources has sufficient granularity, when combined with the literature and existing data sets, to build a model of a patient's health. Drawing inspiration from the manufacturing industry, I conceptualised creating a digital twin of an oncogeriatric population to simulate treatment outcomes and their determinants. This created the fourth research question, which concerned using computational, statistical and artificial intelligence methods to model a synthetic oncogeriatric population towards an aggregate digital twin.

A complex model of an oncogeriatric population was developed which exhibited high fidelity to RWD. The complex model generated an experimental sandbox to explore predictive models, which are useful at the population level to select patients for GA and identify high risk individuals. However, at the individual level it was predominantly a clinical-clinical representation of an oncogeriatric patient. For clinical translative purposes this is an important layer to start, but the ability to model at the physiological and multi-omic levels within oncogeriatrics is missing. This motivates future research opportunities to prototype a system to consume the available IPD and generate a single high-fidelity digital twin instance for simulating cancer treatment and modelling individual outcomes.

In summary this thesis explored oncogeriatrics from an implementation science, health economic, digital health, socio-technological systems and artificial intelligence perspective creating novel insights. Some of the former findings can be operationalised today in clinical practice. The later findings demonstrated proof-of-concept, setting the foundations for exciting future research to optimise decision-making in cancer care and improve outcomes for older adults with cancer.

8.2 Comparisons to previous research

To the best of my knowledge, a body of work of this trans-disciplinary extent has never been conducted, which reinforces the novelty of the research presented in this thesis. However, the individual methods employed can be compared to existing research and this section summarises both individual experimental work and trans-disciplinary work broadly within geriatric medicine.

ASCO undertook a survey in 2019 of 1,277 cancer providers treating patients ≥65 years old regarding the implementation of OGA (559). As highlighted in **Chapter 2**, the primary barrier raised was lack of awareness of the ASCO guidelines published in 2018 recommending OGA. Even for those providers who were aware of the guidelines, GA was clearly not implemented completely with domains such as mood and cognition assessed rarely. The frequently cited barriers, such as lack of time and staff demonstrate the importance of abstracting OGA provision away from oncology providers. In the context of community oncology provision in the USA, access to geriatric services is very limited as found in a 2017 survey responded to by 504 practices (560). They reiterated the value of patient reported GA and protocolised interventions to facilitate implementation of GA in community practices, as discussed in **Chapter 2**, utilised in **Chapter 5** and evaluated in **Chapter 6**.

Kocman *et al*. (92) studied the delivery of CGA in the perioperative pathway using QI methods and NPT. Many of the challenges they identified, including the need for geriatrician leadership, professional domain insecurities and competing patient priorities were identified in **Chapter 2**. Timing of CGA was also an issue and attempting to embed CGA in the preoperative assessment setting represents an exceptionally late part of the cancer pathway **Figure 4**. This was a key reason why the OGA service developed in **Chapter 5** was designed to start as early as possible in the cancer pathway, even before a cancer diagnosis was confirmed. Technology utilisation also appeared minimal in their study. It is well known that bundles and toolkits, whilst comprehensive, can be overwhelming for clinical staff. The need to democratise access to scarce domain knowledge from geriatric medicine is clear. Technologically assisted systems can aid this provided they are safe, transparent and validated for clinical use with appropriate study, including software as a medical device certification (561) where necessary.

The closest study of health economics in oncogeriatrics related to perioperative geriatrics for non-cancer pathology by Partridge *et al*. (96), which was described in **Chapter 4**. It should be reiterated that this study represents a success story and an idealised model of care, namely the POPS service. Centres may struggle to realise the same effect sizes used in the study by Partridge *et al*. (96) because of their experience, workforce, funding, implementation maturity, leadership and numerous other systemic factors. Although cancer and arterial disease share lifestyle-based risk factors (e.g., smoking and obesity), they are different diseases and cancer is highly heterogenous with intensely competing causes of mortality. A USA-perspective health economic evaluation of the recent GAIN trial (59) would be interesting to support the notion that cost-effectiveness is favourable in patients selected for chemotherapy only.

Several studies have explored using digital technology to facilitate GA data collection, which were discussed in **Chapter 6**. The overall message confirms that digital-first OGA is suitable for older adults with cancer, and this can be undertaken early in the cancer pathway. Remote delivery of OGA was not tested in this thesis, because of limitations in obtaining the necessary safety and governance requirements in the thesis timeframe. There are some studies of remote rapid GA completion, for example Alex *et al*. (562) undertook a pilot study of Malaysian adults ≥60 years via an online survey. Although implementation appeared feasible, they identified a prevalence of frailty of 4.5%, whereas in meta-analyses pooled frailty prevalence in cancer is 43% (277, 563). Remote offerings for OGA need to consider that a significant number of patients will still require telephone or face-to-face support to complete an OGA, including falling back to clinician-led assessments. A cross-sectional study (564) of virtual geriatric

consultations via telephone and videoconferencing found that patients with frailty or without a caregiver reduced the odds of videoconference consultation. It seems reasonable to extrapolate that frail cohorts may also have lower completion levels of remote, patient reported OGA, delivered by a software application.

Barbiero and Lió (565) developed a computational model of a patient with diabetes and COVID-19 and Barbiero *et al*. (555) further proposed a system of forecasting medical conditions using AI. This work relates to modelling an individual patient, versus a population in aggregate like **Chapter 6**. They employed the use of ordinary differential equations, utilising previously published physiological or pharmacological models of normal systems and their alteration by pathology. Using the time series data derived from solving the ordinary differential equations, they then used graph neural networks to learn the signal from the data. Principal component analysis was employed to reduce the complexity of the dynamics of the data in response to changes in variables. The clinical translation was not clear in their work, as they modelled predominantly at the physiological multi-omic levels, but the integration of different models was novel. It would be interesting to combine the clinical-clinical interactions generated in **Chapter 6** with multi-omic models. There has been better clinical translation of digital twin models in the intensive care setting. Lal *et al*. (566) created a digital twin used to model and predict the treatment response of adults with sepsis within the first 24 hours. The basis of the model relied on an expert-curated and iteratively optimised DAG, like the overall DAG developed in **Chapter 6**. The use of AUROC for predictive accuracy, instead of Kappa coefficient for interrater reliability, would have been preferrable. This would have aided comparison to future studies and be in keeping with preferred reporting measures in the machine learning community. However, the TRIPOD-AI reporting guidelines are still awaited to help harmonise reporting across the research community (567). There were many errors reported in the model testing (52%), reflecting the complexity of the DAG and associated rules. Furthermore, only single interventions were modelled, compared to the frequent use of multiple interventions in intensive care settings. However, this was a useful example of a direct clinical translation of digital twin technology to an important problem at the individual patient level.

8.3 Strengths of this thesis

The strengths of this thesis derive firstly from the novel application of trans-disciplinary methods to explore inadequately addressed research questions in oncogeriatrics. The use of realist theory had previously not been utilised to comprehensively explore and summarise the implementation factors within oncogeriatrics. A model-based health economic evaluation of

oncogeriatric service provision within the NHS had not been conducted. A digital-first approach to OGA had not been piloted in the NHS previously. Developing a patient reported digital OGA, mapped specifically to existing predictive models was previously untested. Previous work using digital technology in OGA had been conducted mainly in the US healthcare system with predominantly college-educated participants. A digital twin of an oncogeriatric population of older adults with cancer had not been published in the world literature.

Research is increasingly becoming trans-disciplinary and indeed this thesis was situated within a trans-disciplinary research group, consisting of different clinical and research academics from diverse clinical, research and subspeciality interests. Since the overall research agenda involved a complex health problem, the use of different methods, supervised by different experts from various disciplines created a vibrant research environment. This thesis represents many of the recommended components of a transdisciplinary research model (568), including i) co-learning – members of our research group were able to learn from other and our work was interlinked in many cases; ii) development and conceptualisation – we underwent extensive peer review of research strategy and methods through diversely attended scientific forums; iii) reflection and refinement – the COVID-19 pandemic forced our group to reflect on the remainder of our research, our individual strengths and refine our research questions, such as the pivot in this thesis towards computational modelling; iv) investigation and implementation – I was able to rapidly develop, test and implement my research through the innovative creation of a new digital-first OGA service. This may not have been possible without a trans-disciplinary approach.

This thesis used different methods rather than mixed methods. The use of mixed methods would have required an extensive process of integration of research and careful planning of the underlying methods. By employing different methods in separate studies, an opportunity to address the outstanding 'how' questions in the OGA literature were created, including modelling the data generated from OGA. However, the absence of a mixed methods approach also misses the opportunity for a synthesis of quantitative and qualitative components, to develop overall inferences that may have more clinical or research significance than individual study inferences.

8.4 Limitations of this thesis

The limitations of this thesis derive from individual methodological limitations of experiments in the former sections and the lack of clinical validation in the later sections. The implementation and improvement science aspects of this thesis are limited by the lack of a traditional approach to these disciplines. For example, formal qualitative interviews in **Chapter 2** and **Chapter 5** were not utilised as part of a formative evaluation process or as part of a theory-based approach using NPT or CAS. Formal plan-do-study-act processes were also not utilised, although this was planned once the OGA service was more established. Unfortunately, the disruption from the COVID-19 pandemic prevented this from happening.

The methodological approach outlined in **Chapter 3** is also limited by the approaches chosen, including the use of pragmatism, CAS theory and the lack of a mixed methods research approach to inference generation. Pragmatism has been criticised on several levels, including its ignorance of philosophy and theory, excessive focus on the research question(s) and its lack of acknowledgement over 'who for' and 'what end' questions regarding research outcomes (569). However, as a clinical academic the research questions are of profound importance. In **Chapter 3**, it was discussed that the social injustice element of the TRANSFORMing Cancer Outcomes in Yorkshire group could fit with a transformative emancipatory perspective. I argued that this was best reserved as a high-level purpose rather than the core philosophical underpinning. Since OGA has a core purpose of identifying unmet patient needs, I felt a duty to patients, funders and colleagues to focus on unmet research needs, versus focussing on philosophical debate. This empowered me to achieve the maximum research impact possible in a short time. The operationalisation of the OGA service and extensive work with a consultant geriatrician to develop an oncogeriatrics inpatient liaison service, meant that the recipients and outputs of this research endeavour have been explicit. Although theoretical considerations were not a core focus of this thesis, theory has been utilised. Realist theory was used in **Chapter 2** and CAS theory was considered throughout this thesis to varying degrees. For example, CAS theory was used to illustrate the way implementation factors operate in **Chapter 2** and explain why health economic study is difficult in **Chapter 4**. CAS theory was used extensively to understand the high-level assumptions of an OGA service positioned within a health system in **Chapter 5**. Since CAS theory was inspired by biological systems, the use of a graphical approach in **Chapter 7** to model interactions between clinical variables and outcomes also fits within a CAS theoretical framework.

Whilst using CAS theory provided advantages, such as exploring relationships and how implementation factors influence this in a non-linear setting, there are limitations within this thesis and the wider literature. Firstly, CAS theory has not been empirically verified in this thesis and this is unfortunately a common caveat. CAS theory *per se* has also not offered any specific predictive value towards OGA implementation or outcomes. However, it could be argued that the unification of predictive models into a single questionnaire and model in **Chapter 5**-**Chapter 7** have created emergence and connectivity. The process of OGA service operationalisation leading to permanent organisational change with the introduction of a geriatrician-led service provides evidence of iteration and self-organisation. Furthermore, COVID-19 pandemic forced the self-organisation of the OGA service towards remote telephone-based assessments. These are all well regarded components of a CAS (570) and whilst suggestive that a CAS was operating in theory, this cannot be verified empirically.

This thesis also does not report the in-depth interviews undertaken to complement the OGA service evaluation in **Chapter 6**. This data, combined with the quantitative data were initially planned for a traditional mixed methods analysis. This will be undertaken outside this thesis and published accordingly. The OGA service operated at a single centre and sample size numbers were low, limiting both internal and external validity of the findings, although the data is in keeping with previous findings. From a technology perspective, industrial testing and evaluation of new low-risk, digital health technologies that do not fall under medical devices are often limited to very few patients, if any, prior to implementation. In keeping with a lean-agile approach to implementation outlined in **Chapter 5**, early user testing is essential to establish customer discovery and early adoption. However, patient co-design was limited as the primary customer for adoption of the OGA service was identified as the healthcare organisation.

The health economic evaluation in **Chapter 4** followed a synthetic model-based approach and whilst this is acceptable in this discipline, the original plan was to undertake a cost consequences analysis using data from the OGA service itself. This was also limited by the lack of use of a suitable HRQoL instrument in the patient reported questionnaire, which would have prevented a cost-effectiveness analysis. However, this would have blurred the line between research and service development, and the former would have required that the OGA service be considered research. Although REC concerns with this were unlikely, to aid implementation it is important that OGA is not seen by organisations solely as a research process. This was especially important considering the work by Jackson *et al*. (510) who

undertook a feasibility study of OGA within HUTH. The normalisation of OGA is imperative to embed it into routine care without needing the justification of a research study. Given that OGA has continued under a liaison model and soon including an outpatient model, the work to normalise OGA can be deemed a success.

The complex model in **Chapter 7** was limited by using synthetic IPD and the lack of RWD data of events. This meant that outcomes were determined stochastically with detrimental network effects or were artificially tuned leading to significant inflation of the AUROC values for outcomes. This also leads to instability in the derived predictive models as decision trees are very sensitive to small changes. However, the predictive models exemplified are not intended to be used clinically, more to illustrate the use of a sandbox environment for experimental modelling. The more interesting aspect of the complex modelling is towards the development of a digital twin. This thesis is limited in that the full digital twin was not used in production under experimental conditions, although the blueprint is provided to create a MVP.

8.5 Applications to clinical practice

Many insights and recommendations from this thesis can be operationalised in clinical practice today. When clinicians are attempting to introduce an OGA service, the considerations in **Chapter 2** can assist in implementation planning and troubleshooting. There are numerous theoretical and practical frameworks that can be used when planning implementation. In this thesis, I employ concepts from NPT, CAS theory and customer discovery. Clinicians have flexibility when choosing frameworks and stakeholder consultations do not have to be formal or recorded. In developing a virtual perioperative geriatrics service, Joughin *et al*. (571) utilised informal consultations with thematic analytical methods. A very recent survey of radiation oncologists reiterated the same implementation issues identified in **Chapter 2** and found around one third lacked any awareness of OGA guidelines (572). The authors concluded that this subspeciality appears relatively behind surgical and medical oncology (572).

The missing component in the introduction of OGA services often appears to stem from the lack of a single highly motivated intrapreneur to drive change. This is a common feature from implementation and improvement science and change management perspectives. This individual helps propagate knowledge, overcomes implementation barriers and ideally shares the knowledge with the clinical and research community. Perhaps better incentivisation for early adopters and change leaders needs to be integrated into healthcare systems. Additionally, the unification of implementation and improvement science and change management

principles into a common healthcare intrapreneurs toolkit may enable clinicians to choose the approach that resonates with them and overcome disciplinary territorialism. Finally, one criticism of the NHS England Clinical Entrepreneurs programme is its bias towards *entrepreneurialism* and the development of for-profit businesses. Unfortunately, this can result in highly motivated individuals leaving the NHS to lead these organisations. Resigning from clinical practice is a common condition of venture capital funding for founders and C-suite members of health technology start-ups. A better programme name may be NHS England Visionaries to support those (clinical or non-clinical) who have ideas, whether centered around early adoption, novel products or services. There are NHS leadership initiatives offered by the NHS Leadership Academy, but there is a need to focus on innovation, improvement and implementation from a business perspective. Highly successful conglomerates such as Alphabet Inc., still operate with a start-up strategy. This mentality of 'failing fast' is in keeping with rapid implementation and prototyping strategies reported in the recent literature. Last *et al*. (573) undertook a pilot study utilising these rapid participatory methods, including a tournament of crowdsourced ideas for change from within the health organisation. One important issue highlighted was the limitation of already approaching motivated and engaged stakeholders. Whilst early adopters often formulate the first users of new solutions, there can be stakeholder generalisability issues, which can lead to confirmation bias regarding the value, motivation or likelihood of success of implementation.

Health economics, stakeholder involvement and implementation are interlinked. The cost-consequences, cost-effectiveness from **Chapter 4** and implementation and improvement details of OGA from **Chapter 5** and **Chapter 6 Chapter 4**can therefore be combined into a single business strategy for introduction of OGA services. The modelling of four different implementation configurations enables the satisfaction of different stakeholders' views on the reality of cost-effectiveness, although QALY measures are better reserved for policy-level stakeholders (574). Cost-consequences appeal to stakeholders with a pragmatic view, especially decision-makers within an organisation. This combination of innovation principles, implementation science and health economics sets a new precedent for the body of work that must be undertaken and presented for new health technologies or services. The POPS model was able to demonstrate important cost consequences from an early stage, leading to sustainability (130). Organisational stakeholders are placing increasing emphasis on return on investment from the adoption of new health technologies, given their opportunity costs. The concept of a testbed is a powerful concept at multiple levels, as it allows the generation of the

necessary data at the organisational level. Some NHS organisations are comfortable with this operational risk, such as Southend University Hospital NHS Foundation Trust and Guy's and St Thomas' NHS Foundation Trust. These organisations have significant intrapreneurial leaders driving these changes and the concept of creating a testbed can be a powerful way to promote more widespread implementation and scaling. For example, the public company Babylon Health, who created the Babylon GP at Hand service, a digital-first model of primary care provision consisting of videoconferencing and a mobile application, started with a single London practice. The independent evaluation of Babylon GP at Hand in 2019 (575) raised many important considerations for this model of care but was unable to complete an economic evaluation. However, the findings of a viable, well implemented service were sufficient to enable the Babylon GP at Hand model to scale to Wolverhampton and Birmingham NHS services in the UK. In summary, some combination of implementation, improvement or decision sciences is required to convince key stakeholders of the value proposition for new innovations.

The complex model in **Chapter 7** formulates the model layer of a digital twin, whilst **Chapter 6** forms the basis of the RWD pipeline. Being able to aggregate important predictive outputs using established and validated algorithms from OGA data provides a MVP, which has been demonstrated in this thesis. If this technology could be embedded in cancer MDTs and oncology practice successfully, using improvement and/or implementation methodologies, further advancement employing more granular modelling could be considered worthwhile. This may include lumped parameter models of physiological systems, discrete event simulation of critical events during cancer treatment or more complex agent-based modelling or tumour-host dynamics.

8.6 Future research priorities

Future research priorities stemming from this thesis derive from the diversity of methods utilised. Dedicated implementation studies or hybrid effectiveness-implementation RCTs evaluating the implementation success of various configurations outlined in **Chapter 2** are necessary to confirm or refute those findings. However, these are difficult and expensive to setup and there is a question regarding the need to evaluate OGA as a predictive tool when this has established value. This highlights the role of the mobilisation of implementation and improvement science knowledge in this field, using evidence from local implementation success stories such as POPS. Formal reporting of centre-level economics, mapped to successful implementation configurations may further support the findings of **Chapter 4**.

There is ongoing effort to demonstrate the value of OGA as a complex intervention. The recently published GAIN trial (59) has demonstrated a favourable effect on chemotherapy toxicity reduction. Interestingly, the success of the GAIN trial lay on the key implementation enabler of autonomising the OGA service to implement interventions and ensure their completion. Future studies of the OGA as a complex intervention must consider the implementation factors outlined in **Chapter 2**.

The process of patient reported OGA evaluated in **Chapter 6** can be extended to include intelligent and deeper insight into detected vulnerabilities. For example, malnutrition, falls, mental health can be explored further through questioning using probabilistic graphical modelling. Conversational AI including natural language processing may enrich the UX and capture greater insight from unstructured responses. This can then be fed back to the clinical team for review. When a remote reporting is utilised, the same application used for OGA can be used to deliver OGA interventions. Loh *et al*. (576) piloted a tablet application specifically for delivering OGA-guided interventions and demonstrated feasibility and usability by older adults with cancer. Furthermore, additional aspects of cancer care could be navigated and delivered, including patient reported outcome and experiences measures, symptom checking, condition monitoring, follow-up, videoconferencing, automated engagement and nudges. The later refers to nudge theory from behaviour economics aiming to help change behaviour (e.g., missed appointments), based on targeted interventions in the form of subtle nudges (577). Evaluating such a comprehensive application is an avenue for research, although would incur high development costs and the economics would need to be evaluated.

An immediate clinical research priority should concern the introduction of the minimum viable digital twin (digital OGA data collection and aggregate basic predictive model) into cancer MDT decision-making. Contemporaneously, early exploratory work of more advanced digital twin technology to simulate individual responses to cancer treatment could take place similar to the ITU digital twin developed by Lal *et al*. (566). Additional complexity can be introduced in a modular fashion building to multi-omic scale by incorporating genomic and physiological data. Furthermore, agent-based modelling to simulate networked tumour-patient interactions would be interesting.

8.7 Conclusion

This thesis developed an evidence-based system to facilitate the predictive assessment and optimisation of older adults with cancer. Consideration of the whole system was necessary to

circumvent implementation barriers and digital-first OGA was implementable by a single intrapreneur. Proof-of-concept was demonstrated for NHS patients to self-report an OGA during the early stages of a cancer pathway. OGA may be cost-effective when used with the correct implementation configuration, but generally requires the OGA process to improve perioperative outcomes. Modelling an oncogeriatric population using synthetic IPD and machine learning techniques had high fidelity to RWD and generated interesting insights for clinical validation.

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Appendix

Quality criteria	How the criteria were fulfilled
1. The research problem	
The research topic is appropriate for a realist approach	We aimed to review the heterogenous literature on implementation of geriatric assessment (GA) in oncology settings (context) to understand the different implementation context configurations of GA and the mechanisms they trigger to enable successful implementation (outcome). Realist review centres around the study of the relationships between context, mechanism and outcomes and therefore this aim was well suited for a realist approach.
The research question is constructed in such a way as to be suitable for a realist synthesis	We sought to explain how certain mechanisms led to successful implementation of GA in different implementation context configurations within oncology.
2. Understanding and applying the underpinning principles of realist reviews	
The review demonstrates understanding and application of realist philosophy and realist logic which underpins a realist analysis.	We utilise realist concepts, such as 'mechanisms' and 'contexts' consistently and throughout the review. Explanations of programme theories used realist logic in the form of context-mechanism-outcome configurations extensively.
3. Focussing the review	
The review question is sufficiently and appropriately focussed.	We initiated the review prior to the introduction of a new oncogeriatric service and several parallel research studies. We undertook extensive patient and public involvement work and stakeholder analysis. We identified a gap in knowledge regarding systematic review of the implementation literature for GA. Using an iterative approach, the stakeholder group provided feedback to develop, test and refine the programme theories.
4. Constructing and refining a realist programme theory	
An initial realist programme theory is identified and developed.	This is covered in detail in the results section where four key programme theories were identified and developed.
5. Developing a search strategy	
The search process is such that it would identify data to enable the review team to develop, refine and test programme theory or theories.	A two-stage approach was undertaken: i) systematic searches with structured data extraction combined with iterative key stakeholder consultations to develop programme theories for implementing GA in oncology settings; ii) synthesis to refine programme theories. Medline, Embase, PsycInfo, Cochrane Library, CINAHL, Web of Science, Scopus, ASSIA, Epistemonikos, JBI Database of Systematic Reviews and Implementation Reports, DARE and Health Technology Assessment were searched. Search terms were developed from the initial programme theories and previous systematic reviews. We included all study designs and used forward and backward

	searching accordingly. The search strategy is reported in detail in **Figure 1**.
6.Selection and appraisal of documents	
The selection and appraisal process ensures that studies relevant to the review containing material of sufficient rigour to be included are identified. In particular, the studies identified allow the reviewers to make sense of the topic area; to develop, refine and test theories; and to support inferences about mechanisms.	The inclusion and exclusion criteria were developed as the literature was explored and are included in **Figure 2,** since programme theory development, testing and refining was an ongoing iterative process**.** Relevant critical appraisal tools, depending on the study design were used to assess rigour of the included studies.
7.Data extraction	
The data extraction process captures the necessary data to enable a realist review.	We utilised data extraction forms which were initially piloted to capture key descriptive and methodological details, and relevant data both qualitative and quantitative was extracted according to the programme theory under study. 25% of data extractions were double-checked by a second reviewed.
8.Reporting	
The realist synthesis is reported using the items listed in the RAMESES Reporting standard for realist syntheses	The study is reported in accordance with the RAMESES reporting standards for realist syntheses.

Table 14 – Realist And Meta-narrative Evidence Syntheses: Evolving Standards (RAMESES) Quality standards.
Abbreviations: GA = geriatric assessment.

STANDARD			COMMENTS
TITLE			
1	-	In the title, identify the document as a realist synthesis or review	The title identifies the document as a systematic realist review
ABSTRACT			
2	-	While acknowledging publication requirements and house style, abstracts should ideally contain brief details of: the study's background, review question or objectives; search strategy; methods of selection, appraisal, analysis and synthesis of sources; main results; and implications for practice.	All of this is included, but in keeping with the house style of the journal, this is brief. Moreover, feedback during peer-review we state an aim in the abstract rather than a research question or objectives.
INTRODUCTION			
3	Rationale for review	Explain why the review is needed and what it is likely to contribute to existing understanding of the topic area.	This is explained in the introductory section including the knowledge gap of this area.
4	Objectives and focus of review	State the objective(s) of the review and/or the review question(s). Define and provide a rationale for the focus of the review.	After feedback during peer-review, we have stated an aim of the review in the introduction, in keeping with the title and abstract.
METHODS			
5	Changes in the review process	Any changes made to the review process that was initially planned should be briefly described and justified.	There were no changes to the review process.
6	Rationale for using realist synthesis	Explain why realist synthesis was considered the most appropriate method to use.	We have explained the use of realist synthesis to explore the contexts, mechanisms and outcomes of GA implementation in this setting
7	Scoping the literature	Describe and justify the initial process of exploratory scoping of the literature.	We undertook a single comprehensive search strategy, as opposed to an iterative search strategy, to ensure we fully understood the heterogenous research base and capture its diversity (117).
8	Searching processes	While considering specific requirements of the journal or other publication outlet, state and provide a rationale for how the iterative searching was done. Provide details on all the sources accessed for information in the review. Where searching in	We have outlined the search strategy in a box (**Figure 1**), which includes the name of the databases, search terms used, dates of coverage and last search

STANDARD			COMMENTS
TITLE			
		electronic databases has taken place, the details should include, for example, name of database, search terms, dates of coverage and date last searched. If individuals familiar with the relevant literature and/or topic area were contacted, indicate how they were identified and selected.	date. Key stakeholders were identified by peer recommendations from the professional network of the steering group, and then informal consultations were conducted to test and refine programme theories
9	Selection and appraisal of documents	Explain how judgements were made about including and excluding data from documents and justify these.	The quality of the evidence was determined by its ability to build or test the relevance of a programme theory, based on established methodology for realist reviews
10	Data extraction	Describe and explain which data or information were extracted from the included documents and justify this selection.	Data extraction followed for articles meeting this test of relevance and were primarily extracted by one team member (the lead author), with a random 25% independently checked by a second team member.
11	Analysis and synthesis processes	Describe the analysis and synthesis processes in detail. This section should include information on the constructs analyzed and describe the analytic process.	We presented stakeholders with proposed solutions to successfully implement geriatric assessment (GA) and invited them to express how the contextual elements of GA may impact on the behaviours of those involved in its implementation. These consultations were documented by the lead author and used in combination with literature synthesis to support or refute programme theories. Data synthesis was further supported from a combination of individual reflection and group discussion in order to challenge the integrity of each theory, judge competing theories and compare the stated theory with actual practice. Data from the studies or stakeholder consultations were used to confirm, refute or refine the candidate theories. Alternative theories were sought where theories could not explain the data.

STANDARD			COMMENTS
TITLE			
RESULTS			
12	Document flow diagram	Provide details on the number of documents assessed for eligibility and included in the review with reasons for exclusion at each stage as well as an indication of their source of origin (for example, from searching databases, reference lists and so on). You may consider using the example templates (which are likely to need modification to suit the data) that are provided.	A PRISMA Flow Diagram has been included (**Figure 3**)
13	Document characteristics	Provide information on the characteristics of the documents included in the review.	This was included in a supplementary
14	Main findings	Present the key findings with a specific focus on theory building and testing.	We present the key findings in detail as a synthesis of literature, authors reflection and key stakeholder consultation.
DISCUSSION			
15	Summary of findings	Summarize the main findings, taking into account the review's objective(s), research question(s), focus and intended audience(s).	The first paragraph of the discussion summarises the key findings aligned to the readership of this journal.
16	Strengths, limitations and future research directions	Discuss both the strengths of the review and its limitations. These should include (but need not be restricted to) (a) consideration of all the steps in the review process and (b) comment on the overall strength of evidence supporting the explanatory insights which emerged. The limitations identified may point to areas where further work is needed.	We dedicate text for both strengths and limitations
17	Comparison with existing literature	Where applicable, compare and contrast the review's findings with the existing literature (for example, other reviews) on the same topic.	At the time of manuscript writing, a single previous realist review had been undertaken for GA, but in a different setting (care home). Comparisons were made with this review.
18	Conclusion and recommendations	List the main implications of the findings and place these in the context of other relevant literature. If appropriate, offer recommendations for policy and practice.	The discussion concludes accordingly with clear recommendations towards next policy and practice.

STANDARD			COMMENTS
TITLE			
19	Funding	Provide details of funding source (if any) for the review, the role played by the funder (if any) and any conflicts of interests of the reviewers.	This is outlined at the end of the document

Table 15 – Realist And Meta-narrative Evidence Syntheses: Evolving Standard reporting standards.
Demonstration of how this review meets the Realist And Meta-narrative Evidence Syntheses: Evolving Standards (RAMESES) reporting standards. Abbreviations: GA = geriatric assessment.

First author	Year	Type of study	Location	Population	Main implementation findings	Reference
Bagayogo	2016	In-depth interviews of healthcare professionals	Montreal, Canada	Older adults with cancer, median age 80 years	The role of the geriatrician is not clearly differentiated from others in cancer care and the responsibility for coordination, evaluation and psychosocial support was unclear	(122)
Bagayogo	2016	Case study with semi-structured interviews of healthcare professionals, document analysis and informal discussions	Montreal, Canada	Older adults with cancer, median age 80 years	Inter-professional networks develop their collaborative nature through sustained persuasion, knowledge sharing, skill demonstration and trust building by less powerful professional groups to secure buy-in from more powerful professional groups	(123)
Baitar	2015	Secondary data analysis of implementation study	Belgium	≥70 years with all cancers (except non-melanoma skin cancer)	At least one geriatric recommendation was performed in 52.1% of patients. Only 7.3% of patients needed referral to geriatrics	(124)
Banerjee	2019	Diagnostic test accuracy validation study	New Dheli, India	≥60 years with confirmed cancer and pre-treatment	Developed a short geriatric assessment tool specifically for an inner city Indian tertiary cancer unit with favourable psychometrics	(172)
Blanco	2016	Prospective observational implementation study	Terrassa, Spain	≥70 years with malignant solid tumour (superficial bladder cancer excluded)	A dual MDT consisting of a tumour and oncogeriatric committee was unnecessary and the centre have since stopped its use	(171)
Clough-Gorr	2013	Cross-sectional study	Switzerland	≥65 years newly diagnosed or relapsed cancer for initiation of new chemotherapy treatment (1st line or subsequent)	Designed the Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung cancer-specific geriatric assessment, which was a feasible and practical tool for use in clinical practice	(149)
Conroy	2019	Mixed methods study	UK	≥65 years in acute hospital settings	Toolkits aimed at enhancing the delivery of GA by non-specialists demonstrated some usefulness but require prolonged geriatrician support and implementation work	(94)
Decoster	2017	Cohort study	Belgium	≥70 newly diagnosed cancer or cancer progression/ relapse at decision-making	Treating physician require further education on the usefulness of GA: only 43% actively consulted GA results when available	(125)

				point of care. Subanalysis of colorectal cancer patients		
Dougoud-Chauvin	2018	Prospective observational implementation study	Florida, USA	≥70 years with a malignancy requiring a decision at any stage	Real time data-driven teleconsultation in geriatric oncology is feasible	(168)
Driessen	2018	Survey of oncologists	Netherlands	≥75 years with non-small cell lung cancer stage III	Logistical barriers including time and geriatrician availability are the dominant implementation barriers for using GA in standard care	(126)
Droz	2017	Literature review and expert consensus	-	Older adults with urological cancer	Patients should be evaluated using the G8 screening tool and if positive undergo GA. Formal mechanisms are required to achieve inter-professional and inter-disciplinary cooperation	(141)
Extermann	2011	Expert consensus	Global	Older adults with cancer	Priorities should include educational and training initiatives (e.g., curriculum changes for medical professionals), clinical practice enhancements (e.g., geriatric oncology clinics) and research opportunities (e.g., screening tool development)	(167)
Festen	2019	Prospective observational implementation study	Netherlands	Older adults with cancer	A nurse-led GA and assessment of patient priorities with integration of findings into the MDT with geriatrician support. Only 12.6% (n = 25) of patients were referred to the geriatrics outpatient clinic.	(578)
Ghignone	2016	Survey of cancer surgeons	European Union and USA	Older patients with cancer	GA is rarely used and collaboration with geriatricians is uncommon. 70.52% of responders would allocate up to four weeks for prehabilitation before elective cancer surgery where this may lead to better functional recovery.	(173)
Girones	2018	Survey of Spanish Society of Medical Oncology members	Spain	Older adults with cancer	There is a perceived need for more training in geriatric oncology	(140)

Gulasingam	2019	Semi-structured interviews and ethnographic study	Toronto, Canada	≥70 years with oncologic diagnosis attending oncology outpatients	Implementation enablers for the use of the G8 tool include local consensus discussions, local championing, educational material distribution and preparation of patients to become active participants	(128)
Hamaker	2014	Survey of geriatricians	Netherlands	Older patients with cancer	Only 25% of respondents reported routine GA prior to oncological treatment and many did not view optimising older adults with cancer as a priority at their centre	(129)
Handforth	2019	Prospective observational study	Sheffield, UK	Men >60 years with advanced prostate or multiple myeloma, previously treated and considered for further treatment	Patient reported GA was viewed positively by participants and clinicians in the outpatient setting	(150)
Harari	2007	Implementation-trial/hybrid study	London, UK	≥65 years with elective surgery planned	The early embedding of a proactive multidisciplinary CGA service for older adults undergoing elective surgery allowed identification of cost-effectiveness data that helped secure mainstream funding	(130)
Horgan	2012	Cohort study	Toronto, Canada	≥70 years, with gastrointestinal or lung cancer	Implementation barriers included physician reluctance to refer due to concern over the benefit available over standard assessment processes and a smaller degree of patient reluctance to attend. There was also uncertainty over how best to use information from GA and only 60% of recommendations made for management of additional problems were acted upon.	(131)
Hurria	2016	Prospective observational implementation study	New York, USA	≥65 years with a cancer diagnosis	The majority of older adults are able to complete a computer-based GA with minimal guidance	(151)

Hurria	2011	Secondary data analysis of randomised controlled trials	USA	≥65 years, diagnosis of malignancy, any performance status level, and enrolment in a cooperative group treatment trial but treatment not yet started	The inclusion of a brief, primarily self-administered GA tool was feasible in cooperative group clinical trials	(502)
Hurria	2005	Prospective observational implementation study	New York and Illinois, USA	≥65 years with breast, lung, colorectal or lymphoma and in receipt of standard chemotherapy for either adjuvant or metastatic treatment	A brief, self-administered CSGA questionnaire is feasible in an outpatient oncology clinic	(106)
Hurria	2007	Prospective observational implementation study	Memorial Sloan-Kettering Cancer Center, USA	≥65 years with cancer	A brief, self-administered CSGA questionnaire is feasible in an outpatient oncology clinic	(153)
Ingram	2002	Prospective observational implementation study	North Carolina, USA	Older adults with cancer	GA can be conducted using a self-reported postal questionnaire in a community outpatient cancer setting	(154)
Jonker	2014	Survey of medical oncologists and nurse specialists	Netherlands	Older adults with cancer	Barriers identified include lack of time, availability of geriatricians and uncertainty over implementation	(174)
Kenis	2013	Prospective observational implementation study	Belgium	≥70 years with breast, colorectal, ovarian, lung, prostate cancer or haematological malignancies	71% of patients benefit from GA but the information does not always reach the treating physician	(41)
Kenis	2018	Prospective, multicentre, observational cohort study	Belgium	≥70 years with cancer	In 79.2% of patients at least 1 different recommendation was made with a median of two different geriatric recommendations per patient. The most common recommendations were referral to dietetics (59.5%), geriatrics	(169)

					(53.8%) and social workers (47.6%). Overall adherence was 70%	
Kenis	2014	Cross-sectional survey to all primary investigators of a Belgian implementation study of GA	Belgium	≥70 years with cancer	Trained healthcare workers play a key role in coordination of GA processes. Geriatricians can be integrated into the geriatric interventions, although attempts should be made to ensure they focus on the most complex patients	(143)
Kenis	2015	Cross-sectional survey to all primary investigators of a Belgian implementation study of GA	Belgium	≥70 years with cancer	Preselection of patients for GA based on tumour type increases feasibility but is an exclusive policy. The availability of GA results in MDTs are often lacking. Barriers tend to be organisational (e.g., high workload). Facilitators are mainly collaborative (e.g., shared appreciation of relevance). The use of trained healthcare workers to coordinate the project is a facilitator	(133)
Korc-Grodzicki	2017	Care delivery review	USA	Older adults with cancer	Barriers encountered in the introduction of a geriatric service in cancer centre include recognition of need, workforce recruitments, inter-disciplinary alignment, protocolisation, organisational change, outpatient space limitations, timeliness, research limitations and longitudinal care	(160)
Lin	2019	Prospective feasibility study	New York, USA	≥50 years and older with haematological cancer awaiting hematopoietic cell transplantation	A patient reported, electronic GA screening instrument is feasible	(161)
Loh	2018	Prospective single-arm pilot study	New York, USA	≥65 years and diagnosed with a solid tumour or hematologic malignancy and on systemic cancer treatment	A mobile application used to assist in the delivery of geriatric interventions is feasible and usable	(166)

Magnuson	2018	Randomised controlled trial	USA	≥70 with a diagnosis of an advanced (stage III or IV) solid tumour malignancy	The implementation rates of GA-based recommendations by the primary oncologists was only 35.4% so reliance on them for implementation limits feasibility	(461)
McCleary	2013	Prospective observational implementation study	Boston, USA	≥70 years initiating chemotherapy treatment for gastrointestinal cancer	Computer-based GA was feasible although approximately half of patients require assistance	(155)
Mohile	2015	Delphi consensus of US leaders in geriatric oncology	USA	Older adults with cancer	GA-guided care processes can be algorithmically developed	(460)
Molina-Garrido	2011	Cross-sectional study	Alicante, Spain	≥70 years with cancer	CSGA	(170)
Monfardini	2007	Survey of Geriatric Oncology clinical services	Global	Older adults with cancer	The establishment of Geriatric Oncology Programmes is highly variable, and efforts should be made to enhance clinical governance, training opportunities and sustainability of these services where possible.	(163)
O'Donovan	2015	Delphi consensus	Global	Older adults with cancer	Incorporating geriatricians into cancer MDTs should be a primary aim of organisations.	(148)
Puts	2010	Semi-structured interviews of oncology and geriatric medicine physicians	Montreal, Canada	Older adults with cancer	Care of older adults is heterogenous and typified by a desire for increased collaboration between geriatricians and oncologists	(147)
Rittberg	2019	Survey of cancer staff	Manitoba, Canada	Older adults with cancer	Barriers include perceived lack of time and knowledge to manage older adults	(162)
Schulkes	2017	Survey of Dutch Taskforce for Pulmonary Malignancies of the Dutch Lung Society	Netherlands	Older adults with lung cancer	Closer collaboration between lung cancer specialists and geriatrician is desired	(135)
Shahrokni	2017	Retrospective review of clinical service with patient survey	New York, USA	≥75 years with cancer with surgical intervention planned	An electronic GA-based fitness assessment was feasible in a preoperative assessment setting	(258)

Sifer-Riviere	2010	Ethnographic study with semi-structured interviews	France	≥75 years with cancer before MDT meetings	Inter-disciplinary collaboration between oncologists and geriatricians can be hindered by professional rivalry and competing demands	(144)
Sifer-Riviere	2011	Qualitative sociological survey of a Pilot Oncogeriatric Coordination Unit	France	≥75 years with cancer	Geriatricians role within geriatric oncology has not be fully recognised and embedded	(145)
To	2019	Survey of Members of the Medical Oncology Group of Australia	Australia	Older adults with cancer	Access to geriatric oncology services is a barrier for referral despite perceived value.	(137)
To	2010	Prospective cross-sectional analysis	Adelaide, Australia	≥70 years referred to medical oncology	A self-reported CSGA and MDT-driven management process was feasible and acceptable	(159)
Whittle	2017	Prospective observational and subsequent interventional cohort	London, UK	≥65 years with lymphoma (pilot), ≥70 years undergoing cancer treatment	A self-reported patient questionnaire for GA delivered via post in advance of appointments was acceptable to older adults and feasible	(156)
Wildiers	2014	Expert consensus	Global	Older adults with cancer	The model of implementation should adopt to local processes and structures and wherever possible include interaction with multi-disciplinary geriatric teams for selected patients.	(44)
Williams	2014	Prospective observational feasibility study	USA	≥65 years with cancer	A self-reported CSGA is feasible in community oncology clinics with modest time and resource commitments	(157)
Williams	2019	Prospective observational feasibility study	Alabama, USA	>60 years with gastrointestinal cancer	An outpatient self-reported CSGA is feasible and acceptable	(158)
Zereshkian	2019	Survey of Canadian radiation oncologists	Canada	Older adults with non-metastatic prostate cancer	66% of Canadian radiation oncologists do not use GA although they are open to considering their use	(138)

Zullig	2019	Prospective observational feasibility study	North Carolina, USA	≥60 years and within 12 months of a cancer diagnosis (breast, lung, colorectal, pancreas, oesophageal)	A GA embedded within an electronic health record with protocolised intervention strategy was feasible	(146)

Table 16 – Summary of included studies.
All 53 studies included in this review are tabulated with their first author, year of publication, summarised study type/design, location research undertaken, population specifics and main implementation findings are reported above. Abbreviations: UK = United Kingdom; USA = United States of America; GA = geriatric assessment; CSGA = cancer-specific geriatric assessment; MDT = multi-disciplinary team.

	Study design	Relevant main findings	Utilisation in economic evaluation	Ref.
Baitar *et al*. (2015)	Multicentre prospective cohort study in nine Belgian hospitals with secondary follow-up analysis of implementation. Patients ≥70 years with cancer were screened for vulnerability using G8 screening tool, and then underwent GA via a trained healthcare worker if positive. Recommendations were made regarding onward referrals to other healthcare professionals.	1,550 patients were analysed with median age 77 years. The reported geriatric recommendations (e.g., referrals to dietician, social workers and psychologist) were high, up to 60% in those undergoing GA.	The referral rates were used as a major guide to construct the healthcare utilisation rates for the GA arm. The rate of referrals to the falls clinic appeared to be low, considering the high prevalence in this population, therefore we uprated this (see **Table 4**). We grouped referrals to a geriatrician, geriatric liaison unit and geriatric day unit into single patient contact episodes with a consultant geriatrician, due to the variable availability of these services.	(101)
Lund *et al*. (2021)	Phase 3 randomised controlled trial based in two Danish hospitals, comparing GA-guided interventions against standard care who were ≥70 years, vulnerable (G8 ≤14 points) and undergoing adjuvant or first-line palliative chemotherapy for colorectal cancer.	142 included patients with no loss to follow-up and median age 75 in both arms. Significantly more patients completed planned treatment (primary endpoint) at the initial dose in all planned cycles for the intervention vs. control group (p = 0.0366). Grade 3 or more toxicity in the intervention group was 28% vs 39% in the control group (p = 0.156), although hospitalisation was equal between groups (30% vs 32%, p = 0.857).	The finding that GA significantly improves treatment completion is an important consequence (see **Table 3**), although not relevant to cost-effectiveness. The statistically insignificant finding that chemotherapy toxicity is reduced (28.2% reduction) following GA is relevant to cost-effectiveness modelling, because at scale this may reduce hospitalisations. Clinically ineffective results, as deemed by statistical tests, can still be cost-effective (210), provided the results are interpreted with caution (579). The effect size was transformed into a relative risk with uncertainty modelled using a Log-Normal distribution (see **Supplementary Data Equations 6-10**).	(209)
Partridge *et al*. (2017, 2021)	Single-centre randomised controlled trial in a National Health Service tertiary hospital for patients ≥65 years undergoing elective vascular surgery (aortic aneurysm repair or lower limb arterial bypass). Intervention group received a CGA and the control group standard preoperative care.	209 included patients with no loss to follow-up or withdrawal. Postoperative medical complications occurred in 72% of the control arm and 50% in the CGA arm ($p < 0.05$).	The significant reduction in postoperative complications of 30.6% with GA is relevant to model the best possible clinical effect. The findings of this group may be difficult to replicate, so sensitivity analyses will include the removal of this effect. The effect size was transformed into a relative risk with uncertainty modelled using a Log-Normal distribution (see **Supplementary Data Equations 6-10**).	(61, 96)

Table 17 – Summary of important studies used in this health economic evaluation.
Abbreviations: GA = geriatric assessment; CGA = comprehensive geriatric assessment; G8 = geriatric 8 score.

Cost	Time (mins)	Healthcare professional	Cost (£) per minute	Total cost (£)	Ref
Pre-treatment costs					
GA using tablet (technology)		-		2.00	(219)
GA using tablet (human resources)	35	Nurse (B6)	1.97	68.78	
GA using face-to-face consultant review	30	Consultant	4.71	141.18	
GA using face-to-face registrar review	30	Registrar	1.88	56.41	
GA using nurse-led review[1]	60	Nurse (B6)	1.97	117.91	(580)
Patient contact with dietician	30	Dietician	1.97	58.96	
Patient contact with social worker	30	Social worker	1.08	32.51	
Patient contact with occupational therapist	30	Occupational therapist	2.01	60.23	
Patient contact with physiotherapist	30	Physiotherapist	2.01	60.23	
Patient contact with falls clinic		-		747.07	(581)
Outpatient contact with physician	30	Consultant	4.71	141.18	(580)
CBT treatment course		-		1,053.40	(582)
Posttreatment costs					
Cost per excess bed day		-		366.01	(583)
Admission to high dependency unit/intensive care		-		2,160.21	(584)
Chemotherapy toxicity admission $<$ 5 days		-		614.75	(585)
Chemotherapy toxicity admission $\geq$ 5 days		-		3,437.29	
Emergency department visits		-		169.92	(586)
Surgical readmission within 30 days of discharge		-		3,522.70	(586)

Table 18 – Per patient unit costs for health and social care services and professionals.
The per patient unit costs used in this health economic analysis for health and social care service and professionals. [1]The same unit cost is used whether the assessment occurs via the telephone or face-to-face. *Abbreviations: GA = geriatric assessment; B6 = Band 6; CBT = cognitive behavioural therapy.* All costs have been uprated to 2019/2020 financial year prices using the Hospital and Community Health Services (HCHS) and NHS cost inflation indices (NHSCII), and then further inflated to 2021 prices using the geometric mean of prices from 2007-2020(218).

Parameter	Mean	SD	Distribution (parameters)	Ref
Cancer treatment	-		Dirichlet (0.34, 0.083, 0.21, 0.15, 0.05, 0.07, 0.07, 0.03)[1]	(587)
QALY baseline	0.73	0.06	Beta (38, 14)	(221)
Chemotherapy mortality	3.0%	1.8%	Beta (3, 91)	(588)
Chemotherapy toxicity	53.0%	10%	Beta (12, 11)	(589)
Chemotherapy decrement[2]	0.32	0.03	Beta (77, 164)	(227)
Unscheduled chemotherapy readmission	13.1%	0.04%	Beta (9, 61)	(238)
LOS following chemotherapy readmission (days)	4.4	4.4	Gamma (1, 1/0.227[3])	(238)
Any surgical complication	40.0%	0.5%	Beta (3799, 5703)	(590)
Major surgical complications	10.1%	0.3%	Beta (961, 8599)	(590)
Requiring ITU	9.7%	-	Binomial (1, 0.097)	(591)
LOS following surgery (days)	6.5[4]	3.7[4]	Gamma (2, 3)	(592-596)
Unscheduled readmission post-surgery	10.3%[5]	5.1%[5]	Beta (3.6, 31.5)	(597-602)
Surgical mortality	1.4%	0.1%	Beta (130, 9320)	(590)
Emergency department use	0.11%	0.11%	Beta (0.78, 6.3)	(603)
Usual care and geriatric assessment				
Dietetics	59.8%	13.7%	Beta (7, 5)	(604)
Falls clinic	4.4%	14.3%	Beta (0, 1)	(101, 605, 606)
Occupational therapy	3.6%	5.1%	Beta (0, 12)	(101, 607)
Physiotherapy	5.9%	5.0%	Beta (1, 20)	
Social worker	40.4%	11.6%	Beta (7, 10)	(101, 608)
Mental health services	28.8%	12.1%	Beta (4, 9)	(101, 609, 610)
Geriatrician[6]	31.2%	3.3%	Beta (61, 133)	(101)
Other physician	9.0%	4.2%	Beta (4, 40)	
Usual care				
Dietetics	10.2%	21.2%	Beta (0, 1)	(604)
Falls clinic	0.2%	1.0%	Beta (0, 23)	(101, 605, 606)
Occupational therapy[7]	0.0%	0.0%	-	(101, 607)
Physiotherapy[7]	0.0%	0.0%	-	
Social worker[7]	0.0%	0.0%	-	(101, 608)
Mental health services	7.2%	7.1%	Beta (1, 12)	(101, 609, 610)
Geriatrician[7]	0.0%	0.0%	-	(101)
Other physician[7]	0.0%	0.0%	-	
Potential effects (in favour of additional geriatric assessment)				
Reduced postoperative complications (RR, (RRR))	0.55 (0.45)	0.69 (0.31)	Log-Normal (-1.07, 0.97)	(61)
Reduced chemotherapy toxicity (RR, (RRR))	0.84 (0.16)	0.87 (0.13)	Log-Normal (-0.53, 0.85)	(233)

Table 19 – Model parameters used in health economic evaluation.

[1]These values represent the percentage of treatment combinations in the following order: other care; chemotherapy only; surgery only; radiotherapy only; chemotherapy and radiotherapy; surgery and chemotherapy; surgery and radiotherapy; surgery, radiotherapy and chemotherapy. [2]This applies for the first year after treatment only. [3]The reciprocal value represents using the second parameter of the Gamma distribution ($\boldsymbol{\lambda}$) as a rate versus a scale ($\boldsymbol{\beta}$). [4]Calculated as the mean of the mean length of stay reported for thyroid, breast, lung, colorectal and gastric cancer surgery as a representation of all cancers. [5]Calculated as the mean of the mean readmission rate reported following colorectal, lung, head and neck, gastric, breast and prostate cancer surgery. [6]This does not apply if reviewed by a geriatrician during initial geriatric assessment. [7]There is no evidence available of the background rate of referrals to these professionals, although expert opinion suggests that this does not happen due to the absence of these

members in the usual cancer MDT. *Abbreviations: SD = standard deviation*, *QALY = quality adjusted life year, LOS = length of stay, ITU = intensive therapy unit; RR = relative risk; RRR = relative risk reduction (calculated as 1 – RR).*

$$\alpha = \left(\frac{1-\mu}{\sigma^2} - \frac{1}{\mu}\right)$$

Equation 4 – Solving α parameter given mean and standard deviation.
α = alpha parameter of Beta distribution, μ = mean and σ = standard deviation.

$$\beta = \alpha\left(\frac{1}{\mu} - 1\right)$$

Equation 5 – Solving β parameter given α parameter and mean.
β = beta parameter of Beta distribution and μ = mean.

$$\sigma = \frac{(UL - LL)}{3.92} \times \left(\sqrt{n}\right)$$

Equation 6 – Estimating standard deviation given a 95% confidence interval.
$\boldsymbol{\sigma}$ = standard deviation, UL = upper limit of 95% confidence interval, LL = lower limit of 95% confidence interval and 3.92 represents the standard errors of a 95% confidence interval. Usually, the square root of the sample size, *n* is multiplied by the range of the confidence interval over the relevant standard errors. In some situations, the sample size is unknown, therefore the standard error was treated as the standard deviation when creating parameters for Beta distributions. The actual distributions were visualised using a histogram to check their suitability in representing the mean and range provided.

$$\alpha = (\mu\sigma)^2$$

Equation 7 – Estimating the α parameter using the mean and standard deviation.
The **α** parameter is estimated as the squared product of the mean, **μ** and standard deviation, **σ**.

$$\lambda = \mu\sigma^2$$

Equation 8 – Estimating the λ parameter using the mean and standard deviation.
The **λ** parameter is estimated as the product of the mean, **μ**, and standard deviation, **σ**, squared.

$$RR = \frac{a/N_1}{b/N_0}$$

Equation 9 – Calculating the relative risk from study data.
The relative risk (***RR***) is calculated where, $\boldsymbol{a}$ = number of cases in the intervention/geriatric assessment group, $\boldsymbol{b}$ = number of cases in the control/standard care group, $\boldsymbol{N_1}$ is the total number in the intervention group and $\boldsymbol{N_0}$ is the total number in the control group.

$$SE[ln(RR)] = \sqrt{1/a - 1/N_1 + 1/b - 1/N_0}$$

Equation 10 – Calculating the standard error of the relative risk from study data.
The standard error (***SE***) of the natural log of the relative risk (***RR***) or $\boldsymbol{ln(RR)}$ is calculated where, $\boldsymbol{a}$ = number of cases in the intervention/geriatric assessment group, $\boldsymbol{b}$ = number of cases in the control/standard care group, $\boldsymbol{N_1}$ is the total number in the intervention group and $\boldsymbol{N_0}$ is the total number in the control group.

$$SD[X] = \sqrt{exp(2\,ln(RR) + 2SE[ln(RR)]^2) - exp(2\,ln(RR) + SE[ln(RR)]^2)}$$

Equation 11 – Calculating the standard deviation of the relative risk from study data.
The standard deviation (***SD***) of the relative risk (***RR***), where ***X*** has a lognormal distribution is calculated where, ***SE***[***ln***(***RR***)] is derived from **Equation 10**.

$$\sigma' = \sqrt{ln(SD[X]^2 + exp(2\,ln(RR)) - 2\,ln(RR)}$$

Equation 12 – Calculating the corrected standard deviation of the relative risk from study data.
The corrected standard deviation (***σ′***) of the relative risk (***RR***) is calculated where ***SD***[***X***] is derived from **Equation 11**.

$$\mu' = ln(RR) - \frac{1}{2}\sigma'^2$$

Equation 13 – Calculating the corrected mean of the relative risk from study data.
The corrected mean (***μ′***) of the relative risk (***RR***) is calculated where ***σ′*** is derived from **Equation 12**.

$$tp(t_u) = 1 - \frac{S(t)}{S(t-u)}$$

Equation 14 – Calculating the transition probability from the survival function.
The transition probability $tp(t_u)$ is calculated given the survival function, *S(t)* and a Markov cycle of length *u,* where *t* is the current cycle of the Markov chain.

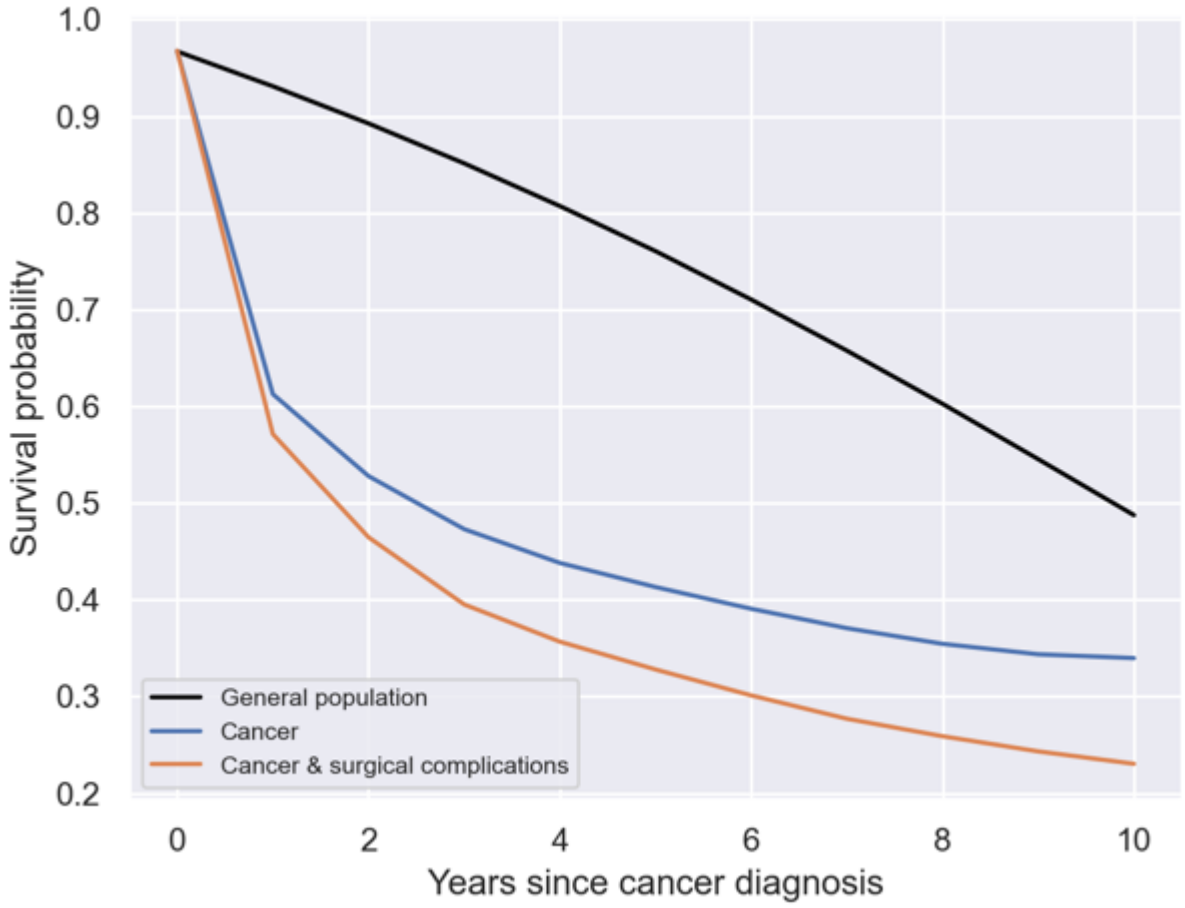


Figure 49 – Weighted mean 10-year survival probability (Kaplan–Meier) plot for common cancers diagnosed at 77-years.
General population survival data were derived from UK national lifetables for 77-87 years of life(611). The presence of cancer is associated with a significant inflection point in weighted mean survival at one year, with a steady decline in survival up to 10 years. Survival probabilities between 1-, 5- and 10-year survival were imputed using piecewise cubic Hermite interpolating polynomial. The ratios of the extracted Moonsinghe *et al.*(243) survival data were calculated based on gender weighted national lifetable data for 63-73 years. These ratios were used to calculate the additional risk of death for 77–87-year-old patients with cancer, who sustained post-operative complications.

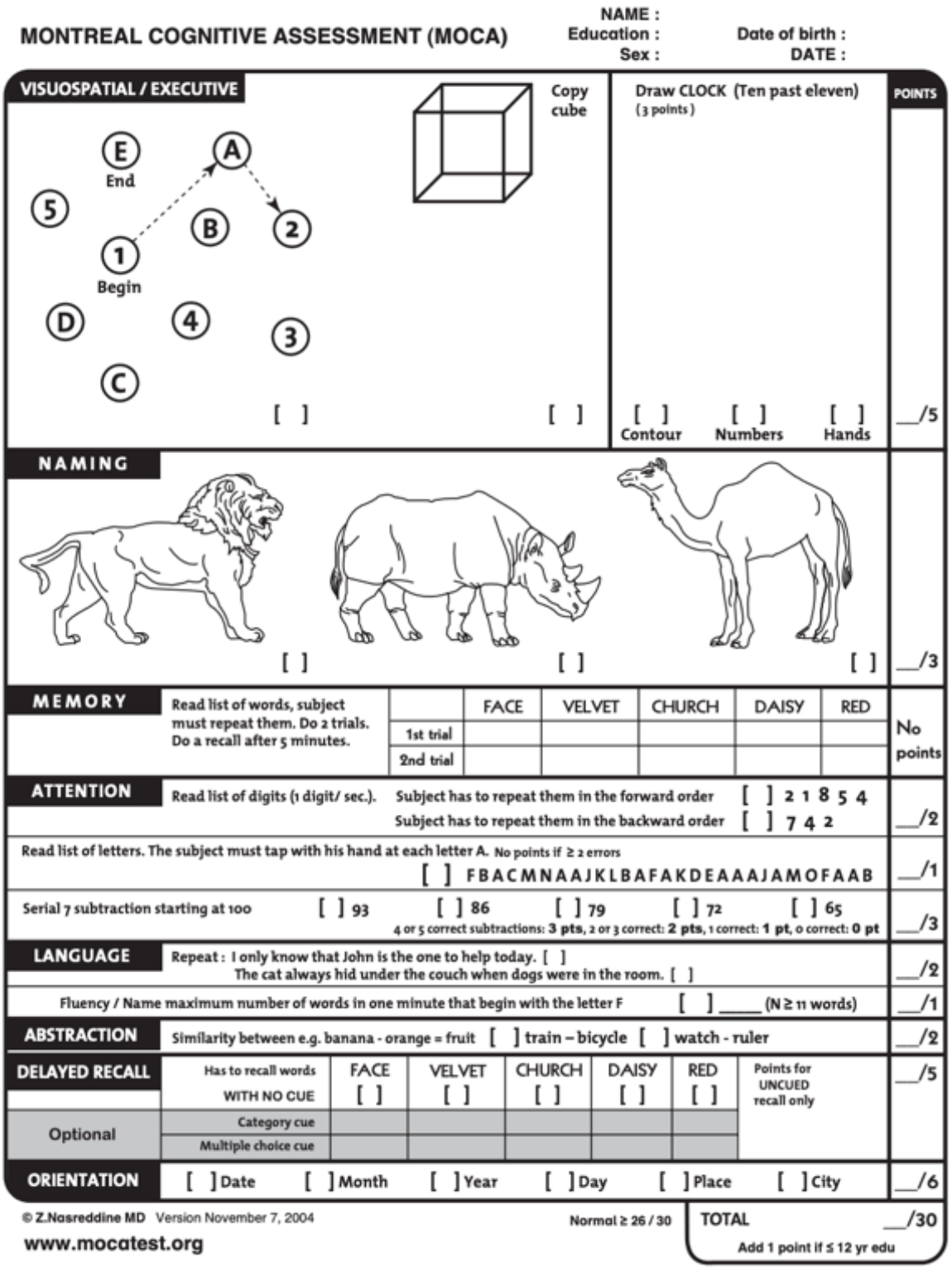


Figure 50 – The Montreal Cognitive Assessment.
The Montreal Cognitive Assessment (MoCA) is a validated tool used to screen for cognitive disorders, which is assesses multiple domains of cognition. Reproduced from https://www.mocatest.org [last accessed 8th November 2021]

1.	**Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?** o 0 = severe decrease in food intake o 1 = moderate decrease in food intake o 2 = no decrease in food intake
2.	**Weight loss during the last 3 months** o 0 = weight loss greater than 3kg (6.6lbs) o 1 = does not know o 2 = weight loss between 1 and 3kg (2.2 and 6.6 lbs) o 3 = no weight loss
3.	**Mobility** o 0 = bed or chair bound o 1 = able to get out of bed / chair but does not go out o 2 = goes out
4.	**Has suffered psychological stress or acute disease in the past 3 months?** o 0 = yes o 2 = no
5.	**Neuropsychological problems** o 0 = severe dementia or depression o 1 = mild dementia o 2 = no psychological problems
6.	**Body Mass Index (BMI) = weight in kg / (height in m)^2** o 0 = BMI less than 19 o 1 = BMI 19 to less than 21 o 2 = BMI 21 to less than 23 o 3 = BMI 23 or greater

Table 20 - Mini Nutritional Assessment-short form.
The Mini Nutritional Assessment-short form. A score of 0–7 indicates malnutrition; 8–11 indicates risk of malnutrition; and 12–14 normal nutritional status. Adapted from Vella *et al*. (302)

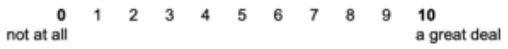
Domain	Question	Answers	Rationale
Falls	How many falls have you had in the LAST YEAR?	1. None 2. One 3. Two or more	Identification of individuals at risk of falls, either for data on unmet needs for quality improvement or for referral to relevant services for optimisation before cancer treatment. The question regarding falls in the last six months maps to the CARG chemotherapy toxicity score.
	↳ Have you had any falls in the last SIX MONTHS?	1. Yes 2. No	
	Do you have any difficulty with walking and balance?	1. Yes 2. No	
Nutrition	Has your food intake become less over the past THREE MONTHS due to loss of appetite, digestive problems, chewing or swallowing difficulties?	1. Yes, very badly 2. Yes, quite badly 3. Not at all	Identification of malnutrition through screening allows optimisation efforts to begin before treatment. Malnourished individuals are around twice as a likely to die than patients without malnutrition.
	Have you lost weight over the last THREE MONTHS?	1. More than 3kg (about half a stone) 2. Between 1kg and 3kg (less than half a stone) 3. I do not know 4. No weight loss	
	How is your mobility?	1. I can only stay in bed or on a chair 2. I am able to get out of bed or a chair, but I do not go out of the house 3. I am able go out of the house	
Mood	See Appendix Table 23		In the absence of a fully validated patient reported measure for older adults with cancer, the Center for Epidemiologic Studies of Depression (CESD-R) measure appears most useful. Screening for depression offers value in predicting postoperative outcomes and optimisation before treatment.
Functional status (basic activities of daily living)	See **Appendix Table 24**		The question regarding bathing maps into the Suemoto Index (**Appendix** **Table** 26)

Functional status (instrumental activities of daily living)	See **Appendix** Table **25**		Transportation issues may limit follow-up recommendations and hypofractionation, brachytherapy, or stereotactic radiotherapy techniques may be considered where transportation issues are poor.
Functional capacity	Are you able to climb TWO FLIGHTS of STAIRS?	1. Yes 2. No	In the context of known ischaemic heart disease this determines the need for preoperative stress testing
	Are you able to walk MORE THAN 100 METERS OUTSIDE (about 7 bus lengths)?	1. Yes 2. No	This maps to the CARG chemotherapy toxicity risk prediction model (**Appendix** **Table** 22)
	Because of a health problem would you have difficulty WALKING ABOUT 500 METERS OUTSIDE (about 36 bus lengths)?	1. Yes 2. No	This maps to the Suemoto Index (**Appendix** **Table** 26**)** for non-cancer mortality prediction. This also helps to map to the clinical frailty scale.
	Do you undertake in VIGOROUS PHYSICAL EXERCISE or SPORTS (e.g., **heavy house work**, **gardening**, **physical job**, **aerobics**, **running, swimming**, or **bicycling**) THREE OR MORE TIMES PER WEEK?	1. Yes 2. No	
Breathlessness	Do you ever get breathless?	1. I only get breathless with strenuous exercise 2. I get short of breath when hurrying on level ground or walking up a slight hill 3. On level ground, I walk slower than people of the same age because of breathlessness, or	To screen for breathlessness and identify the need for preoperative investigation. Referral to a breathlessness clinic can be considered.

		I have to stop for breath when walking at my own pace on the level 4. I stop for breath after walking about 100 yards or after a few minutes on level ground 5. I am too breathless to leave the house, or I am breathless when dressing	
Self-reported health	In general, how would you describe your health?	1. Excellent 2. Very good 3. Good 4. Fair 5. Poor	This maps to the Suemoto Index (**Appendix Table** 22**)** for non-cancer mortality prediction
Social circumstances	Who do you live with?	1. I live alone 2. Partner 3. Family 4. Friend 5. I live in a care home	Lack of social support may require adapted radiotherapy regimens. Inadequate social support may require a needs assessment from social services. Financial needs and carers assessments can also be arranged where necessary.
	↳ Could the person or people you live with help you to look after yourself if needed?	1. Several times a day 2. Daily 3. Weekly 4. When needed 5. Very occasionally 6. Never	
	Do any of the following people help look after you (tick all that apply)?	1. Family 2. Friend 3. Neighbour 4. Faith group 5. Community group 6. Volunteer	
	Do any of the following people visit you at home (tick all that apply)?	1. Care agency 2. District nurse 3. Social worker 4. Volunteer	

		5. Hospice nurse 6. Age UK befriender 7. Meals on Wheels	
	How often can you get support if you need it?	1. Several times a day 2. Daily 3. Weekly 4. When needed 5. Very occasionally 6. Never	
	Do you feel you get enough support from others for your needs, including your feelings and emotions?	1. Yes 2. It's okay but I would like more 3. No	
	Are you a carer for anyone?	1. Yes 2. No	
	↳ Have you been seen by a Carers Support worker?	1. Yes 2. No 3. Unsure	
	↳ Have you had a carer's assessment by Social Care?	1. Yes 2. No 3. Unsure	
	↳ Do you receive Carers Allowance?	Yes No Unsure	
	Have you had a 'needs assessment' by social services?	1. Yes 2. No 3. Unsure	
	Do you receive any of the following benefits (tick all that apply)?	1. Attendance allowance 2. Mobility allowance 3. Disability living allowance 4. Income support 5. Housing benefit 6. Pension credit	

	Does anyone have a Power of Attorney for your health, property or affairs? ↳ If so who?.....	1. Yes 2. No 3. Unknown	
	Has your physical or emotional health become so bad that your social life has been affected (e.g., meeting with friends, visiting family)?	1. Yes 2. No	This maps to the CARG chemotherapy toxicity risk prediction model (**Appendix** **Table** 22)
Hearing	What would you rate your hearing?	1. Excellent 2. Good 3. Fair 4. Poor	This maps to the CARG chemotherapy toxicity risk prediction model (**Appendix** **Table** 22) Refer to audiology for hearing assessment if no aiding and fair or poor-quality hearing. Advise to self-refer to audiological services if wears a hearing aid and it is not somewhat or less helpful. Poor hearing is a falls risk and ensuring sensory deprivation is corrected can help prevent postoperative delirium.
	If you wear a hearing aid how good is it at improving your hearing?	1. I do not wear a hearing aid 2. A great deal 3. Somewhat 4. Not at all	
Continence	Do you have a problem with leaking urine when you don't want to?	1. Yes 2. No	Consider referral to continence advisory services (if available) or refer back to GP for review
	↳ How often do you leak urine?	1. Never 2. About once a week or less often 3. Two or three times a week 4. About once a day 5. Several times a day 6. All the time	

	↳ How much urine do you usually leak (whether you wear protection or not)?	1. None 2. A small amount 3. A moderate amount 4. A large amount	
	↳ Overall, how much does leaking urine interfere with your everyday life?	Please ring a number between 0 (not at all) and 10 (a great deal) 	
	↳ When does urine leak? (Please tick all that apply to you)	1. Never – urine does not leak 2. Leaks before you can get to the toilet 3. Leaks when you cough or sneeze 4. Leaks when you are asleep 5. Leaks when you are physically active/exercising 6. Leaks when you have finished urinating and are dressed 7. Leaks for no obvious reason 8. Leaks all the time	
	Do you ever leak or lose control of stool (your bowels)?	1. Yes 2. No	Further assessment and/or referral accordingly.
Alcohol	How often did you have a drink containing alcohol in the past year?	1. Never 2. Monthly or less 3. Two to four times a month 4. Two to four times a week 5. Four or more times a week	For females: Scores ≥3 are consistent with alcohol misuse. For males: Scores ≥4 are consistent with alcohol misuse. Offer to refer to alcohol services if positive.
	How many drinks containing alcohol did you have on a typical day when you were drinking in the past year?	1. 1 or 2 drinks 2. 3 or 4 drinks 3. 5 or 6 drinks 4. 7 to 9 drinks 5. 10 or more	

	How often did you have six or more drinks on one occasion in the past year?	1. Never 2. Less than monthly 3. Monthly 4. Weekly 5. Daily or almost daily	
Smoking	Have you ever smoked?	1. Never 2. Past 3. Current	Current smoking increases the risk of a range of postoperative complications and other oncological and treatment outcomes, therefore referral should be offered for current smokers.

Table 21 – Rationalised domains and questions of a patient reported oncogeriatric assessment.
The domains of an oncogeriatric assessment, plain English example questions with their answers and a rationalisation of their value has been tabulate.

Risk factor	Score
Age ≥ 72 years	**2**
Cancer type: gastrointestinal or genitourinary	**2**
Chemotherapy dosing: standard dose	**2**
Number of chemotherapy drugs: polychemotherapy	**2**
Haemoglobin <11g /dl (male), <10 g/dl (female)	**3**
Creatinine clearance (Jelliffe formula – ideal weight): <34 mL/min	**3**
Hearing described as fair or worse*	**2**
Number of falls in last 6 months: 1 or more*	**3**
Needs assistance with taking medications*	**1**
Limited in walking one block*	**2**
Decreased social activity because of physical or emotional health*	**1**

Table 22 – The Cancer and Ageing Research Group chemotherapy toxicity prediction score.
The Cancer and Ageing Research Group chemotherapy toxicity prediction score can be used to predict chemotherapy toxicity in older adults with cancer. Low risk (0-5 points, 36.7%), medium risk (6-9 points, 62.4%) and high risk (10-23 points, 70.2%) for developing grade 3-5 chemotherapy toxicity. *Suitable for patient self-report and mapped to patient reported questionnaire. Adapted from Hurria *et al.* (589)

	During the past week				Nearly every day for 2 weeks
	Not at all or less than 1 day	1-2 days	3-4 days	5-7 days	
	0 points	**1 point**	**2 points**	**3 points**	**4 points**
1. My appetite was poor					
2. I could not shake off the blues.					
3. I had trouble keeping my mind on what I was doing.					
4. I felt depressed.					
5. My sleep was restless.					
6. I felt sad.					
7. I could not get going.					
8. Nothing made me happy					
9. I felt like a bad person					
10. I lost interest in my usual activities					
11. I slept much more than usual					
12. I felt like I was moving too slowly					
13. I felt fidgety.					
14. I wished I were dead.					
15. I wanted to hurt myself.					
16. I was tired all the time.					
17. I did not like myself.					
18. I lost a lot of weight without trying to					
19. I had a lot of trouble getting to sleep.					
20. I could not focus on the important things.					

Table 23 – The Center for Epidemiologic Studies of Depression-Revised measure for depression.
The Center for Epidemiologic Studies of Depression-Revised measure for depression has been noted to be one of the most reliable and useful measures of depression in older adults with cancer. The total score is calculated by adding together all the scores.

Figure 51 – The Rockwood Clinical Frailty Scale.
The 9-point revised Rockwood Clinical Frailty Scale with descriptors and pictograms to aid understanding between health professionals. Reproduced from https://www.dal.ca/sites/gmr/our-tools/clinical-frailty-scale.html [last accessed 8th November 2021]

Activity	Original	Patient reported	Original	Patient reported
	Independence (1 point) No supervision, direction or personal assistance		**Dependence (0 points)** With supervision, direction, personal assistance or total care	
Bathing	Bathes self completely or needs help in bathing only a single part of the body such as the back, genital area or disabled extremity	I can bath myself completely I need help bathing only one part of the body (e.g., back, genital area or a disabled limb)	Needs help with bathing more than one part of the body, getting in or out of the bath or shower. Requires total bathing.	I need help bathing more than one part of the body or getting in or out of the bath or shower[1] I require full help to have a bath or shower[1]
Dressing	Gets clothes from closets and drawers and puts on clothes and outer garments complete with fasteners. May have help tying shoes.	I can get clothes from closets and drawers and put on all clothes including any fasteners. I can get clothes from closets and drawers and put on all clothes including any fasteners, but I need help tying my shoes	Needs help with dressing self or needs to be completely dressed.	I need help with dressing myself I need to be completely dressed
Toileting	Goes to toilet, gets on and off, arranges clothes, cleans genital area without help.	I can go to the toilet, get on or off, clean myself and arrange my clothes again all without any help	Needs help transferring to the toilet, cleaning self or uses bedpan or commode.	I need help transferring to the toilet or cleaning myself I use a bedpan or commode
Transferring	Moves in and out of bed or chair unassisted. Mechanical transferring aides are acceptable.	I can move in or out of bed or a chair without help or aides. I use some aides to help me move in or out of bed or a chair	Needs help in moving from bed to chair or requires a complete transfer	I need help from someone to move from bed to a chair I need a complete transfer
Feeding	Gets food from plate into mouth without help. Preparation of food may be done by another person.	I can get food from my plate to my mouth without help I can get food from my plate to my mouth without help, but I need help preparing food	Needs partial or total help with feeding or requires parenteral feeding.	I need help from someone with feeding I am fed through a tube in my stomach or neck

Table 24 – The Katz 5-item activities of daily living scale with original and modified patient reported responses.
The Katz 5-item is a validated and reliable tool for activities of daily living assessment and can be easily modified for patient-reporting. [1]This is mapped to the Suemoto Index (**Figure 52**)

Activity	Original	Patient reported	Score
Telephone	Operates telephone on own initiative; looks up and dials numbers	I can use a telephone, look up and dial numbers	1
	Dials a few well-known numbers	I can dial a few well-known numbers	1
	Answers telephone but does not dial	I can answer the phone, but do not dial numbers	1
	Does not use telephone at all	I do not use a telephone at all	0
Shopping	Takes care of all shopping needs independently	I can take care of all shopping needs independently	1
	Shops independently for small purchases	I can manage small purchases from the shops only	0
	Needs to be accompanied on any shopping trip	I need someone with me to go shopping	0
	Completely unable to shop	I am completely unable to shop	0
Food preparation	Plans, prepares, and serves adequate meals independently	I can plan, prepare and serve meals independently	1
	Prepares adequate meals if supplied with ingredients	I can prepare meals if someone else gets me the ingredients	0
	Heats and serves prepared meals or prepares meals but does not maintain adequate diet	I can heat and serve prepared meals or prepare meals, but they are not enough	0
	Needs to have meals prepared and served	I need help to prepare and serve meals	0
Housekeeping	Maintains house alone with occasion assistance (heavy work)	I can maintain my house alone with some assistance for heavy work	1
	Performs light daily tasks such as dishwashing, bed making	I can do light housework like dishwashing and bed making	1
	Performs light daily tasks, but cannot maintain acceptable level of cleanliness	I can do some light tasks but cannot keep my house clean enough	1
	Needs help with all home maintenance tasks	I need help with all housekeeping tasks	1
	Does not participate in any housekeeping tasks	I do not get involved with housekeeping tasks	0
Laundry	Does personal laundry completely	I can do all personal laundry completely	1
	Launders small items, rinses socks, stockings, etc	I can launder small items, rinse socks or stockings	1
	All laundry must be done by others	All my laundry is done by others	0
Transportation	Travels independently on public transportation or drives own car	I can travel using public transport or drive my own car	1
	Arranges own travel via taxi, but does not otherwise use public transportation	I can travel on my own in a taxi, but I do not use public transport	1
	Travels on public transportation when assisted or accompanied by another.	I can travel on public transport when I am with someone else[1]	1

	Travel limited to taxi or automobile with assistance of another	I can only travel in a taxi or car with someone else with me[1]	0
	Does not travel at all	I do not travel at all[1]	0
Medications	Is responsible for taking medication in correct dosages at correct time	I can take all my own medicines at the correct dose and time	1
	Takes responsibility if medication is prepared in advance in separate dosages	I can take all my medication if it is prepared into separate doses	0
	Is not capable of dispensing own medication	I am unable to take all of my own medication[2]	0
Finances	Manages financial matters independently (budgets, writes checks, pays rent and bills, goes to bank); collects and keeps track of income	I can manage all my own finances (budgets, cheques, rent, bills, banking, collection)	1
	Manages day-to-day purchases, but needs help with banking, major purchases, etc	I can manage my finances generally but need help with banking and big purchases	1
	Incapable of handling money	I am unable to handle my own money	0

Table 25 – The Lawton instrumental activities of daily living scale.
The Lawton instrumental activities of daily living scale in both its original from and with modified patient reported wording. Adapted from Lawton *et al*. [1]Transportation issues may mean that hypofractionated, brachytherapy, or stereotactic radiotherapy is better suited. Limitations to follow-up recommendations should also be considered. [2]Mapped to Cancer and Ageing Research Group chemotherapy toxicity prediction model (
Table 22). Adapted from Lawton *et al*.(325)

NHS
Health Research Authority
Yorkshire & The Humber - South Yorkshire Research Ethics Committee
NHSBT Newcastle Blood Donor Centre
Holland Drive
Newcastle upon Tyne
NE2 4NQ

Tel: 0207 104 8079

Please note: This is the favourable opinion of the REC only and does not allow the amendment to be implemented at NHS sites in England until the outcome of the HRA assessment has been confirmed.

14 August 2020

Dr Gordon McKenzie
Doctoral Research Fellow and Specialist Registrar in Otolaryngology
Hull York Medical School
Allam Medical Building
University of Hull, Hull
HU6 7RX

Dear Dr McKenzie

Study title:	**Developing an evidence-based system to facilitate the predictive assessment and optimisation of older adults with cancer**
REC reference:	**19/YH/0382**
Protocol number:	**RS125**
Amendment number:	**RS125/1**
Amendment date:	**22 July 2020**
IRAS project ID:	**265639**

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Completed Amendment Tool [Complete Amendment Tool]	1	22 July 2020
Completed Amendment Tool	RS125/1	22 July 2020

Covering letter on headed paper [Cover Letter]	2	22 July 2020
Non-validated questionnaire [Survey Questionnaire]	2, Clean	22 July 2020
Non-validated questionnaire [Survey Questionnaire]	2, Track Change	22 July 2020
Other [Response to Queries raised by REC]		
Participant information sheet (PIS) [PIS]	2.4, Clean	22 July 2020
Participant information sheet (PIS) [PIS]	2.4, Track change	22 July 2020
Research protocol or project proposal [Protocol]	1.9, Track change	11 August 2020
Research protocol or project proposal [Protocol]	1.9, tracked change	11 August 2020

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

Working with NHS Care Organisations

Sponsors should ensure that they notify the R&D office for the relevant NHS care organisation of this amendment in line with the terms detailed in the categorisation email issued by the lead nation for the study.

Amendments related to COVID-19

We will update your research summary for the above study on the research summaries section of our website. During this public health emergency, it is vital that everyone can promptly identify all relevant research related to COVID-19 that is taking place globally. If you have not already done so, please register your study on a public registry as soon as possible and provide the HRA with the registration detail, which will be posted alongside other information relating to your project.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

HRA Learning

We are pleased to welcome researchers and research staff to our HRA Learning Events and online learning opportunities– see details at: https://www.hra.nhs.uk/planning-and-improving-research/learning/

IRAS Project ID - 265639:	**Please quote this number on all correspondence**

Yours sincerely
Pp

Dr Ian Woollands
Chair

E-mail: southyorks.rec@hra.nhs.uk

Enclosures: *List of names and professions of members who took part in the review*

Yorkshire & The Humber - South Yorkshire Research Ethics Committee

Attendance at Sub-Committee of the REC meeting via correspondence

Committee Members:

Name	*Profession*	*Present*
Dr Alison Patrick	Lecturer in Law and Ethics	Yes
Dr Ian Woollands (Chair)	Retired Clinical Director, Occupational Health	Yes

Also in attendance:

Name	*Position (or reason for attending)*
Miss Donna Bennett	Approvals Administrator

Figure 52 – Regional Ethics Committee acceptance letter.

Question	Answers
What is the sex of your patient?	Female Male
How old is your patient?	60-64 65-74 75-79 80-84 85+
Does your patient have diabetes?[1]	No Yes
Does your patient have heart disease?[1]	No Yes
Does you patient have lung disease?[1]	No Yes
Does your patient have cancer?[2]	**No** Yes
Does your patient smoke?[3]	Never Currently In the past
Does your patient currently use alcohol?[3]	No Yes
What is your patient's body mass index (BMI)?[4]	< 20 kg/m^2 20 to < 25 kg/m^2 25 to 30 kg/m^2 ≥ 30 kg/m^2
Does your patient participate in vigorous physical exercise or sports (such as heavy house work, a job that involves physical work, aerobics, running, swimming, or bicycling) three or more times per week?[3]	No Yes
Because of a health problem, does your patient have any difficulty with bathing or showering?[3]	No Yes
Because of a health problem, does your patient have any difficulty walking several blocks?[3]	No Yes
Did your patient report today's date correctly (day/month/year)?[5]	No Yes
How does your patient report his/her health?[3]	Excellent, very good, or good Fair, poor

Table 26 – Suemoto Index.
The Suemoto Index is a validated model for the prediction of 10-year all-cause mortality. [1]Information regarding co-morbidities can be obtained from the co-morbidity review. [2]The option for cancer can be allocated 'no' by default to estimate non-cancer mortality, which is more useful for shared decision-making. [3]These aspects can be patient reported. [4]Body mass index can be obtained from the physical examination component of the OGA. [5]Both the Montreal Cognitive Assessment and Mini Mental State Examination include an orientation component for reporting of the current date.

Outcome	Relative risk (95% confidence interval)
General morbidity	1.52 (1.33-1.74)
Wound complications	2.15 (1.87-2.49)
General infections	1.54 (1.32-1.79)
Pulmonary complications	1.73 (1.35-2.23)
Neurological complications	1.38 (1.01-1.88)
Admission to intensive care unit	1.60 (1.14-2.25)

Table 27 – The effects of smoking on postoperative complications.
Smoking has a significant effect on postoperative outcomes (305).

Outcome	Relative risk (95% confidence interval)
General morbidity	1.56 (1.31-1.87)
Wound complications	1.23 (1.09-1.40)
General infections	1.73 (1.32-2.28)
Pulmonary complications	1.80 (1.30-2.49)
Prolonged stay at the hospital	1.24 (1.18-1.31)
Admission to intensive care unit	1.29 (1.03-1.61)
Mortality	2.68 (1.50-4.78)

Table 28 – The effects of alcohol on postoperative complications.
Alcohol has a significant effect on postoperative outcomes (378).

CO-MORBIDITY	ADVICE	REFERENCE
Cardiac		
Percutaneous coronary intervention: bare mental stent	○ Elective surgery *should* be delayed for 30 days. Refer to cardiology. ○ Active malignancy is a strong independent risk factor for in-stent thrombosis (HR 4.50). Strongly recommended to discuss with cardiology before withdrawing dual antiplatelet therapy during chemotherapy in the context of thrombocytopenia	(612, 613)
Percutaneous coronary intervention: drug-eluting stent	○ Elective surgery *should optimally* be delayed for 6 months. Refer to cardiology. ○ Active malignancy is a strong independent risk factor for in-stent thrombosis (HR 4.50). Strongly recommended to discuss with cardiology before withdrawing dual antiplatelet therapy during chemotherapy in the context of thrombocytopenia	
Ischaemic heart disease	○ Poorly controlled or unstable disease requires referral to cardiology preoperatively. If metabolic equivalents are less four, preoperative stress testing is advised for risk stratification	(318)
Known or suspected valvular heart disease (excludes plastic, breast or thyroid surgery)	○ A preoperative resting echocardiogram is advised (unless one has recently been undertaken), with early cardiology or anaesthetic referral if planning surgery ○ Critical aortic stenosis may warrant pre-operative intervention	(318)
Hypertension >160/100 mmHg	○ Delay surgery until BP < 160/100 mmHg. ○ If hypertension >180/110 or target organ damage, pre-operative antihypertensives should be commenced.	(418) (318)
Permanent pacemaker	○ Preoperative referral to cardiac pacing services is necessary to establish if perioperative reprogramming is required to allow electrocautery. Battery and threshold checks are also required within the last year prior to surgery ○ Referral to cardiology/pacing services is recommended as device malfunction can occur in up to 3% of radiotherapy courses	(614)
Implantable cardioverter defibrillator	○ Preoperative referral to cardiac pacing services is necessary to plan deactivation and reactivation ○ Referral to cardiology/pacing services is recommended as device malfunction can occur in up to 3% of radiotherapy courses	(615)
Left heart failure	○ Referral to cardiology for optimisation of medical management is required along with early anaesthetic review ○ 50% of patients with severe heart failure (i.e., symptomatic with frequent presentations) will die within one year ○ New or poorly controlled heart failure requires commencement of uptitration of an angiotensin converting enzyme inhibitor (unless contraindicated) whilst formal assessment is awaited	(616) (338) (617)

	○ Critical care admission should be considered postoperatively ○ Odds of postoperative sepsis are 2.53x higher ○ Odds of postoperative pulmonary complications are 2.94 times higher (95% CI 1.02 to 8.43)* ○ Diastolic dysfunction is an independent risk factor for postoperative pulmonary oedema/congestive heart failure (OR 3.90, 95% CI, 2.23-6.83), myocardial infarction (OR 1.74, 95% CI, 1.14-2.67), major adverse cardiovascular events (OR 2.03, 95% CI 1.24-3.32)	(616)
Right heart failure (see also pulmonary hypertension)	○ Very high-risk surgical profile – the necessity of any surgery should be carefully considered with supported-decision making between the surgeon, anaesthetist and patient ○ Odds of postoperative sepsis are 2.53x higher	
Respiratory		
Severe chronic obstructive pulmonary disorder (Medical Research Council breathlessness scale 3+ or functional limitations)	○ Early referral to anaesthetist and respiratory consultant advised for investigation and bronchodilator therapy optimisation. ○ Arrange urgent lung function tests if surgical candidate and COPD is suspected but unconfirmed ○ Evidence of *cor pulmonale* requires preoperative echocardiography ○ Significant hypoxia (saturations less than 93% on air) require an arterial blood gas preoperatively to evaluate carbon dioxide retention and an echocardiogram ○ FEV1 <25% predicted may mean that benefits from major surgery are outweighed by respiratory mortality	(358) (338)
Pulmonary hypertension	○ Early referral to anaesthetist and respiratory consultant advised. Surgical risk is very high: 1-18% mortality, 14-42% morbidity including respiratory failure, myocardial infarction and acute kidney injury ○ Require preoperative echocardiography ○ Intensive care admission postoperatively is required	(618)
Restrictive lung disease	○ Early referral to anaesthetist and respiratory consultant advised	
Haematological		
Unexplained anaemia	○ Establish aetiology if uncertain and start preoperative iron therapy if necessary ○ Aim Hb > 13 for all elective major surgery ○ Avoid peri-operative transfusion ○ Arrange IV iron therapy if surgery planned within next 6 weeks ○ Arrange subsequent endoscopy for unexplained iron deficiency anaemia	(81, 619)
Anticoagulation	○ Warfarin interacts with fluorouracil causing international normalised ratio abnormalities	(620)
Gastrointestinal		

Inflammatory bowel disease	○ Radiotherapy is not an absolute contraindication but there is a 10–15% risk of any grade ≥ 3 toxicity, <5% risk of grade 4 toxicity, and <1% risk for grade 5 toxicity	(621)
Endocrine		
Diabetes mellitus Poor glycaemic control (e.g., HbA1c >69 mmol/mol) or hypoglycaemic unawareness	○ At risk of perioperative dysglycaemia, increased surgical site infections (OR 1.53, 95% CI 1.11-2.12), post-operative complications, critical care admission and inpatient mortality ○ Consider delaying surgery until HbA1c <8.5% (< 69mmol/mol) ○ Advised to refer to a diabetologist to optimise anti-diabetic agents preoperatively control within two to three weeks of surgery ○ Consideration of avoiding neurotoxic chemotherapy agents in the context of baseline neuropathy ○ Higher risk of chemotherapy-induced neutropenia in diabetes and hyperglycaemia (OR 1.32, 95% CI 1.06-1.64)	(81, 375, 622-624)
Adrenal insufficiency (e.g., Addison's disease)	○ Consider the need for stress dose steroids perioperatively on an individualised basis ○ Baseline corticosteroid use of ≥ 10 mg of prednisone equivalent has been associated with poorer outcomes in non-small-cell lung cancer patients treated with programmed death ligand 1 inhibitors	(625) (626)
Musculoskeletal		
Rheumatoid arthritis	○ Patients should have preoperative flexion and extension views of the cervical spine interpreted by a senior radiologist, due to the risk of atlanto-axial subluxation and consequent spinal cord injury, especially if head and neck surgery is possible ○ Refer to rheumatology if taking disease-modifying anti-rheumatic drugs or biologicals for perioperative or pre-chemotherapy planning ○ Consider the need for stress dose steroids perioperatively on an individualised basis ○ Radiotherapy is not an absolute contraindication but there is a 10–15% risk of any grade ≥ 3 toxicity, <5% risk of grade 4 toxicity, and <1% risk for grade 5 toxicity	(625) (621)
Neurological		
Pain	○ The presence of preoperative pain (OR 1.21, 95% CI 1.10-1.32) and preoperative analgesia (OR 1.54, 95% CI 1.18-2.03) predicts poor postoperative pain control ○ Long-term opiate use will often necessitate postoperative doses that are up to four time higher than those that opiate-naïve patients will require. ○ Advanced interventions, such as spinal cord stimulators and intrathecal drug delivery systems require specialist pain team referral for perioperative management	(306) (627)

Delirium	○ A past history of delirium has been found to confer around six times higher odds of experiencing postoperative delirium (OR 6.4, 95% CI 2.2-17.9).	(278)
Transient ischaemic attack (TIA)/stroke	○ Advise high risk of perioperative stroke. ○ Where possible, surgery *should* be delayed within three months of a stroke due to higher risk of a major adverse vascular event. ○ Carotid artery and cerebral imaging are recommended for stroke or TIA in the preceding six months prior to surgery. ○ Non-cardiac surgery should be delayed for symptomatic carotid disease (stroke or TIA of the corresponding vascular territory) in the past six months.	(318)
Parkinson's disease	○ Increased risk of postoperative pneumonia and increased length of postoperative stay ○ Enteral or parenteral access must be available for medication to be administered with adherence to strict dosing schedules ○ Pre-operative consultation or advice is recommended from a specialist in Parkinson's disease	(628)
Epilepsy	○ Elevated risk of postoperative infection, acute kidney injury and stroke ○ Patient should be advised to contact their epilepsy team (e.g., specialist nurse) to discuss medication changes if undergoing surgery	(628)
Peripheral neuropathy	○ Recommended to avoid neurotoxic agents due to higher risk of chemotherapy-induced peripheral neuropathy	(375)
Renal		
Chronic kidney disease	○ High risk for perioperative acute kidney injury ○ Odds for postoperative sepsis are 1.26x higher ○ Renal-dosing for anti-cancer therapies and opioids required	(629) (616) (375)
Solid organ transplant		
Solid organ transplant recipient	○ Transplant team can be consulted for advice during cancer management concerning perioperative or systemically administered therapies and immunosuppressant management	(629)
Systemic		
Collagen vascular disease (e.g., systemic lupus erythematosus, systemic sclerosis or other vasculitidies)	○ Radiotherapy is not an absolute contraindication but there is a 10–15% risk of any grade ≥ 3 toxicity, <5% risk of grade 4 toxicity, and <1% risk for grade 5 toxicity ○ Referral to rheumatology recommended where biologics, immunosuppressants or antimalarial agents are currently prescribed, and chemotherapy or surgery is planned ○ Consider the need for stress dose steroids perioperatively on an individualised basis	(621) (625)

Table 29 – Cancer Pathway Comorbidity Assessment System.
International guidelines from authoritative bodies and systematic reviews were identified for major organ systems. The Cancer Pathway Comorbidity Assessment System was developed to identify opportunities for optimisation before surgery rather than predict mortality. However, utilising this system may also highlight opportunities to refer older adults with unoptimised complex multimorbidity for evaluation by a consultant geriatrician, regardless of shared treatment decision. *All older adults (65+ years) have 2.09-3.04 higher odds of postoperative pulmonary complications (338): 60-69 years (OR 2.09, 95% CI, 1.70-2.58) and 70-79 years (OR 3.04, 95% CI 2.11-4.39)

Medication	**Chemotherapeutic agent**	**Mechanism (reference)**
Metformin	Sorafenib for hepatocellular carcinoma	Metformin causes resistance to sorafenib (412)
Acid supressing agents (PPIs and H2 antagonists)	Erlotinib, dasatinib and gefitinib	Reduced absorption – recommended to avoid acid-supressing agents (412)
	Imatinib, nilotinib and sorafenib	Possible reduced absorption – recommended to change proton pump inhibitors to H2 blockers and separate administration (412)
Paroxetine	Tamoxifen	Possible increased mortality – recommended to avoid (412)
Furosemide, NSAIDs, PPIs, salicylates, sulfa drugs	High-dose methotrexate	Nephrotoxicity (412)
Warfarin	Capecitabine	Increased in bleeding (412)
Phenobarbital, phenytoin, carbamazepine or a combination	Etoposide, cyclophosphamide, mercaptopurine for B-lineage leukaemia	Worse event-free survival, haematological relapse and central nervous system relapse (412)

Table 30 – Established drug-drug interactions between medications and chemotherapeutic agents.
Some drug-drug interactions between common medications and chemotherapeutic agents have been established (412). Highlighting these early within the OGA process support the predictive assessment goal of OGA. *Abbreviations: PPI: proton pump inhibitor; H2: histamine 2; NSAID: non-steroidal anti-inflammatory drugs.*

Parameter	Score
Age (years)	
≤50	0
51-80	**3**
>80	16
Preoperative SpO_2	
≥96%	0
91-95%	8
≤90%	24
Respiratory infection in the last month	
No	0
Yes	17
Preoperative anaemia (Hb ≤ 10g/dl)	
No	0
Yes	11
Surgical incision	
Peripheral	0
Upper abdominal	15
Intrathoracic	24
Duration of surgery (hours)	
<2	0
2-3	**16**
>3	**23**
Emergency procedure	
No	**0**
Yes	8

Table 31 – The Seven Assess Respiratory Risk in Surgical Patients in Catalonia risk score predictors.
The Assess Respiratory Risk in Surgical Patients in Catalonia risk score is used to predict the risk of postoperative pulmonary complications. Three levels of risk are indicated by the following cut off score: low risk (<26 points), moderate risk (26-44 points), high risk (≥45 points). Older adults undergoing elective major cancer surgery (assuming >2-3 hours surgical duration) will automatically attract a score of between 19-26, making them generally low risk at baseline (as highlighted in bold). The oldest old (>80 years) are moderate risk at baseline. Modified from Moza *et al.* (431).

Risk factor	Description	Points
High-risk surgery	Intraperitoneal; intrathoracic; suprainguinal vascular	+1
History of ischaemic heart disease	History of myocardial infarction (MI); history of positive exercise test; current chest pain considered due to myocardial ischemia; use of nitrate therapy or ECG with pathological Q waves	+1
History of congestive heart failure	Pulmonary oedema, bilateral rales or S3 gallop; paroxysmal nocturnal dyspnoea; chest x-ray showing pulmonary vascular redistribution	+1
History of cerebrovascular disease	Prior transient ischemic attack or stroke	+1
Pre-operative treatment with insulin	--	+1
Pre-operative creatinine >2 mg/dL / 176.8 µmol/L	--	+1

RCRI Score	Risk of major cardiac event (95% CI)*
0	3.9% (2.8-5.4%)
1	6.0% (4.9-7.4%)
2	10.1% (8.1-12.6%)
≥3	15% (11.1-20.0%)

Table 32 – The Revised Cardiac Risk Index.
The Revised Cardiac Risk Index (RCRI) can predict perioperative major adverse cardiac event (30-day risk of death, myocardial infarction or cardiac arrest). The bottom table shows the interpretation of the score. Abbreviations: CI = confidence interval.

Predictor	Odd ratio (95% CI)	Action
History of delirium	6.4 (2.2-17.9)	Preventative measures
Frailty	4.1 (1.4-11.7)	
Cognitive impairment	2.7 (1.9-3.8)	
Impairment in activities of daily living	2.1 (1.6-2.6)	
Impairment in instrumental activities of daily living	1.9 (1.3-2.8)	
Preoperative sleep disturbance	2.90 (2.28-3.69)*	
Obstructive sleep apnea	4.75 (2.65-8.54	
Psychotropic medication	2.3 (1.4-3.6)	Consider modification
Smoker	3.41 (1.08-10.73)	Advise self-referral

Table 33 – Postoperative delirium risk assessment.
A postoperative delirium risk assessment can be undertaken by considering established risk factors (278, 458). *Pooled relative risk from prospective studies. Abbreviations: CI = confidence interval.

NPT component	Question	Considerations
Coherence (i.e., meaning and sense making by participants)	**Is the intervention easy to describe?**	The OGA service can be described in plain language suitable for clinicians and patients as an 'assessment of older adults with cancer'. However, given the intervention may be used before a cancer diagnosis has been confirmed it could equally be described as an 'assessment of older adults under intervention'.
	Is it clearly distinct from other interventions?	The OGA service offers predictive assessment and optimisation rather than traditional cancer diagnosis or treatment intervention. Some patients may have cancer excluded and be suffering from a benign condition or have an incidentaloma but may still benefit from an OGA and any geriatric interventions. This is a unique position between hospital-wide CGA, oncogeriatrics and existing cancer care without comprehensive assessment.
	Does it have a clear purpose for all relevant participants?	An OGA facilitates thorough assessment for patients and an opportunity for optimisation with the intention of improving cancer outcomes or improving their health and wellbeing. OGA also generates extra data for clinicians and patients to use in shared decision-making.
	Do participants have a shared sense of its purpose?	The data that OGA generates is intended for use in shared decision-making. In this sense, the data can be shared between MDT members and the patient.
	What benefits will the intervention bring and to whom?	An OGA service offers abstraction of comprehensive assessment away from cancer MDTs. Older patients can benefit from a holistic approach to cancer care and geriatric interventions where necessary. Both the cancer MDT members and the patients can benefit from extra data to aid shared decision-making.
	Are these benefits likely to be valued by potential participants?	It is hoped that most clinicians will value the extra data that OGA generates, abstraction of the OGA process from their workload and the knowledge that beneficial geriatric interventions can be undertaken behind the scenes. However, there may be some cancer MDT members who do not value OGA and feel that conventional clinical decision-making is sufficient. We also cannot exclude that conscious or unconscious ageism will not exist for some MDT members. In this situation, little value will be appreciated to the OGA service, as some clinicians may use chronological age inappropriately as a decision-making proxy. However, at a higher level the institution can fulfil international recommendations. We expect patients to value the OGA process, as the top priorities for cancer care in the James Lind Alliance were more information and co-ordination.
	Will it fit with the overall goals and activity of the organisation?	One of the organisation's goals is to provide 'great care'. Undertaking OGA within cancer fits with this goal as it is internationally recommended, and the benefits have been established from multiple systematic reviews.

Cognitive participation (i.e., commitment and engagement by participants)	**Are target user groups likely to think it is a good idea?**	The target user groups will be enabled to undertake comprehensive assessment and utilise its data and co-ordinate care for complex needs. There would be few clinical staff who would disagree that is idea is not a good element of care.
	Will they see the point of the intervention easily?	The point of OGA is to enable comprehensive assessment of older adults with suspected or confirmed cancer and utilise its data in shared decision-making. Vulnerabilities can be identified for optimisation before treatment begins.
	Will they be prepared to invest time, energy and work in it?	Due to minimal levels of existing implementation within the NHS we are aware of existing knowledge mobilisation gaps and various implementation barriers. A common barrier is the perception of lack of time to invest in undertaking OGA. However, this OGA services has been designed to have the lowest impact on time for its users to abstract the burden of time and energy from the users. We hope that with appropriate reinforcement, the data can be embedded into MDTs, which may marginally increase the time of an MDT, at least initially. However, the higher-level aim is to embed OGA into cancer pathways so that cognitive participation is only limited to use of its outputs.
Collective action (i.e., the work participants do to make the intervention function)	**How will the intervention affect the work of user groups?**	The user groups will receive more information during MDT meetings; however, this information is useful for shared decision-making. In addition, clinical activities will happen 'behind the scenes', which international guidelines recommend. This will not enter the workload of the user groups and this may be praised and appreciated.
	Will it promote or impede their work?	The addition of OGA data mat marginally prolong MDT meetings, which could be viewed as an impediment. We know anecdotally that sometimes MDT discussion are impeded by a lack of knowledge about a patient. If geriatric interventions can be undertaken that improve patients experience and outcomes following treatment, this will promote clinicians work. The addition of extra data for shared decision-making will promote discussions about treatment options.
	What effect will it have on consultations?	Consultations before an MDT decision in the investigative phase of the cancer pathway can focus on this, knowing that the OGA service will be able to better address other biopsychosocial domains of health. Consultations following an MDT decision will be able to use data generated from OGA for shared decision-making.
	Will staff require extensive training before they can use it?	The cancer MDT members will require minimal to no training before they can use the data from the OGA service. It is hoped that with normalisation, another (non-medical) clinician can be trained in the operation of the OGA service. This will require training, but it is hoped that this will not be extensive. A general raising of awareness strategy will be required for referral targets (e.g., allied health professionals)

	How compatible is it with existing work practices?	The OGA service could be viewed simplistically as an extension of outpatients or the cancer MDT. When viewed from a CAS perspective it is a system operating within a network of other systems. Whether it is viewed from a low- or high-level perspective, there is compatibility with established practices.
	What impact will it have on division of labour, resources, power, and responsibility between different professional groups?	The OGA service empowers the MDT to consider the whole patient and their predicted outcomes. The OGA service reduces net labour of the cancer MDT, although may increase the labour of its referral targets (e.g., allied health professionals). However, the increase in labour of referral targets represents the identification of previously unmet need and therefore generates unknown business data for expansion of services. The OGA service will consume resources. In its current model, the OGA service requires a dedicated staff member to operate the service, although the hope is that once developed this will not need to be a doctor. The higher-level aim is to embed OGA within cancer pathways without it representing a separate service. A dedicated person may have oversight of the service, but this will be at a managerial rather than clinical level (i.e., they can operate within their normal role as well). An OGA attempts to flatten power hierarchies between professional groups in cancer MDTs, by providing generic whole-patient data for all members to understand. This may aid clinical decision-making and places less responsibility on individual MDT members to understand the comprehensive multidimensional aspects of their patients' health.
Reflexive Monitoring (i.e., participants reflect on or appraise the intervention)	**How are users likely to perceive the intervention once it has been in use for a while?**	Once established, a dependency on the OGA service may develop. For example, cancer MDT members may expect referral for geriatric interventions to occur in the background. Once OGA data is embedded within MDT processes, its absence may be questioned or even raised as a concern. Clinicians could of course fallback to conventional decision-making, although it is hoped that cancer MDTs members may regret not having OGA data were it to be missing.
	Is it likely to be perceived as advantageous for patients or staff?	The cancer MDT members will perceive the abstraction of additional (but important/essential) work from their workflow as advantageous. The addition of extra data for shared decision-making will be an advantage for both patients and staff, which has been identified as a key priority by the James Lind Alliance. Patients may also see the OGA service as advantageous to obtain help in psychosocial elements that had been unaddressed until engagement with the service. To better understand the views, understanding and experiences of patients using the OGA service, we will be undertaking depth interviews.
	Will it be clear what effects the intervention has had?	At follow-up appointments, clinicians may see that a particular decision for a patient, assisted by OGA data, was the better decision. They may also hear of the benefits from the geriatric interventions that occurred, without any of their effort.

	Can users/staff contribute feedback about the intervention once it is in use?	Cancer MDT members will be able to contribute feedback concerning the OGA service dynamically and easily through monthly interactions with the OGA service operator at MDT meetings. This feedback will directly contribute towards ongoing formative evaluation.
	Can the intervention be adapted or improved based on experience?	With experience, questions used within the OGA, protocols, predictive scoring systems and algorithms can be adapted regularly. OGA is modelled as a dynamic system operating with other core systems as a network within a CAS. Adaptation is a core feature. The monthly audit cycles will inform QI measures to enable improvement. Given the ongoing parallel research elements, the results from these elements will factor into formative evaluation.

Table 34 – Baseline normalisation process theory for the OGA service.
Based on an existing framework by Murray *et al*. (271) a baseline, pre-implementation normalisation process theory (NPT) evaluation was undertaken for the oncogeriatric assessment (OGA) service, covering the four key components: coherence, cognitive participation, collective action and reflexive monitoring. Abbreviations: MDT – multidisciplinary team; CAS – complex adapting system and QI – quality improvement

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Date
Name & Address

Dear […]

Study: Developing an evidence-based system to facilitate the predictive assessment and optimisation of older adults under investigation

I am a doctor and researcher at the Hull York Medical School and would like to invite you to take part in a research project looking at ways to assess people who have to attend a hospital clinic for some investigations. You have been invited because you have an appointment coming up with the **Assessment of Older adults Under Investigation** service. To help you decide, I have enclosed a leaflet, which sets out what research is being done and how you can help.

If you are interested in taking part, you will have the opportunity to discuss this further and ask about anything which is not clear. Thank you for taking the time to read the leaflet.

Yours sincerely

Dr Gordon McKenzie
Doctoral Research Fellow and Honorary Specialist Registrar in Otolaryngology
Hull York Medical School
3rd Floor Allam Medical Building
University of Hull,
Hull, HU6 7RX

Gordon.McKenzie@hyms.ac.uk

Figure 53 – Invitation letter.
The invitation letter used for research purposes.

Participant Information Sheet

Developing an evidence-based system to facilitate the predictive assessment and optimisation of older adults under investigation

A large-print version of this sheet is available on request.

Invitation

We would like to invite you to take part in a research project. To help you decide, the following leaflet sets out what research is being done and how you can help.

If you are interested in taking part, you will have the opportunity to discuss this further and ask about anything which is not clear. If you would like to ask any questions please contact the researcher, Dr Gordon McKenzie (his contact details are at the end of this leaflet). Thank you for taking the time to read this leaflet.

What is the purpose of the study?

A thorough assessment whilst someone is being investigated for an illness is recommended to help doctors plan the best treatment for each person.

Such an assessment includes finding out about existing medical problems, medication, memory problems, mental health problems (e.g., low mood), day-to-day activities and diet. The aim is to make sure that all conditions are treated as well as possible before treatment, and to find conditions which would make particular treatments too dangerous for the patient. The results help the doctors looking after you choose the best plan of treatment.

A new service has started at Hull University Teaching Hospitals NHS Trust to make sure that the people who need this assessment are able to have one.

We want to find out what patients think and feel about these assessments, so we can understand the best way to carry them out in clinical care and improve the service.

We also want to understand how information gathered through the assessment can be used to improve the whole process and make it easier for patients to use and the hospital to run.

Information from this study will help us design a better system to assess older adults who are under investigation, to make sure they get the best treatment plan with the least disruption to themselves and their families.

Why have I been invited?

You have been invited because you are a patient who is 65 years or older, under investigation for an illness and are using the Assessment for Older Adults under Investigation service.

Do I have to take part?

No. It is up to you to decide if you wish to take part. Once we explain the study and answer any questions, if you do decide to participate then you will be asked to confirm this by signing a consent form.

It is important to note that **you are free to leave the study at any time**, even after it has started, without giving a reason and without it having any effect on your treatment. **You will still be able to have an assessment as normal**.

What will happen to me if I take part?

If you agree to take part, we will ask you to fill in a 5 to 10 minute survey after your appointment. The survey may be on paper or on a computer or tablet device. This is so we can understand how people are finding the assessment and how we could improve it.

At least 4 weeks later, Dr McKenzie, (a doctor researcher at Castle Hill Hospital and the University of Hull) might interview you in person, if you are willing, about your experience for approximately 30 minutes to 1 hour. Not everyone who fills in the survey will be needed to be interviewed. Wherever possible we can arrange this before or after any outpatient appointments you have at Castle Hill Hospital. Or, if you prefer, he can arrange to do the interview in your home. The interview will be audio-recorded to make sure we have an accurate record.

We will also use the information gathered during the assessment to try and understand if there are easier ways to collect new information or use information that is in your medical record already. We will inform your GP of your participation in the study and contact him or her to collect a piece of information called the electronic frailty index (eFI). The eFI gives an idea if you have a condition called "frailty", which can make people more likely to have health problems in the future. You do not need to do anything further for this part of the research as the hospital and your GP will have all the information anyway.

Expenses and payments

There will be no payments for this study. However, if you need to make a special visit to the hospital for the interview, we can refund your travel expenses.

What are the possible disadvantages and risks of taking part?

We do not anticipate any risk to yourself. Talking about your journey with an illness may be upsetting for you. If you do become upset during the interview, you do not have to carry on and are free to leave at any time or take a break and continue, depending on what you prefer to do. If you need further support to talk through upsetting issues, this will be available from your usual clinical team.

What are the possible benefits of taking part?

You may not directly benefit yourself, but you will be helping to improve upon the current assessment system for older adults who are under investigation with a view to making it easier for patients get a thorough assessment before any treatment plans are made.

Will my taking part in the study be kept confidential?

The University of Hull is the sponsor for this study based in the United Kingdom. We will be using information from you and your medical records to undertake this study and we will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. The University of Hull will keep identifiable information

about you for 3-6 months after the study has finished. Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible. You can find out more about how we use your information by contacting Mr Luke Thompson, Information Compliance Officer, University of Hull, l.thompson3@hull.ac.uk.

Hull University Teaching Hospitals NHS Trust will collect information from you and your medical records for this research study in accordance with our instructions. Hull University Teaching Hospitals NHS Trust will use your name and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from the University of Hull and regulatory organisations may look at your medical and research records to check the accuracy of the research study. Hull University Teaching Hospitals NHS Trust will pass these details to the University of Hull along with the information collected from you and your medical records. The only people in the University of Hull who will have access to information that identifies you will be the researchers who need to contact you to about taking part in a study interview. The people who analyse the information will not be able to identify you and will not be able to find out your name or contact details. Hull University Teaching Hospitals NHS Trust will keep identifiable information about you from this study for 3-6 months after the study has finished.

If you agree to take part in the study, the information about your health and care may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research**.** The information will not identify you and will not be combined with other information in a way that could identify you. The information will only be used for the purpose of health and care research and cannot be used to contact you or to affect your care.

What will happen if I do not want to carry on with the study?

If you wish to leave the study, you can do so at any time. You do not have to give a reason for doing so and it will not affect your care in any way if you do.

What will happen to the results of the research study?

The results of the study will be published in medical journals and provided to professional and policy bodies. It will also inform the design of our next study. If you wish we will send you a summary of the findings at the end of the study. Anonymous quotes may be used in presentations and medical journal publications from the study; you will not be identifiable from these. Anonymous information may be used for similar research studies by authorised researchers.

What if there is a problem?

If you have a concern about any aspect of this study, you may wish to speak to Professor Mike Lind, who is leading this project and who will do his best to answer your questions (contact number: 01482 461236).

If you are not happy with your involvement in this study and feel unable to raise this directly with a member of the research team, or if you have any concerns about the way the researcher has carried out this study, or any other aspects of your care, you may contact:

Danielle Smith, Research Governance and Policy Manager, University of Hull.

Tel: 01482 466962 or d.g.Smith@hull.ac.uk

In the unlikely event something should go wrong and you are harmed due to someone's negligence, then you may have grounds for a legal action for compensation against the University of Hull, but you may have to pay your legal costs.

Who is organising the research?

The study has been organised and is being conducted by Hull York Medical School. The members of the research team are: Professor Mike Lind, Professor Miriam Johnson, Dr Gordon McKenzie. Yorkshire Cancer Research has funded the study. Approval has been given by the HYMS Research Ethics Committee and <<insert>> NHS Research Ethics Committee, and the Health Research Authority of England. The study is sponsored by the University of Hull.

Thank you for taking the time to read this information sheet. We are very grateful to you for considering participation in this study.

Professor Mike Lind

Professor of Oncology

Academic Oncology

Castle Hill Hospital

Castle Road,

Cottingham,

HU16 5JQ

Tel: (01482) 461236

M.J.lind@hull.ac.uk

Dr Gordon McKenzie

Doctoral Research Fellow and Honorary Specialist Registrar in Otolaryngology

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Figure 54 – Participant information leaflet.
The participant information leaflet provided to prospective participants.

NHS
Health Research Authority
Yorkshire & The Humber - South Yorkshire Research Ethics Committee
NHSBT Newcastle Blood Donor Centre
Holland Drive
Newcastle upon Tyne
NE2 4NQ

Tel: 0207 104 8079

Please note: This is the favourable opinion of the REC only and does not allow the amendment to be implemented at NHS sites in England until the outcome of the HRA assessment has been confirmed.

14 August 2020

Dr Gordon McKenzie
Doctoral Research Fellow and Specialist Registrar in Otolaryngology
Hull York Medical School
Allam Medical Building
University of Hull, Hull
HU6 7RX

Dear Dr McKenzie

Study title:	**Developing an evidence-based system to facilitate the predictive assessment and optimisation of older adults with cancer**
REC reference:	**19/YH/0382**
Protocol number:	**RS125**
Amendment number:	**RS125/1**
Amendment date:	**22 July 2020**
IRAS project ID:	**265639**

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Completed Amendment Tool [Complete Amendment Tool]	1	22 July 2020
Completed Amendment Tool	RS125/1	22 July 2020

Covering letter on headed paper [Cover Letter]	2	22 July 2020
Non-validated questionnaire [Survey Questionnaire]	2, Clean	22 July 2020
Non-validated questionnaire [Survey Questionnaire]	2, Track Change	22 July 2020
Other [Response to Queries raised by REC]		
Participant information sheet (PIS) [PIS]	2.4, Clean	22 July 2020
Participant information sheet (PIS) [PIS]	2.4, Track change	22 July 2020
Research protocol or project proposal [Protocol]	1.9, Track change	11 August 2020
Research protocol or project proposal [Protocol]	1.9, tracked change	11 August 2020

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

Working with NHS Care Organisations

Sponsors should ensure that they notify the R&D office for the relevant NHS care organisation of this amendment in line with the terms detailed in the categorisation email issued by the lead nation for the study.

Amendments related to COVID-19

We will update your research summary for the above study on the research summaries section of our website. During this public health emergency, it is vital that everyone can promptly identify all relevant research related to COVID-19 that is taking place globally. If you have not already done so, please register your study on a public registry as soon as possible and provide the HRA with the registration detail, which will be posted alongside other information relating to your project.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

HRA Learning

We are pleased to welcome researchers and research staff to our HRA Learning Events and online learning opportunities– see details at: https://www.hra.nhs.uk/planning-and-improving-research/learning/

IRAS Project ID - 265639:	**Please quote this number on all correspondence**

Yours sincerely
Pp

Dr Ian Woollands
Chair

E-mail: southyorks.rec@hra.nhs.uk

Enclosures: *List of names and professions of members who took part in the review*

Yorkshire & The Humber - South Yorkshire Research Ethics Committee

Attendance at Sub-Committee of the REC meeting via correspondence

Committee Members:

Name	*Profession*	*Present*
Dr Alison Patrick	Lecturer in Law and Ethics	Yes
Dr Ian Woollands (Chair)	Retired Clinical Director, Occupational Health	Yes

Also in attendance:

Name	*Position (or reason for attending)*
Miss Donna Bennett	Approvals Administrator

Figure 55 – Regional Ethics Committee amendment approval letter.

CONSENT FORM

Title: Developing an evidence-based system to facilitate the predictive assessment and optimisation of older adults under investigation

Participant Identification Number for this study:

Name of lead researcher: **Professor Mike Lind**

Please initial all boxes

1. I confirm that I have read and understand the information sheet dated 16th April 2019 (version 1) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily and I agree to participate in the study.	☐
2. 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.	☐
3. I agree to an audio-recorded interview if needed for the study.	☐
4. If interviewed, I agree that direct quotes may be published, provided I cannot be identified.	☐
5. I understand that relevant sections of my medical notes and data collected during this study may be looked at by responsible individuals from the research team, 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 data and using it within this study.	☐
6. I agree that anonymised data may be provided to other authorised researchers working on similar studies.	☐
7. I agree to my GP being informed of my participation in the study and the collection of my electronic Frailty Index data from my GP record.	☐
8. I would like a copy of the summary results of the study.	☐

Name of participant	Date	Signature
Name of researcher	Date	Signature

Figure 56 – Research consent form. Consent form provided to prospective participants.

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University of Hull
Hull, HU6 7RX, UK

York
University of York
York, YO10 5DD, UK

T 0870 1245500
info@hyms.ac.uk
www.hyms.ac.uk

Date
Name & Address

Dear Doctor […]

RE: [PATIENT SURNAME, PATIENT FIRSTNAME, PATIENT NHS NUMBER, PATIENT DATE OF BIRTH]

Study Title: **Developing an evidence-based system to facilitate the predictive assessment and optimisation of older adults with cancer**

I am writing to inform you that your patient has consented to participate in the above research study.

The study is a Yorkshire Cancer research funded study to improve outcomes in older cancer patients in Hull. I enclose a copy of the Patient Information Sheet, but a summary is given below. The aim of the study is to develop an evidence-based system for the assessment, optimisation and prediction of outcomes for older adults with suspected or confirmed cancer.

Patients aged 65 years or older, with suspected or confirmed cancer are eligible. Participants will have had a comprehensive geriatric assessment at our new Systematic OncoGeriatric Assessment (SOGA) service operated by Dr Gordon McKenzie. The SOGA service has been developed to improve the assessment of older adults towards better shared decision-making and identifying unrecognised problems for optimisation. **You will have received a separate copy of a clinical letter from the SOGA service.**

As part of the research studies running in parallel to the SOGA service, patients are invited to undertake a survey of the patient-reported assessment component of the SOGA service, an interview at a later date and for us to utilise their clinical data for a secondary analysis.

Continued…

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info@hyms.ac.uk
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Your patient has consented for secondary data analysis as part of this study (please see attached Consent Form) and we will contact the practice by telephone to obtain their electronic Frailty Index (eFI) in due course.

Many thanks in advance for your cooperation.

If you have any further questions about this research study, please do not hesitate to contact the Study Investigator:

Dr Gordon McKenzie, Tel: 01482 462221 Gordon.McKenzie@hyms.ac.uk

Yours sincerely

Dr Gordon McKenzie
Doctoral Research Fellow and Honorary Specialist Registrar in Otolaryngology
Hull York Medical School
3rd Floor Allam Medical Building
University of Hull,
Hull, HU6 7RX

Principal Supervisor: Prof Mike Lind, Foundation Professor of Oncology/ Head of the Joint Centre for Cancer Studies, University of Hull

Figure 57 – Letter to general practitioner informing of research participation.

RESEARCH SURVEY QUESTIONNAIRE

Internet use

1) **Do you have access to the internet at home or through your mobile phone?**
   a) Yes
   b) No

2) **[if answered YES to Question 1] How do you mainly access the internet?**
   a) Computer
   b) Tablet
   c) Mobile phone

3) **[if answered NO to Question 1] Do you know anyone else who could help you access the internet?**
   a) Yes
   b) No

4) **[if answered YES to Question 3] Who could help you access the internet (tick all that apply)?**
   - Friend
   - Relative
   - Neighbour
   - Carer
   - Partner

5) **[if answered NO to Question 3] If someone could help you access the internet, would you prefer to do this questionnaire at home?**
   a) Yes
   b) No

6) **[if answered YES to Question 1] Would you prefer to do the assessment at home?**
   a) Yes
   b) No

Experience of the hospital questionnaire

7) **[If the participant used a computer to complete their questionnaire] How easy did you find the computer to use?**
   a) Very easy
   b) Easy
   c) Neutral
   d) Difficult
   e) Very difficult

f) I rarely/never use a computer
g) I don't know
h) Other – state what

8) [If the participant used a tablet to complete their questionnaire] How easy did you find the tablet to use?

a) Very easy
b) Easy
c) Neutral
d) Difficult
e) Very difficult
f) I rarely/never use a tablet
g) I don't know
h) Other – state what

9) How easy did you find answering these questions?

a) Very easy
b) Easy
c) Neutral
d) Difficult
e) Very difficult

10) How easy did you find it to change answers to questions?

a) Very easy
b) Easy
c) Neutral
d) Difficult
e) Very difficult

11) How easy did you find moving between questions?

a) Very easy
b) Easy
c) Neutral
d) Difficult
e) Very difficult

12) How was the screen size?

a) Very good size
b) Good size
c) Neutral
d) Small size
e) Very small size

13) How easy were the questions and answers to read?

a) Very easy
b) Easy
c) Neutral
d) Difficult
e) Very difficult

14) How was the brightness of the screen?

a) Very bright
b) Bright
c) Neutral
d) Dull
e) Very dull

15) How long did it take to fill out the assessment questions?

a) Very long
b) Long
c) About right
d) Quick
e) Too quick

16) How easy were the questions and answers to understand?

a) Very easy
b) Easy
c) Neutral
d) Difficult
e) Very difficult

17) Would you have preferred to do the questions on paper?

a) Strongly agree
b) Agree
c) Undecided
d) Disagree
e) Strongly disagree

18) What did you LIKE MOST about the assessment?

19) What could be IMPROVED regarding your assessment, including anything which we should NOT do?

Finally, one further question about you

20) Which of the below best describes your HIGHEST LEVEL of education?

a) Higher degree or postgraduate qualifications
b) Degree (undergraduate) (including B. Ed.), Postgraduate diplomas or Certificates (including PGCE), Degree apprenticeship (Level 6 or 7), Professional qualifications at degree level (e.g., chartered accountant/surveyor), NVQ / SVQ Level 4 or 5
c) Diplomas in higher education or other HE qualifications, HNC/HND/BTEC Advanced, Teaching qualifications for schools or further education (below degree level), Higher apprenticeship (Level 4-7), Nursing or other medical qualifications (below degree level), RSA Higher Diploma, Foundation degree
d) A/AS levels or SCE Higher / Scottish Certificate 6th Year Studies, Advanced apprenticeship (Level 3), NVQ / SVQ / GSVQ level 3 / GNVQ Advanced, ONC / OND / BTEC National, City and Guilds Advanced Craft / Final level / Part III/RSA, Advanced Diploma
e) O level/GCSE grades A*-C or SCE Standard/Ordinary grades 1-3, CSE grade 1, Intermediate apprenticeship (Level 2), NVQ / SVQ / GSVQ level 2 / GNVQ intermediate, BTEC / SCOTVEC first / General diploma, City and Guilds Craft / Ordinary level / Part II / RSA Diploma
f) O level / GCSE grades D-G / SCE Standard / Ordinary below grade 3, CSE grades 2-5, NVQ / SVQ / GSVQ level 1 / GNVQ foundation, BTEC / SCOTVEC first / General Certificate, City and Guilds part 1 / RSA Stage I-III, SCOTVEC modules / Junior certificate
g) None of the above
h) Don't know
i) Do not wish to answer

Figure 58 – Research survey.
The research survey used in **Chapter 6**.

eature	Modelling	Labels[1]																						Rationale[2]	Refs.
		NH	FD	PIMS	LOS	ASC	CPR	ITU	PONC	POPC	POS	POD	POP	WC	MACE	CT	NE	30DM	10YM	CESA	CECA	CEGA	CEOB		
Calculated																									
Electronic frailty index (eFI)	Published algorithm																							Readily available in primary care and increasingly used in risk prediction	**(630)**
Polypharmacy	Custom algorithm			X		X						X											X	Calculate eFI	**(630)**
Multimorbidity	Custom algorithm																							To explore relationships between frailty, multimorbidity and disability	(631)
Co-morbidity	Count co-morbidity																X				X	X		To calculate neutropaenic events risk	(402)
10-year mortality	Suemoto index																		X			X		Assess risk of non-cancer mortality against expected cancer mortality	(71)
ASA grade	Custom algorithm							X							X			X		X		X	X	Calculate 30-day postoperative mortality risk	(455)
CARG score	Published algorithm															X					X	X	X	Calculate chemotherapy toxicity risk	(7)
Gupta score	Published algorithm														X					X		X	X	Calculate MACE risk	(319)
NCEPOD SORT score	Published algorithm																	X		X		X		Calculate 30-day postoperative mortality risk	(455)
BMI	Published formula																		X			X		Calculate Suemoto index and test relationships between activity and BMI	(71)
Generated																									
Aerobically active	Stochastic																		X			X		Calculate Suemoto index and negating adverse ageing	(71)
Age	Stochastic						X								X	X			X		X	X	X	Determine age-specific prevalence for various disease states	(71)
Alcohol use disorder	Bayesian network				X	X		X		X	X			X						X		X	X	Significant associated with adverse surgical outcomes	**(378)**
Anaemia	Bayesian network							X								X	X			X	X	X	X	Component of CARG chemotherapy toxicity score	(7)
Angina	QRisk® algorithm											X							X			X	X	Calculate Suemoto index	(71)
Anorexia	Stochastic/BN																							Calculate eFI	**(630)**
Arthritis	Stochastic																							Calculate eFI	**(630)**
Asthma	Stochastic																		X			X		Calculate eFI and Suemoto index	**(630)**
Atrial fibrillation	Stochastic																		X			X		Calculate eFI and Suemoto index	**(630)**
Bipolar affective disorder	Stochastic																							Used in QRisk® algorithm	(547)
Breathlessness	Stochastic																							Calculate eFI	**(630)**
Cancer site	Stochastic (Simulacrum)															X					X		X	Calculate chemotherapy toxicity risk	(7)

Chronic kidney disease	Bayesian network						X				X	X				X					X		X	Calculate chemotherapy toxicity risk	(7)
Chronic pain	Bayesian network																							Calculate eFI	**(630)**
Connective tissue disorder	Stochastic																							Calculate eFI	**(630)**
COPD	Bayesian network																	X			X			Calculate Suemoto index	(71)
Decreased social activity	Bayesian network															X					X	X	X	Calculate chemotherapy toxicity risk	(7)
Dementia	Stochastic											X								X		X	X	Calculate eFI	**(630)**
Deprivation quintile	Stochastic (Simulacrum)																							Used in QRisk® algorithm	(547)
Difficulty walking	Fuzzy logic																							Used internally by Bayesian networks	(632)
Difficulty walking outside	Stochastic	X														X			X	X	X	X	X	Calculate chemotherapy toxicity risk	(7)
Dizziness	Bayesian network																							Calculate eFI	**(630)**
Drinks alcohol	Stochastic																	X			X			Calculate Suemoto index	(71)
Erectile dysfunction	Stochastic																							Used in QRisk® algorithm	(547)
Ethnicity	Stochastic (Simulacrum)																							Used in QRisk® algorithm	(547)
Falls	Bayesian network															X					X	X	X	Calculate chemotherapy toxicity risk	(7)
Family history of cardiovascular disease	QRisk® algorithm																							Used internally in QRisk® algorithm	(547)
Fear of falling	Stochastic																							Used internally by Bayesian networks	(633)
Foot problems	Bayesian network																							Calculate eFI	**(630)**
Fragility fracture	Bayesian network																							Calculate eFI	**(630)**
Frailty	Bayesian network	X			X	X		X	X	X	X	X		X						X		X	X	Associated with various adverse outcomes	(18)
Hearing loss	Stochastic															X					X	X	X	Calculate chemotherapy toxicity risk	(7)
Heart failure	Bayesian network									X	X	X							X	X		X	X	Calculate Suemoto index	(71)
Heart valve disease	Stochastic																		X			X		Calculate Suemoto index	(71)
Height	Stochastic (ELSA)																							Calculate chemotherapy toxicity risk (although little value isolated)	(7)
History of delirium	Bayesian network											X								X		X	X	Strong risk factor for post-operative delirium	(278)
Homebound	Bayesian network																							Calculate eFI	**(630)**
Hypertension	Stochastic											X								X		X	X	Calculate eFI	**(630)**

Impaired BADL	Bayesian network	**X**			**X**		**X**					**X**								**X**			**X**	**X**	Associated with various adverse outcomes	(70, 331)
Impaired IADL	Bayesian network		**X**		**X**							**X**				**X**				**X**	**X**	**X**	**X**	Calculate chemotherapy toxicity risk	(7)
Incorrect date reported	Custom algorithm																		**X**			**X**		Calculate Suemoto index	(71)
Liver disease	Bayesian network																							Calculate eFI	**(630)**
Lives alone	Bayesian network																							Calculate eFI	**(630)**
Lower urinary tract symptoms	Stochastic																							Calculate eFI	**(630)**
Malnutrition	Bayesian network																							Calculate eFI	**(630)**
Migraine	Stochastic																							Used in QRisk® algorithm	(547)
Mild cognitive impairment	Stochastic											**X**								**X**			**X**	**X**	Calculate eFI	**(630)**
Myocardial infarction	QRisk® algorithm											**X**							**X**	**X**			**X**	**X**	Calculate Suemoto index	(71)
Osteoporosis	Stochastic																							Calculate eFI	**(630)**
Parkinson's disease	Stochastic																							Calculate eFI	**(630)**
Peptic ulcer	Stochastic																							Calculate eFI	**(630)**
Peripheral vascular disease	Bayesian network																							Calculate eFI	**(630)**
Requires care	Fuzzy logic																							Calculate eFI	**(630)**
Rheumatoid arthritis	Stochastic																							Used in QRisk® algorithm	(547)
Schizophrenia	Stochastic																							Used in QRisk® algorithm	(547)
Self-reported health	Custom algorithm																		**X**			**X**	**X**	Calculate Suemoto index	(71)
Sex	Stochastic															**X**			**X**		**X**	**X**	**X**	Determine sex-specific prevalence for various disease states, calculate chemotherapy toxicity risk and Suemoto index	(7)
Skin ulcers	Bayesian network																							Calculate eFI	**(630)**
Sleep disturbance	Bayesian network																							Calculate eFI	**(630)**
Smoking status	Stochastic	**X**				**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**					**X**	**X**		**X**	**X**	Calculate Suemoto index, associated with various adverse outcomes	(71)
Socially isolated	Bayesian network																							Calculate eFI	**(630)**
Stroke	QRisk® algorithm											**X**								**X**		**X**	**X**	Calculate eFI	**(630)**
Syncope	Bayesian network																							Calculate eFI	**(630)**
SLE	Stochastic																							Used in QRisk® algorithm	(547)
T1DM	Stochastic			**X**							**X**	**X**					**X**		**X**			**X**	**X**	Calculate Suemoto index	(71)
T2DM	Stochastic			**X**							**X**	**X**					**X**		**X**			**X**	**X**	Calculate Suemoto index	(71)

Thyroid disease	Stochastic																					Calculate eFI	**(630)**
Timed Up and Go test result	Stochastic as per published diagnostic accuracy																					Use as a proxy to frailty	(432)
Transient ischaemic attack	QRisk® algorithm										**X**										**X**	**X**	Calculate eFI	**(630)**
Urinary incontinence	Stochastic																						Calculate eFI	**(630)**
Uses walking aid	Stochastic																						Used internally by Bayesian networks	(634)
Visual impairment	Stochastic										**X**										**X**	**X**	Calculate eFI	**(630)**
Weight	Stochastic (ELSA)																						Calculate chemotherapy toxicity risk (although little value isolated)	(7)
Weight loss	Stochastic/ Bayesian network															**X**							Calculate eFI	**(630)**

Table 35 – Model architecture.
Features were modelled using a mixture of stochastic processes, published algorithms/formulae, custom algorithms, Bayesian networks and fuzzy logic. [1]Labels can also be features and may be modelled as either a risk or a final state. [2]This represents the primary rationale, although with Bayesian networks parameters are inter-related through the directed acyclic graph. Abbreviations: NH = nursing home admission; FD = functional decline; PIMS = potentially inappropriate medicines; LOS = increased length of hospital stay; ASC = any surgical complication; CPR = cardiopulmonary resuscitation failure; ITU = postoperative intensive care unit admission; PONC = postoperative neurological complication; POPC = postoperative pulmonary complications; POS = postoperative sepsis; POD = postoperative delirium; WC = postoperative wound complications; MACE = postoperative major adverse cardiac event; CT = chemotherapy toxicity; NE = neutropaenic events; 30DM = 30-day postoperative mortality; 10YM = 10-year (non-cancer) mortality; CESA = composite endpoint for surgical adverse events; CECA = composite endpoint for chemotherapy adverse events; CEGA = composite endpoint for general adverse events; CEOB = compositive endpoint where oncogeriatric assessment would be beneficial.

Package	Version
aplus	0.11.0
appnope	0.1.2
argon2-cffi	20.1.0
asciimatics	1.13.0
astropy	4.2.1
async-generator	1.10
attrs	21.2.0
backcall	0.2.0
blake3	0.1.8
bleach	3.3.1
bqplot	0.12.29
cachetools	4.2.2
catboost	1.0.0
certifi	2021.5.30
cffi	1.14.6
chardet	4.0.0
cloudpickle	1.6.0
copulas	0.5.1
ctgan	0.4.3
cycler	0.10.0
dask	2021.7.0
debugpy	1.3.0
decorator	4.4.2
deepecho	0.2.1
defusedxml	0.7.1
docx	0.2.4
entrypoints	0.3
Faker	4.14.2
frozendict	2.0.3
fsspec	2021.7.0
future	0.18.2
graphviz	0.17
h5py	3.3.0
idna	2.10
imbalanced-learn	0.8.0
imblearn	0.0
iniconfig	1.1.1
ipydatawidgets	4.2.0
ipykernel	6.0.2
ipyleaflet	0.14.0

ipympl	0.7.0
ipython	7.25.0
ipython-genutils	0.2.0
ipyvolume	0.5.2
ipyvue	1.5.0
ipyvuetify	1.8.0
ipywebrtc	0.6.0
ipywidgets	7.6.3
jedi	0.18.0
Jinja2	3.0.1
joblib	1.0.1
jsonschema	3.2.0
jupyter-client	6.1.12
jupyter-core	4.7.1
jupyterlab-pygments	0.1.2
jupyterlab-widgets	1.0.0
kaleido	0.2.1
kiwisolver	1.3.1
llvmlite	0.36.0
locket	0.2.1
lxml	4.6.3
MarkupSafe	2.0.1
matplotlib	3.4.2
matplotlib-inline	0.1.2
matplotlib-venn	0.11.6
miceforest	2.0.6
mistune	0.8.4
mpi4py	3.1.1
nbclient	0.5.3
nbconvert	6.1.0
nbformat	5.1.3
nest-asyncio	1.5.1
networkx	2.5.1
notebook	6.4.0
numba	0.53.1
numexpr	2.7.3
numpy	1.21.0
packaging	21.0
pandas	1.1.4
pandocfilters	1.4.3
parso	0.8.2
partd	1.2.0

patsy	0.5.1
pexpect	4.8.0
pgmpy	0.1.15
pickleshare	0.7.5
Pillow	8.3.0
plotly	5.1.0
pluggy	0.13.1
progressbar2	3.53.1
prometheus-client	0.11.0
prompt-toolkit	3.0.19
psutil	5.8.0
ptyprocess	0.7.0
py	1.10.0
pyarrow	4.0.1
pycparser	2.20
pyerfa	2.0.0
pyfiglet	0.8.post1
Pygments	2.9.0
pyparsing	2.4.7
PyQt5	5.15.5
PyQt5-Qt5	5.15.2
PyQt5-sip	12.9.0
pyqtgraph	0.12.3
pyrsistent	0.18.0
pytest	6.2.4
python-dateutil	2.8.1
python-docx	0.8.11
python-utils	2.5.6
pythreejs	2.3.0
pytz	2021.1
PyYAML	5.4.1
pyzmq	22.1.0
rdt	0.5.3
requests	2.25.1
scikit-learn	0.24.2
scipy	1.7.0
sdmetrics	0.3.2
sdv	0.12.1
seaborn	0.11.1
Send2Trash	1.7.1
simpful	2.4.5
six	1.16.0

sktime	0.5.3
statsmodels	0.12.2
tables	3.6.1
tabulate	0.8.9
tenacity	8.0.1
terminado	0.10.1
testpath	0.5.0
text-unidecode	1.3
threadpoolctl	2.1.0
toml	0.10.2
toolz	0.11.1
torch	1.7.1
torchvision	0.8.2
tornado	6.1
tqdm	4.61.1
traitlets	5.0.5
traittypes	0.2.1
typing-extensions	3.10.0.0
uncertainties	3.1.6
urllib3	1.26.6
vaex	4.3.0
vaex-astro	0.8.2
vaex-core	4.3.0.post1
vaex-hdf5	0.8.0
vaex-jupyter	0.6.0
vaex-ml	0.12.0
vaex-server	0.5.0
vaex-viz	0.5.0
wcwidth	0.2.5
webencodings	0.5.1
widgetsnbextension	3.5.1
xarray	0.18.2

Table 36 – Third party libraries utilised.

	Prevalence		
Factors	**Male**	**Female**	**Ref.**
Cognition			
Mild cognitive impairment	10.7	10.7	(635)
Dementia	1.5	1.8	(636)
History of delirium	1	1	(637)
Nutrition			
Malnutrition	8.5	8.5	(638)
Anorexia of ageing	0.15	0.25	(639)
Mood			
Depression	22	28	(640)
Social health			
Alcohol use disorder	1.2	0.24	(641)
Drinks alcohol	80	72	(642)
Current smoker	8.6	7.1	(643)
Former smoker	47.7	33.3	(643)
Decreased social activity	44	44	(589)
Homebound	5.6	5.6	(644)
Lives alone	10	9	
Requires care	15.8	15.8	(645)
Socially vulnerable	7.4	7.4	(630)
Sensory			
Hearing loss	61.8	28.1	(646)
Visual impairment	4.8	7.2	(647)
Functional			
Aerobically active	57	53	(532)
Difficulty walking outside	17.5	30	(648)
Basic activities of daily living impairment	36.7	36.7	(326)
Instrumental activities of daily living impairment	54.6	54.6	
Co-morbidities			
Anaemia	0.9	1.8	(649)
Angina	8.83	4.66	(650)
Arthritis	33.6	49.1	(651)
Asthma	21.5	21.5	(652)
Atrial fibrillation	3.95	3.95	(653)
Bipolar affective disorder	4.2	4.2	(654)
Chronic obstructive pulmonary disease	10.08	6.3	(655)
Chronic pain	49	52	(656)
Connective tissue disease	0.02	0.37	(657)
Diabetes	15.7	10.4	(658)
Erectile dysfunction	34.4	0	(659)
Faecal incontinence	6.9	5.8	(660)
Foot problems	71	71	(661)
Fragility fracture	23.8	47.3	(662)
Heart failure	2.5	1.5	(663)
Heart valve disease	7.6	9.1	(664)
Hypertension	58	51	(665)
Ischaemic heart disease	11.4	11.4	(666)
Liver disease	3	3	(667)
Lower urinary tract symptoms[1]	72.8	72.8	(668)
Migraine	5	10	(669)
Myocardial infarction	7.05	2.06	(650)
Orthostatic hypotension	22.2	22.2	(670)
Osteoporosis	7.4	20.2	(671)
Parkinson's disease	0.29	0.19	(672)
Peptic ulcer	5	5	(673)
Peripheral vascular disease	11	11.7	(674)
Renal disease[2]	17.65	27.86	(675)
Rheumatoid arthritis	1.14	2.56	(676)
Schizophrenia	0.75	0.75	(654)
Skin ulcers	2.11	1.14	(677)
Sleep disturbance	65	65	(678)
Stroke	7.10	4.20	(679)
Systemic lupus erythematosus	0.05	0.3	(680)
Thyroid disease	7.8	20.5	(681)
Transient ischaemic attack	7.9	7.9	(682)
Urinary incontinence	8.9	20.2	(683)
Symptomatic enquiry			
Syncope	4.74	4.74	(684)
Dizziness	11	11	(685)
Breathlessness	24.5	24.5	(686)

Weight loss	20.3	25	(687)
Polypharmacy	20.5	20.5	(688)
Falls	31.5	31.5	(689)
Frailty[3]	5	6	(690)

Table 37 – Prevalence of baseline factors for 65–69-year-old patients.
[1]Lower urinary tract symptoms prevalence represents a proxy of the prevalence of urinary system disease. [2]Renal disease represents the prevalence of chronic kidney disease stages 3-5 in this case as this has relevance to chemotherapy toxicity prediction. [3]Frailty is calculated separately, prevalence of frailty is for comparison only.

	Prevalence		
Factors	**Male**	**Female**	**Ref.**
Cognition			
Mild cognitive impairment	11.9	11.9	(635)
Dementia	3.1	3	(636)
History of delirium	1	1	(637)
Nutrition			
Malnutrition	8.5	8.5	(638)
Anorexia of ageing	0.15	0.25	(639)
Mood			
Depression	22	28	(640)
Social health			
Alcohol use disorder	1.2	0.24	(641)
Drinks alcohol	80	72	(642)
Current smoker	8.6	7.1	(643)
Former smoker	47.7	33.3	(643)
Decreased social activity	44	44	(589)
Homebound	5.6	5.6	(644)
Lives alone	10	17	
Requires care	18.8	18.8	(645)
Socially vulnerable	7.4	7.4	(630)
Sensory			
Hearing loss			(646)
Visual impairment	4.8	7.2	(647)
Functional			
Aerobically active	57	53	(532)
Difficulty walking outside	17.5	30	(648)
Basic activities of daily living impairment	36.7	36.7	(326)
Instrumental activities of daily living impairment	54.6	54.6	
Co-morbidities			
Anaemia	1.4	3.2	(649)
Angina	8.83	4.66	(650)
Arthritis	37.3	55.6	(651)
Asthma	21.5	21.5	(652)
Atrial fibrillation	3.95	3.95	(653)
Bipolar affective disorder	4.2	4.2	(654)
Chronic obstructive pulmonary disease	27.24	15.9	(655)
Chronic pain	52	57	(656)
Connective tissue disease	0.02	0.37	(657)
Diabetes	15.7	10.4	(658)
Erectile dysfunction	53.4	0	(659)
Faecal incontinence	7.8	7.7	(660)
Foot problems	71	71	(661)
Fragility fracture	23.8	47.3	(662)
Heart failure	2.5	1.5	(663)
Heart valve disease	7.6	9.1	(664)
Hypertension	58	51	(665)
Ischaemic heart disease	11.4	11.4	(666)
Liver disease	3	3	(667)
Lower urinary tract symptoms[1]	72.8	72.8	(668)
Migraine	4	9	(669)
Myocardial infarction	7.05	2.06	(650)
Orthostatic hypotension	22.2	22.2	(670)
Osteoporosis	7.8	27.9	(671)
Parkinson's disease	0.5	0.33	(672)
Peptic ulcer	5	5	(673)
Peripheral vascular disease	14.04	14.21	(674)
Renal disease[2]	17.65	27.86	(675)

Rheumatoid arthritis	1.14	2.56	(676)
Schizophrenia	0.75	0.75	(654)
Skin ulcers	2.11	1.14	(677)
Sleep disturbance	65	65	(678)
Stroke	7.10	4.20	(679)
Systemic lupus erythematosus	0.065	0.27	(680)
Thyroid disease	7.8	20.5	(681)
Transient ischaemic attack	7.9	7.9	(682)
Urinary incontinence	8.9	20.2	(683)
Symptomatic enquiry			
Syncope	4.74	4.74	(684)
Dizziness	11	11	(685)
Breathlessness	24.5	24.5	(686)
Weight loss	20.3	25	(687)
Polypharmacy	21.1	21.1	(688)
Falls	37	27	(689)
Frailty[3]	12	14	(690)

Table 38 – Prevalence of baseline factors for 70–74-year-old patients.

[1]Lower urinary tract symptoms prevalence represents a proxy of the prevalence of urinary system disease. [2]Renal disease represents the prevalence of chronic kidney disease stages 3-5 in this case as this has relevance to chemotherapy toxicity prediction. [3]Frailty is calculated separately, prevalence of frailty is for comparison only.

	Prevalence		
Factors	**Male**	**Female**	**Ref.**
Cognition			
Mild cognitive impairment	12.4	12.4	(635)
Dementia	5.3	6.6	(636)
History of delirium	1	1	(637)
Nutrition			
Malnutrition	8.5	8.5	(638)
Anorexia of ageing	0.15	0.25	(639)
Mood			
Depression	22	28	(640)
Social health			
Alcohol abuse	1.2	0.24	(641)
Drinks alcohol	80	72	(642)
Current smoker	8.6	7.1	(643)
Former smoker	47.7	33.3	(643)
Decreased social activity	44	44	(589)
Homebound	5.6	5.6	(644)
Lives alone	13	27	
Requires care	27.5	27.5	(645)
Socially vulnerable	7.4	7.4	(630)
Sensory			
Hearing loss	83	54.6	(646)
Visual impairment	4.8	7.2	(647)
Functional			
Aerobically active	36	26	(532)
Difficulty walking outside	17.5	30	(648)
Basic activities of daily living impairment	36.7	36.7	(326)
Instrumental activities of daily living impairment	54.6	54.6	
Co-morbidities			
Anaemia	1.4	3.2	(649)
Angina	16.96	11.15	(650)
Arthritis	39.6	55.9	(651)
Asthma	21.5	21.5	(652)
Atrial fibrillation	3.95	3.95	(653)
Bipolar affective disorder	4.2	4.2	(654)
Chronic obstructive pulmonary disease	27.24	15.9	(655)
Chronic pain	52	57	(656)
Connective tissue disease	0.02	0.37	(657)
Diabetes	13.5	10.6	(658)
Erectile dysfunction	53.4	0	(659)
Faecal incontinence	7.8	7.7	(660)
Foot problems	71	71	(661)

Fragility fracture	23.8	47.3	(662)
Heart failure	6.8	6.1	(663)
Heart valve disease	14	12.6	(664)
Hypertension	75	66	(665)
Ischaemic heart disease	15.6	15.6	(666)
Liver disease	1.4	1.4	(667)
Lower urinary tract symptoms[1]	72.8	72.8	(668)
Migraine	2.5	7	(669)
Myocardial infarction	12.08	5.50	(650)
Orthostatic hypotension	22.2	22.2	(670)
Osteoporosis	10.3	37.5	(671)
Parkinson's disease	0.72	0.48	(672)
Peptic ulcer	5	5	(673)
Peripheral vascular disease	17.77	17.17	(674)
Renal disease[2]	33.16	41.68	(675)
Rheumatoid arthritis	1.14	2.56	(676)
Schizophrenia	0.75	0.75	(654)
Skin ulcers	1.79	3.36	(677)
Sleep disturbance	64	64	(678)
Stroke	13.1	10.7	(679)
Systemic lupus erythematosus	0.065	0.27	(680)
Thyroid disease	7.8	20.5	(681)
Transient ischaemic attack	7.9	7.9	(682)
Urinary incontinence	8.9	20.2	(683)
Symptomatic enquiry			
Syncope	4.84	4.84	(684)
Dizziness	11	11	(685)
Breathlessness	24.5	24.5	(686)
Weight loss	20.3	25	(687)
Polypharmacy	23.8	23.8	(688)
Falls	37	27	(689)
Frailty[3]	12	14	(690)

Table 39 – Prevalence of baseline factors for 75–79-year-old patients.
[1]Lower urinary tract symptoms prevalence represents a proxy of the prevalence of urinary system disease. [2]Renal disease represents the prevalence of chronic kidney disease stages 3-5 in this case as this has relevance to chemotherapy toxicity prediction. [3]Frailty is calculated separately, prevalence of frailty is for comparison only.

	Prevalence		
Factors	**Male**	**Female**	**Ref.**
Cognition			
Mild cognitive impairment	12.4	12.4	(635)
Dementia	5.3	6.6	(636)
History of delirium	1	1	(637)
Nutrition			
Malnutrition	8.5	8.5	(638)
Anorexia of ageing	0.15	0.25	(639)
Mood			
Depression	22	28	(640)
Social health			
Alcohol abuse	1.2	0.24	(641)
Drinks alcohol	80	72	(642)
Current smoker	8.6	7.1	(643)
Former smoker	47.7	33.3	(643)
Decreased social activity	44	44	(589)
Homebound	5.6	5.6	(644)
Lives alone	13	27	
Requires care	27.5	27.5	(645)
Socially vulnerable	7.4	7.4	(630)
Sensory			
Hearing loss	83	54.6	(646)
Visual impairment	4.8	7.2	(647)
Functional			
Aerobically active	36	26	(532)
Difficulty walking outside	17.5	30	(648)
Basic activities of daily living impairment	36.7	36.7	(326)
Instrumental activities of daily living impairment	54.6	54.6	
Co-morbidities			

Anaemia	1.4	3.2	(649)
Angina	16.96	11.15	(650)
Arthritis	39.6	55.9	(651)
Asthma	21.5	21.5	(652)
Atrial fibrillation	3.95	3.95	(653)
Bipolar affective disorder	4.2	4.2	(654)
Chronic obstructive pulmonary disease	27.24	15.9	(655)
Chronic pain	52	57	(656)
Connective tissue disease	0.02	0.37	(657)
Diabetes	13.5	10.6	(658)
Erectile dysfunction	53.4	0	(659)
Faecal incontinence	7.8	7.7	(660)
Foot problems	71	71	(661)
Fragility fracture	23.8	47.3	(662)
Heart failure	6.8	6.1	(663)
Heart valve disease	14	12.6	(664)
Hypertension	75	66	(665)
Ischaemic heart disease	15.6	15.6	(666)
Liver disease	1.4	1.4	(667)
Lower urinary tract symptoms[1]	72.8	72.8	(668)
Migraine	2.5	7	(669)
Myocardial infarction	12.08	5.50	(650)
Orthostatic hypotension	22.2	22.2	(670)
Osteoporosis	10.3	37.5	(671)
Parkinson's disease	0.72	0.48	(672)
Peptic ulcer	5	5	(673)
Peripheral vascular disease	17.77	17.17	(674)
Renal disease[2]	33.16	41.68	(675)
Rheumatoid arthritis	2.18	2.99	(676)
Schizophrenia	0.75	0.75	(654)
Skin ulcers	1.79	3.36	(677)
Sleep disturbance	64	64	(678)
Stroke	13.1	10.7	(679)
Systemic lupus erythematosus	0.003	0.118	(680)
Thyroid disease	7.8	20.5	(681)
Transient ischaemic attack	7.9	7.9	(682)
Urinary incontinence	8.9	20.2	(683)
Symptomatic enquiry			
Syncope	4.84	4.84	(684)
Dizziness	11	11	(685)
Breathlessness	24.5	24.5	(686)
Weight loss	20.3	25	(687)
Polypharmacy	23.8	23.8	(688)
Falls	37	27	(689)
Frailty[3]	12	14	(690)

Table 40 – Prevalence of baseline factors for 80–84-year-old patients.
[1]Lower urinary tract symptoms prevalence represents a proxy of the prevalence of urinary system disease. [2]Renal disease represents the prevalence of chronic kidney disease stages 3-5 in this case as this has relevance to chemotherapy toxicity prediction. [3]Frailty is calculated separately, prevalence of frailty is for comparison only.

	Prevalence (%)		
Factors	**Male**	**Female**	**Ref.**
Cognition			
Mild cognitive impairment	14.5	14.5	(635)
Dementia	15.1	20.2	(636)
History of delirium	14	14	(637)
Nutrition			
Malnutrition	8.5	8.5	(638)
Anorexia of ageing	0.150	0.25	(639)
Mood			
Depression	22	28	(640)
Social health			
Alcohol abuse	1.2	0.24	(641)
Drinks alcohol	80	72	(642)
Current smoker	8.6	7.1	(643)
Former smoker	47.7	33.3	(643)
Decreased social activity	44	44	(589)

Homebound	5.6	5.6	(644)
Lives alone	13	27	
Requires care	58.5	58.5	(645)
Socially vulnerable	7.4	7.4	(630)
Sensory			
Hearing loss	96.6	86.1	(646)
Visual impairment	19.2	25.6	(647)
Functional			
Aerobically active	36	26	(532)
Difficulty walking outside	17.5	30	(648)
Basic activities of daily living impairment	36.7	36.7	(326)
Instrumental activities of daily living impairment	54.6	54.6	
Co-morbidities			
Anaemia	3.8	4.1	(649)
Angina	16.96	11.15	(650)
Arthritis	39.6	55.9	(651)
Asthma	21.5	21.5	(652)
Atrial fibrillation	13.5	13.5	(653)
Bipolar affective disorder	4.2	4.2	(654)
Chronic obstructive pulmonary disease	27.24	15.9	(655)
Chronic pain	52	57	(656)
Connective tissue disease	0.02	0.37	(657)
Diabetes	13.5	10.6	(658)
Erectile dysfunction	53.4	0	(659)
Faecal incontinence	11.6	11.7	(660)
Foot problems	71	71	(661)
Fragility fracture	23.8	47.3	(662)
Heart failure	12.6	12.5	(663)
Heart valve disease	14	12.6	(664)
Hypertension	75	66	(665)
Ischaemic heart disease	15.6	15.6	(666)
Liver disease	1.4	1.4	(667)
Lower urinary tract symptoms[1]	72.8	72.8	(668)
Migraine	2	5	(669)
Myocardial infarction	12.08	5.50	(650)
Orthostatic hypotension	22.2	22.2	(670)
Osteoporosis	16.6	47.2	(671)
Parkinson's disease	0.96	0.64	(672)
Peptic ulcer	5	5	(673)
Peripheral vascular disease	27.42	24.48	(674)
Renal disease[2]	44.75	48.61	(675)
Rheumatoid arthritis	2.18	2.99	(676)
Schizophrenia	0.75	0.75	(654)
Skin ulcers	8.29	8.06	(677)
Sleep disturbance	64	64	(678)
Stroke	13.1	10.7	(679)
Systemic lupus erythematosus	0.003	0.118	(680)
Thyroid disease	7.8	20.5	(681)
Transient ischaemic attack	7.9	7.9	(682)
Urinary incontinence	8.9	20.2	(683)
Symptomatic enquiry			
Syncope	4.84	4.84	(684)
Dizziness	11	11	(685)
Breathlessness	27	27	(686)
Weight loss	20.3	25	(687)
Polypharmacy	5	5	(688)
Falls	37	27	(689)
Frailty[3]	24	37	(690)

Table 41 – Prevalence of baseline factors for 85–89-year-old patients.
[1]Lower urinary tract symptoms prevalence represents a proxy of the prevalence of urinary system disease. [2]Renal disease represents the prevalence of chronic kidney disease stages 3-5 in this case as this has relevance to chemotherapy toxicity prediction. [3]Frailty is calculated separately, prevalence of frailty is for comparison only.

	Prevalence		
Factors	**Male**	**Female**	**Ref.**
Cognition			
Mild cognitive impairment	14.5	14.5	(635)
Dementia	22.6	33	(636)

History of delirium	14	14	(637)
Nutrition			
Malnutrition	8.5	8.5	(638)
Anorexia of ageing	0.15	0.25	(639)
Mood			
Depression	22	28	(640)
Social health			
Alcohol abuse	1.2	0.24	(641)
Drinks alcohol	80	72	(642)
Current smoker	8.6	7.1	(643)
Former smoker	47.7	33.3	(643)
Decreased social activity	44	44	(589)
Homebound	5.6	5.6	(644)
Lives alone	13	27	
Requires care	76	76	(645)
Socially vulnerable	7.4	7.4	(630)
Sensory			
Hearing loss	96.6	86.1	(646)
Visual impairment	28.6	39.4	(647)
Functional			
Aerobically active	36	26	(532)
Difficulty walking outside	17.5	30	(648)
Basic activities of daily living impairment	36.7	36.7	(326)
Instrumental activities of daily living impairment	54.6	54.6	
Co-morbidities			
Anaemia	3.8	4.1	(649)
Angina	16.96	11.15	(650)
Arthritis	39.6	55.9	(651)
Asthma	21.5	21.5	(652)
Atrial fibrillation	13.5	13.5	(653)
Bipolar affective disorder	4.2	4.2	(654)
Chronic obstructive pulmonary disease	27.24	15.9	(655)
Chronic pain	52	57	(656)
Connective tissue disease	0.02	0.37	(657)
Diabetes	13.5	10.6	(658)
Erectile dysfunction	53.4	0	(659)
Faecal incontinence	11.6	11.7	(660)
Foot problems	71	71	(661)
Fragility fracture	23.8	47.3	(662)
Heart failure	12.6	12.5	(663)
Heart valve disease	14	12.6	(664)
Hypertension	75	66	(665)
Ischaemic heart disease	15.6	15.6	(666)
Liver disease	1.4	1.4	(667)
Lower urinary tract symptoms[1]	72.8	72.8	(668)
Migraine	2	5	(669)
Myocardial infarction	12.08	5.50	(650)
Orthostatic hypotension	22.2	22.2	(670)
Osteoporosis	16.6	47.2	(671)
Parkinson's disease	0.70	0.47	(672)
Peptic ulcer	5	5	(673)
Peripheral vascular disease	34.48	30.06	(674)
Renal disease[2]	44.75	48.61	(675)
Rheumatoid arthritis	2.18	2.99	(676)
Schizophrenia	0.75	0.75	(654)
Skin ulcers	8.29	8.06	(677)
Sleep disturbance	64	64	(678)
Stroke	13.1	10.7	(679)
Systemic lupus erythematosus	0.003	0.118	(680)
Thyroid disease	7.8	20.5	(681)
Transient ischaemic attack	7.9	7.9	(682)
Urinary incontinence	8.9	20.2	(683)
Symptomatic enquiry			
Syncope	4.84	4.84	(684)
Dizziness	11	11	(685)
Breathlessness	24.3	24.3	(686)
Weight loss	20.3	25	(687)
Polypharmacy	2.4	2.4	(688)
Falls	37	27	(689)
Frailty[3]	65	58	(690)

Table 42 – Prevalence of baseline factors for 90–94-year-old patients.
[1]Lower urinary tract symptoms prevalence represents a proxy of the prevalence of urinary system disease. [2]Renal disease represents the prevalence of chronic kidney disease stages 3-5 in this case as this has relevance to chemotherapy toxicity prediction. [3]Frailty is calculated separately, prevalence of frailty is for comparison only.

	Prevalence		
Factors	**Male**	**Female**	**Ref.**
Cognition			
Mild cognitive impairment	14.5	14.5	(635)
Dementia	28.8	44.2	(636)
History of delirium	14	14	(637)
Nutrition			
Malnutrition	8.5	8.5	(638)
Anorexia of ageing	0.15	0.25	(639)
Mood			
Depression	22	28	(640)
Social health			
Alcohol abuse	1.2	0.24	(641)
Drinks alcohol	80	72	(642)
Current smoker	8.6	7.1	(643)
Former smoker	47.4	33.3	(643)
Decreased social activity	44	44	(589)
Homebound	5.6	5.6	(644)
Lives alone			
Requires care	76	76	(645)
Socially vulnerable	7.4	7.4	(630)
Sensory			
Hearing loss	96.6	86.1	(646)
Visual impairment	28.6	39.4	(647)
Functional			
Aerobically active	36	26	(532)
Difficulty walking outside	17.5	30	(648)
Basic activities of daily living impairment	36.7	36.7	(326)
Instrumental activities of daily living impairment	54.6	54.6	
Co-morbidities			
Anaemia	3.8	4.1	(649)
Angina	16.96	11.15	(650)
Arthritis	39.6	55.9	(651)
Asthma	21.5	21.5	(652)
Atrial fibrillation	13.5	13.5	(653)
Bipolar affective disorder	4.2	4.2	(654)
Chronic obstructive pulmonary disease	27.24	15.9	(655)
Chronic pain	52	57	(656)
Connective tissue disease	0.02	0.37	(657)
Diabetes	13.5	10.6	(658)
Erectile dysfunction	53.4	0	(659)
Faecal incontinence	11.6	11.7	(660)
Foot problems	71	71	(661)
Fragility fracture	23.8	47.3	(662)
Heart failure	12.6	12.5	(663)
Heart valve disease	14	12.6	(664)
Hypertension	75	66	(665)
Ischaemic heart disease	15.6	15.6	(666)
Liver disease	1.4	1.4	(667)
Lower urinary tract symptoms[1]	72.8	72.8	(668)
Migraine	2	5	(669)
Myocardial infarction	12.08	5.50	(650)
Orthostatic hypotension	22.2	22.2	(670)
Osteoporosis	16.6	47.2	(671)
Parkinson's disease	0.70	0.47	(672)
Peptic ulcer	5	5	(673)
Peripheral vascular disease	34.48	30.06	(674)
Renal disease[2]	44.75	48.61	(675)
Rheumatoid arthritis	2.18	2.99	(676)
Schizophrenia	0.75	0.75	(654)
Skin ulcers	8.29	8.06	(677)
Sleep disturbance	64	64	(678)
Stroke	13.1	10.7	(679)
Systemic lupus erythematosus	0.003	0.118	(680)

Thyroid disease	7.8	20.5	(681)
Transient ischaemic attack	7.9	7.9	(682)
Urinary incontinence	8.9	20.2	(683)
Symptomatic enquiry			
Syncope	4.84	4.84	(684)
Dizziness	11	11	(685)
Breathlessness	24.3	24.3	(686)
Weight loss	20.3	25	(687)
Polypharmacy	2.4	2.4	(688)
Falls	37	27	(689)
Frailty[3]	65	58	(690)

Table 43 – Prevalence of baseline factors for 95–99-year-old patients.
[1]Lower urinary tract symptoms prevalence represents a proxy of the prevalence of urinary system disease. [2]Renal disease represents the prevalence of chronic kidney disease stages 3-5 in this case as this has relevance to chemotherapy toxicity prediction. [3]Frailty is calculated separately, prevalence of frailty is for comparison only.

	Prevalence		
Factors	**Male**	**Female**	**Ref.**
Cognition			
Mild cognitive impairment	14.5	14.5	(635)
Dementia	28.8	44.2	(636)
History of delirium	14	14	(637)
Nutrition			
Malnutrition	8.5	8.5	(638)
Anorexia of ageing	0.15	0.25	(639)
Mood			
Depression	22	28	(640)
Social health			
Alcohol abuse	1.2	0.24	(641)
Drinks alcohol	80	72	(642)
Current smoker	8.6	7.1	(643)
Former smoker	47.4	33.3	(643)
Decreased social activity	44	44	(589)
Homebound	5.6	5.6	(644)
Lives alone			
Requires care	76	76	(645)
Socially vulnerable	7.4	7.4	(630)
Sensory			
Hearing loss	96.6	86.1	(646)
Visual impairment	28.6	39.4	(647)
Functional			
Aerobically active	36	26	(532)
Difficulty walking outside	17.5	30	(648)
Basic activities of daily living impairment	36.7	36.7	(326)
Instrumental activities of daily living impairment	54.6	54.6	
Co-morbidities			
Anaemia	3.8	4.1	(649)
Angina	16.96	11.15	(650)
Arthritis	39.6	55.9	(651)
Asthma	21.5	21.5	(652)
Atrial fibrillation	13.5	13.5	(653)
Bipolar affective disorder	4.2	4.2	(654)
Chronic obstructive pulmonary disease	27.24	15.9	(655)
Chronic pain	52	57	(656)
Connective tissue disease	0.02	0.37	(657)
Diabetes	13.5	10.6	(658)
Erectile dysfunction	53.4	0	(659)
Faecal incontinence	11.6	11.7	(660)
Foot problems	71	71	(661)
Fragility fracture	23.8	47.3	(662)
Heart failure	12.6	12.5	(663)
Heart valve disease	14	12.6	(664)
Hypertension	75	66	(665)
Ischaemic heart disease	15.6	15.6	(666)
Liver disease	1.4	1.4	(667)
Lower urinary tract symptoms[1]	72.8	72.8	(668)
Migraine	2	5	(669)
Myocardial infarction	12.08	5.50	(650)

Orthostatic hypotension	22.2	22.2	(670)
Osteoporosis	16.6	47.2	(671)
Parkinson's disease	0.70	0.47	(672)
Peptic ulcer	5	5	(673)
Peripheral vascular disease	34.48	30.06	(674)
Renal disease[2]	44.75	48.61	(675)
Rheumatoid arthritis	2.18	2.99	(676)
Schizophrenia	0.75	0.75	(654)
Skin ulcers	8.29	8.06	(677)
Sleep disturbance	64	64	(678)
Stroke	13.1	10.7	(679)
Systemic lupus erythematosus	0.003	0.118	(680)
Thyroid disease	7.8	20.5	(681)
Transient ischaemic attack	7.9	7.9	(682)
Urinary incontinence	8.9	20.2	(683)
Symptomatic enquiry			
Syncope	4.84	4.84	(684)
Dizziness	11	11	(685)
Breathlessness	24.3	24.3	(686)
Weight loss	20.3	25	(687)
Polypharmacy	2.4	2.4	(688)
Falls	37	27	(689)
Frailty[3]	65	58	(690)

Table 44 – Prevalence of baseline factors for 99–105-year-old patients.
[1]Lower urinary tract symptoms prevalence represents a proxy of the prevalence of urinary system disease. [2]Renal disease represents the prevalence of chronic kidney disease stages 3-5 in this case as this has relevance to chemotherapy toxicity prediction. [3]Frailty is calculated separately, prevalence of frailty is for comparison only.

Feature	Parameters				Distribution	Source
Weight (kg)	**Sex**	**Age**	**Mean**	**SD**	Normal	English longitudinal study of ageing
	Male	65-69	83	13		
		70-74	82	13		
		75-79	79	13		
		80-84	76	12		
		85-89	74	12		
		90-94	71	11		
		95-99	71	11		
		100+	71	11		
	Female	65-69	72	14		
		70-74	71	13		
		75-79	67	12		
		80-84	64	13		
		85-89	60	11		
		90-94	56	10		
		95-99	56	10		
		100+	56	10		
Height (cm)	**Sex**	**Age**	**Mean**	**SD**	Normal	English longitudinal study of ageing
	Male	65-69	173	7		
		70-74	172	6		
		75-79	170	7		
		80-84	169	6		
		85-89	167	7		
		90-94	167	6		
		95-99	167	6		
		100+	167	6		
	Female	65-69	160	6		
		70-74	158	6		
		75-79	156	6		
		80-84	156	6		
		85-89	155	6		
		90-94	153	7		
		95-99	150	9		
		100+	150	9		
Creatinine (µmol/L)	**Sex**	**Age**	**Mean**	**UL**	Normal	(691)
	Male	65-69	101	124		
		70-74	104	135		
		75-79	105	131		
		80-84	108	144		
		85-89	108	141		
		90-94	113	149		
		95-99	113	149		
		100+	113	149		
	Female	65-69	86	109		
		70-74	88	111		
		75-79	90	121		
		80-84	92	121		
		85-89	93	123		
		90-94	97	131		
		95-99	97	131		
		100+	97	131		
Timed Up and Go test (seconds)	**Both sexes**	**Age**	**Mean**	**UL**	Normal	**(692)**
		65-69	8	9		
		70-74	9	10		
		75-79	9	10		
		80-84	12	15		
		85-89	12	15		
		90-94	12	15		
		95-99	12	15		
		100+	12	15		
Date reported correctly (%)	**Sex**	**Age**	**Mean**	**SD**	Truncated normal	English longitudinal study of ageing
	Male	65-69	77	42		
		70-74	70	46		
		75-79	70	46		
		80-84	76	43		
		85-89	86	38		
		90-94	86	38		
		95-99	86	38		
		100+	86	38		

	Female	65-69	81	40		
		70-74	75	43		
		75-79	70	46		
		80-84	70	46		
		85-89	40	50		
		90-94	40	50		
		95-99	40	50		
		100+	40	50		
Self-reported health	**Sex**	**Age**	**Mean**	**SD**	Truncated normal	English longitudinal study of ageing
	Male	65-69	3.1	1.0		
		70-74	3.0	1.1		
		75-79	3.4	1.0		
		80-84	2.8	1.1		
		85-89	2.8	1.1		
		90-94	2.8	1.1		
		95-99	2.8	1.1		
		100+	2.8	1.1		
	Female	65-69	3.1	1.0		
		70-74	3.3	1.1		
		75-79	3.3	1.0		
		80-84	3.2	1.1		
		85-89	2.8	0.5		
		90-94	2.8	0.5		
		95-99	2.8	0.5		
		100+	2.8	0.5		
Smoking status (%)	**Sex**	**Category**		**%**	Multinomial	(643)
	Male	Current		8		
		Former		48		
		Never		44		
	Female	Current		7		
		Former		33		
		Never		60		

Table 45 – Features modelled using a distribution.

Bayesian network inference	Risk factors	Reference
Anaemia	Chronic kidney disease	(693)
Chronic kidney disease	Diabetes	(694)
	Obesity	(695)
	Hypertension	(696)
Chronic obstructive pulmonary disease	Past smoking	(697)
	Current smoking	(697)
	Asthma	(698)
Dizziness	Female	(699)
	Osteoporosis	(699)
Faecal incontinence	Urinary incontinence	(700)
	Diabetes	(700)
	Hypertension	(700)
Foot problems	Female	(701)
Liver disease	Male	(702)
	Obesity	(702)
	Alcohol use disorder	(703)
Ulcers	Urinary incontinence	(704)
Orthostatic hypotension	Diabetes	(705)
	Hypertension	(705)
	Parkinson's disease	(705)
	Dementia	(705)
Heart failure	Male	(706)
	Obesity	(706)
	Hypertension	(706)
	Diabetes	(706)
	Current smoker	(706)
	Myocardial infarction	(706)
	Atrial fibrillation	(706)
Frailty	Hearing loss	(539)
	Diabetes	(540)
	Visual impairment	(541)
	Co-morbidities >= 3	(542)
	Cardiovascular disease	(657)
	Chronic obstructive pulmonary disease	(544)
Basic activities of daily living disability	Diabetes	(707)
	Body mass index > 30 < 35	(708)
	Body mass index > 35 < 40	(708)
	Frailty	(709)
Depression	Frailty	(710)
	Osteoarthritis	(711)
	Basic activities of daily living disability	(712)
	Parkinson's disease	(713)
	Heart failure	(714)
Alcohol use disorder	Depression	(715)
Sleep disturbance	Depression	(716)
	Hypertension	(717)
	Heart disease	(717)
	Diabetes	(717)
	Peptic ulcer	(717)
	Asthma	(717)
	Chronic obstructive pulmonary disease	(717)
Syncope	Stroke	(718)
	Transient ischaemic attack	(718)
	Hypertension	(718)
Instrumental activities of daily living disability	Frailty	(709)
	Diabetes	(707)
	Sleep disturbance	(719)
Peripheral vascular disease	Diabetes	(720)

	Current smoker	(721)
	Former smoker	(721)
	Hypertension	(721)
	Myocardial infarction	(721)
	Angina	(721)
	Heart failure	(721)
	Stroke	(721)
	Transient ischaemic attack	(721)
Falls	Difficulty walking	(722)
	Dizziness	(722)
	Parkinson's disease	(722)
	Osteoarthritis	(723)
	Urinary incontinence	(724)
	Orthostatic hypotension	(425)
	Atrial fibrillation	(725)
	Depression	(726)
	Foot problems	(727)
Social isolation	Hearing loss	(728)
	Falls	(729)
	Difficulty walking outside	(730)
	Basic activities of daily living disability	(731)
Homebound	Depression	(732)
	Social isolation	(732)
	Using walking aid	(732)
	Falls	(732)
	Fear of falling	(732)
	Chronic pain	(732)
Malnutrition	Parkinson's disease	(733)
	Basic activities of daily living disability	(733)
	Mild cognitive impairment	(733)
	Dementia	(733)
Chronic pain	Arthritis	(734)
	Osteoporosis	(734)
	Chronic obstructive pulmonary disease	(734)
	Migraine	(734)
	Heart disease	(734)
	Peptic ulcer disease	(734)
	Diabetes	(734)
History of delirium	Dementia	(370)
	Visual impairment	(370)
Fragility fracture	Weight < 58kg	(735)
	Underweight	(735)
	Obese	(735)
	Weight loss	(735)
	Current smoker	(735)
	Rheumatoid arthritis	(736)
Decreased social activity	Age 70-80	(737)
	Age ≥ 80	(737)
	One major health conditions	(737)
	Two or more major health conditions	(737)
	Depression	(737)
	Cognitive problems	(737)
	One activity of daily living problem	(737)
	Two or more activity of daily living problems	(737)

Table 46 – Bayesian inference of features and their risk factors