HORIZONS Protocol Version 7.0

HORIZONS: a cohort study to explore recovery of health and well-being in adults diagnosed with cancer.

HORIZONS: understanding the impact of cancer diagnosis and treatment on everyday life

- **This protocol has regard for the HRA guidance and order of content**

RESEARCH REFERENCE NUMBERS

PROTOCOL VERSION NUMBER AND DATE – Version 7.0 04.08.2020

REC REFERENCE – 16/NW/0425

SPONSOR - University Hospital Southampton NHS Foundation Trust (RHM CAN1199)

HORIZONS: a cohort study to explore recovery of health and well-being in adults diagnosed with cancer

HORIZONS: understanding the impact of cancer diagnosis and treatment on everyday life

PROTOCOL VERSION NUMBER AND DATE

Version Number	**Author**	**Effective Date**	**Reason for Change**
Version 1.0	C Foster, L Calman, J Haviland, C M May, R Petch, F Doyle, A Din	05/05/16	
Version 2.0	C Foster, L Calman, J Haviland, R Foster, J Turner, R Petch, F Doyle, C M May	21/12/16	End of pilot phase; protocol updates to reflect full study processes
Version 3.0	C Foster, L Calman, R Foster, J Turner, A Cole, F Doyle	19/06/2017	In line with advice from the HORIZONS Programme Management Group
Version 4.0	C Foster, L Calman, R Foster, J Turner, R Brooks, A Cole, F Doyle	27/11/2017	Addition of the vulval subgroup and updates of contact details and exclusion criteria
Version 5.0	C Foster, L Calman, R Foster, J Turner, D Ellis, A Cole, F Doyle, A Cummings, J Frankland	29/11/2018	Removal of references to a short version of the HORIZONS questionnaires. Changes to patient facing documents which improve clarity Changes to reflect the introduction of the General Data Protection Regulations (GDPR) Removal of the NOMAD tool as a proposed questionnaire measure

Version 5.1	C Foster, L Calman, R Foster, J Turner, D Ellis, A Cole, F Doyle, A Cummings, J Frankland	21/01/2019	Change in the number of recruiting centres from 50 to 78 Addition of an Appendix containing the protocol for the qualitative phase of the HORIZONS study Addition of documents designed to boost retention of participants at follow-up points MODIFICATION OF AMENDMENT 9 Removal of HORIZONS Qualitative Decliner Form v1.0 12.09.2018 Removal of reference to use of a Decliner Form in supporting documents
Version 6.0	C Foster, L Calman, R Foster, J Turner, A Wilson	10/10/2019	Changes to the Data Monitoring Committee name and function Changes made to participant status check and sending of follow-up questionnaire processes Changes made to processes in the event of no response
Version 6.1	C Foster, L Calman, R Foster, S Wheelwright, A Cole	11/03/2020	Change of wording relating to using Public Health England (PHE) databases. The wording relates to a change in PHE policy not a change in study procedure.

Version 7.0	C Foster, L Calman, J Frankland, S Wheelwright, D Wright	04.08.2020	Addition of a COVID-19 questionnaire insert Addition of an Appendix 7 containing the protocol for a qualitative COVID-19 sub-study

HORIZONS study: understanding the impact of cancer diagnosis and treatment on everyday life

RESEARCH REFERENCE NUMBERS

IRAS Number:	202342
SPONSORS Number:	RHM CAN1199
FUNDERS Number:	Macmillan HORIZONS Programme - 3546834

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator (CI) agrees to conduct the Study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirements.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the Study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the Study will be given; and that any discrepancies from the Study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: Date: ../../….

.....

Name (please print):

.....

Position: .....

Chief Investigator:

Signature: Date: 04/08/2020

....

Name: (please print)

..... Professor Claire Foster.....

Position: Professor of Psychosocial Oncology and Director of Macmillan Survivorship Research Group

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Joint-sponsor(s) / Co-sponsor(s)	N/A
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STUDY SUMMARY

Study Title	HORIZONS: a cohort study to explore recovery of health and well-being in adults diagnosed with cancer
Internal Ref. No. (or short title)	Macmillan HORIZONS Programme
Study Design	Prospective cohort study
Study Participants	Participants will be individuals diagnosed with non-metastatic cancer, identified through their clinical teams, prior to primary treatment. Participants will be recruited from NHS treatment centres across the UK, with centres chosen from those who express an interest through the Clinical Research Network (CRN) or directly to the study team in Southampton.
Planned Size of Sample (if applicable)	3000 participants
Follow-up Duration (if applicable)	The follow-up period is initially funded for five years. Continuation funding will be sought to extend follow-up with the intention to continue indefinitely with annual questionnaires to assess the longer term implications of cancer.
Planned Study Period	April 2016 to December 2020 initially with subsequent annual follow-up (funding permitting)
Research Question / Aim(s)	The aim of the HORIZONS Programme is to: • Establish a cohort of cancer patients treated with a range of cancers, to capture their health related outcomes and experiences from beginning active treatment and regularly over their life-course. • Maintain and develop the HORIZONS Programme as a national and international resource to explore consequences of different cancer diagnoses and treatments from the individual perspective across the life-course. • Inform policy and practice based innovative solutions to minimise the health burden and maximise support available to them over their life-course. The key research questions are: • What impact does cancer and its treatment have on people diagnosed with cancer in the short, medium and long term? • What are the health outcomes, experiences and self-management activities over the life-course across different cancer types and what influences these? • How do people connect with and mobilise resources which enable them to self-manage consequences of cancer and its treatment?

Programme Summary	The purpose of this study is to invite all people diagnosed with cancer (at included participating centres) who meet the eligibility criteria to complete questionnaires before their treatment begins and at regular intervals over time to assess the impact of cancer and its treatment on people's lives in the short, medium and long term. We will explore a range of factors to determine their role in both recovery of health and well-being and self-management. Although it is known that people who have had cancer are likely to experience a number of physical and psychological problems as a result of the disease and treatment, it is not known what the 'typical' course of recovery of health and well-being looks like, how long it takes and how this can be influenced. We will determine pathways to recovery of health and well-being following cancer diagnosis (initially breast cancer diagnosed <50 years, non-Hodgkin Lymphoma and gynaecological cancers) and identify what factors influence this. This includes assessing the relative importance of the person's illness, personal attributes, perceived burden of treatment, role of the environment they live in, including health / social care and personal networks of support, and their ability and capacity to self-manage. We will identify who is most at risk of problems and what environmental supports and resources people are able to mobilise to support their self-management. We will also explore who has the confidence and ability to manage during and beyond treatment and what factors influence this and whether this leads to earlier problem resolution and restoration of health and well-being. This knowledge will be used to develop and test future supportive interventions to enhance the rapid recovery of health and well-being – our long term aim being to design ways of helping people with cancer in areas we identify as problematic for them.

FUNDING AND SUPPORT IN KIND

FUNDER(S)	FINANCIAL AND NON FINANCIAL SUPPORT GIVEN
Macmillan Cancer Support	£2.4 million (2016-2020)
UHS charity	**tbc**

ROLE OF STUDY SPONSOR AND FUNDER

The HORIZONS Study Sponsor, University Hospital Southampton NHS Foundation Trust (UHSFT), will sponsor the research, and the HORIZONS Study Funder, Macmillan Cancer Support, will fund the research. The HORIZONS Coordinating Centre will make it clear to the public that Macmillan is funding the project and will use Macmillan logos to indicate this.

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITTEES / GROUPS AND INDIVIDUALS

The HORIZONS Coordinating Centre

The Study will be managed by the HORIZONS Coordinating Centre in the Macmillan Survivorship Research Group (MSRG), University of Southampton, delegated this task by the Sponsor. Staff within the HORIZONS Coordinating Centre will be responsible for study design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results.

The Programme Director and members of the HORIZONS Coordinating Centre will engage with Macmillan partners on a regular basis through the design, delivery and dissemination of the research programme.

The Director of the HORIZONS Programme will have responsibility for delivery of the Programme. The research team in the HORIZONS Coordinating Centre, wider team of senior academics (including Co-applicants, Programme Management Group (PMG) and scientific advisors), Strategic Advisory Board (SAB), Tumour Specific Expert Panels (TSEPs), Data Sharing Panel (DSP) and User Reference Group (URG) includes lay experiences of cancer and professional expertise in psychosocial oncology, clinical oncology, social science, nursing, data management, statistics, epidemiology, health economics, demography and social geography. The HORIZONS Programme is included in the National Institute for Health Research (NIHR) CRN Portfolio, and we will provide monthly anonymised reports on study accrual to the NIHR CRN office. We will also provide regular reports on study recruitment and progress to Macmillan and the relevant National Cancer Research Institute (NCRI) Clinical Studies Groups (CSG) and the NCRI Consumer Forum.

Programme and trial managers will support the set up and delivery of the HORIZONS Programme supported by trial coordinators, data manager and administrative staff.

The Strategic Advisory Board (SAB)

The SAB acts as a mechanism to maximise the impact of the Macmillan HORIZONS Programme and to offer advice on its overall progress. The Board meets at least once annually and is chaired by Professor Dame Jessica Corner, membership includes senior clinicians, academics, Macmillan representatives and people affected by cancer as Research Partners. The SAB critically advises on the strategic direction of the HORIZONS Programme; how to develop our strategy to share knowledge, methodological approaches and data for greatest impact.

The Programme Management Group (PMG)

The CI and the PMG including Co-applicants and members of the HORIZONS Coordinating Centre will meet at frequent and regular intervals and oversee the conduct of the Study.

Tumour Specific Expert Panels (TSEPs)

TSEPs inform our methods and involve the disease specific NCRI CSGs. TSEPs include people affected by the cancer type (patient / consumer representatives), oncologists, surgeons, specalist nurses and researchers.

Data Sharing Panel (DSP)

A DSP will be established to review requests to access study data from outside the HORIZONS Coordinating Centre and advise on data sharing protocols.

Patient and Public Involvement (PPI)

The HORIZONS Coordinating Centre research team has a long history of working closely with people living with and beyond cancer to design, develop and deliver research programmes and projects – our PPI Research Partners. We have worked with PPI Research Partners as Co-researchers, for example in the Macmillan

Listening Study [1], and work alongside PPI Research Partners in our URGs and Knowledge Café events where we discuss, involve PPI Research Partners and engage the wider public in research ideas and on-going projects.

Involvement of PPI Research Partners and engagement with the wider public will benefit the HORIZONS Programme by enhancing the awareness, relevance and accessibility of the research. This will be achieved by working closely with PPI Research Partners in the HORIZONS URG to develop more effective ways of working. For example, in the design, development and delivery of the HORIZONS Programme alongside other stakeholders.

The URG advises on all aspects of the Programme such as the way participants are recruited, updated and contacted within the HORIZONS Programme. The group also advises on study design and participant burden and contributes to and reviews study documentation. We invite our URG members to attend events such as the Programme Launch, and they are supported by the HORIZONS' team to contribute to the Programme through means including Knowledge Café Event co-facilitation, data interpretation, paper writing and conference presentations.

We will hold Knowledge Café events in the community during the life of the Study to bring together the public and people living with and beyond cancer to support involvement, engagement as well as public awareness and understanding of the HORIZONS Programme. These events will be advertised using various media to ensure that we engage with and involve the public across the UK. We will proactively seek engagement with and involvement of those typically under-represented in research, e.g. younger and older people, black and minority ethnic groups and those with lower health literacy. The purpose of these events will be to critically examine and develop the research methods to broaden the reach of involvement and participation in the HORIZONS Programme and contribute to the development of new grant applications.

PPI Research Partners will receive training as appropriate for their role within the HORIZONS Programme. This is likely to include Macmillan's *Building Research Partnerships* course designed for professionals and lay people to support PPI in research. PPI Research Partners will also receive programme specific training from the HORIZONS Programme team to support their involvement in the Programme. This will include training in chairing URG meetings. PPI Research Partners will, following INVOLVE guidelines, be paid for their time and reimbursed for their expenses (including travel, subsistence and carer costs) for attending meetings and undertaking other PPI activities.

Protocol contributors

The HORIZONS Coordinating Centre has been delegated by the Sponsor and the Funder for the writing of the protocol. The Funder has approved the proposal for the HORIZONS Programme and the Sponsor has approved the protocol and maintains legal responsibility for the HORIZONS Programme.

The HORIZONS Programme grant application was reviewed by independent external reviewers as well as Macmillan Cancer Support. Macmillan Cancer Support has worked in partnership with the HORIZONS Coordinating Centre on the development of the Study but final decisions about the design of this study and the protocol development were the sole responsibility of the HORIZONS Coordinating Centre. The Funder will not have any role in the decision to submit results for peer reviewed publication but the MSRG will work in partnership with Macmillan Cancer Support to develop analysis plans and disseminate findings. The University of Southampton will own all intellectual property rights and the HORIZONS Coordinating Centre will make the final decision about publication of findings. Macmillan Cancer Support will work in partnership with the HORIZONS Coordinating Centre during the course of the project and joint dissemination activities such as meetings and conferences will be established to ensure that project results are exploited in a timely and effective way to improve the lives of people affected by cancer.

The Study was presented to the relevant NCRI CSGs or CSG sub-groups for comment.

Co-applicants and members of the Tumour Specific Expert Groups commented on the protocol during its development and refinement.

The Sponsor takes primary responsibility for ensuring that the design of the Study meets appropriate standards and that arrangements are in place to ensure appropriate conduct and reporting. See more at: http://www.hra.nhs.uk/resources/before-you-apply/roles-and-responsibilties/sponsor/#sthash.5hd9g6v9.dpuf

PPI has been a key contribution to all aspects of the Study protocol design. Two PPI Research Partners reviewed the protocol and commented on it, these comments were incorporated into the submitted version. The Study was also presented to the NCRI Consumer Forum and feedback from this meeting incorporated into the protocol.

KEY WORDS

Survivorship, Cancer, Recovery, Self-management, Cohort

Contents

GLOSSARY

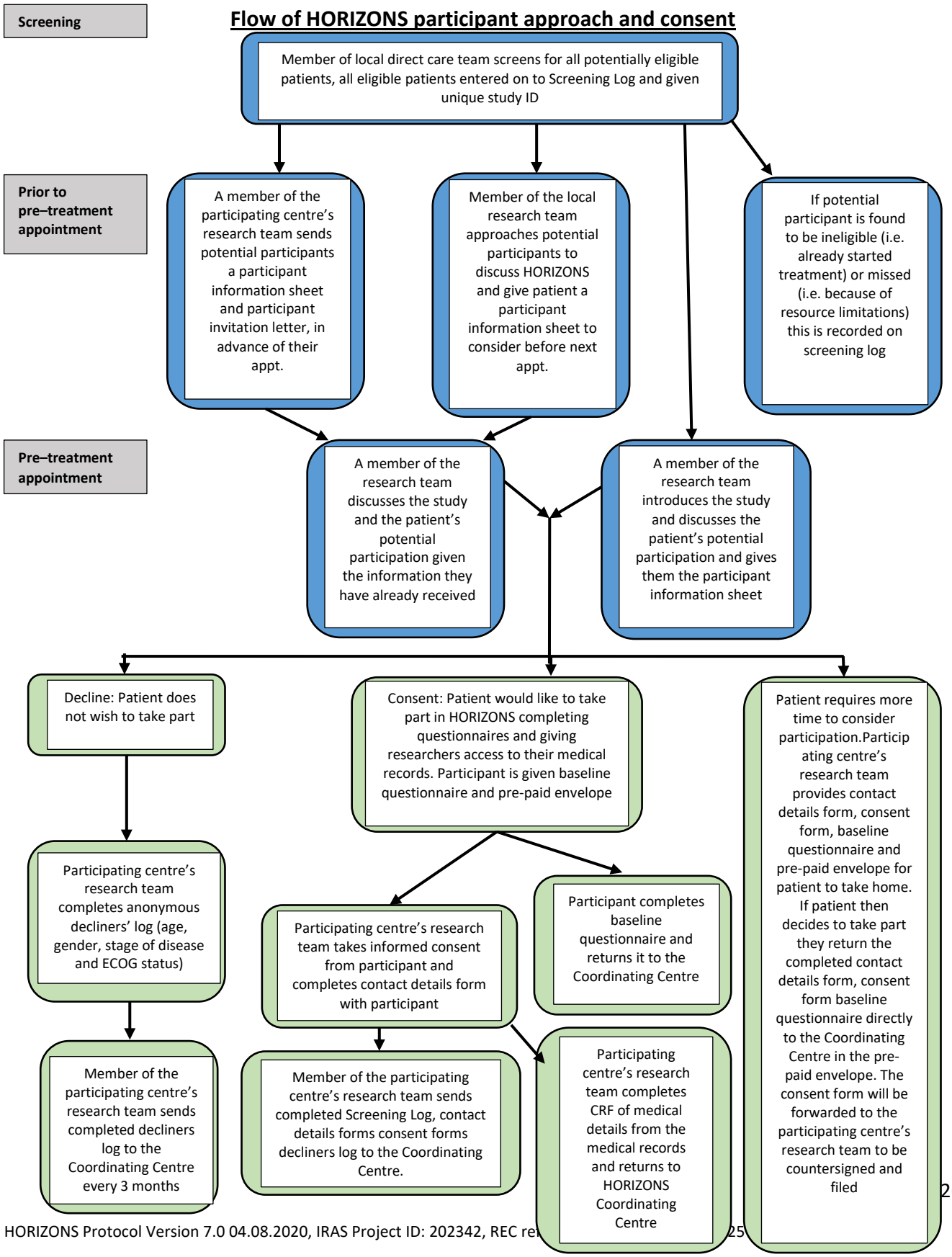
AE	Adverse Event
CI	Chief Investigator
CREW	CREW (ColoREctal Well-being). A cohort study to explore recovery of health and well-being following primary treatment of colorectal cancer
CRF	Case Report Form
CRN	Clinical Research Network
CSG	Clinical Studies Group
DSP	Data Sharing Panel
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
IRAS	Integrated Research Application System
MDT	Multidisciplinary Team
MSRG	Macmillan Survivorship Research Group
NCRI	National Cancer Research Institute
NCSI	National Cancer Survivorship Initiative
NHS	National Health Service
PI	Principal Investigator
PIS	Patient Information Sheet
PPI	Patient and Public Involvement
QLACS*	Quality of Life in Adult Cancer Survivors
QoL	Quality of Life
REC	Research Ethics Committee
SAB	Strategic Advisory Board
SAE	Serious Adverse Event
PMG	Programme Management Group
SOP	Standard Operating Procedure
TSEP	Tumour Specific Expert Panels
UHSFT	University Hospital Southampton NHS Foundation Trust
UK	United Kingdom
URG	User Reference Group
USA	United States of America

* Primary outcome measure; other named validated measures are listed in **Table 1** in section 5.2

Definitions

For the purposes of this protocol the term HORIZONS Coordinating Centre refers to the team of researchers conducting the Study at the MSRG, University of Southampton. The term 'participating centre' refers to the cancer centre within which the Study is recruiting patients, across the UK.

STUDY FLOW CHART



Flow of HORIZONS questionnaire completion

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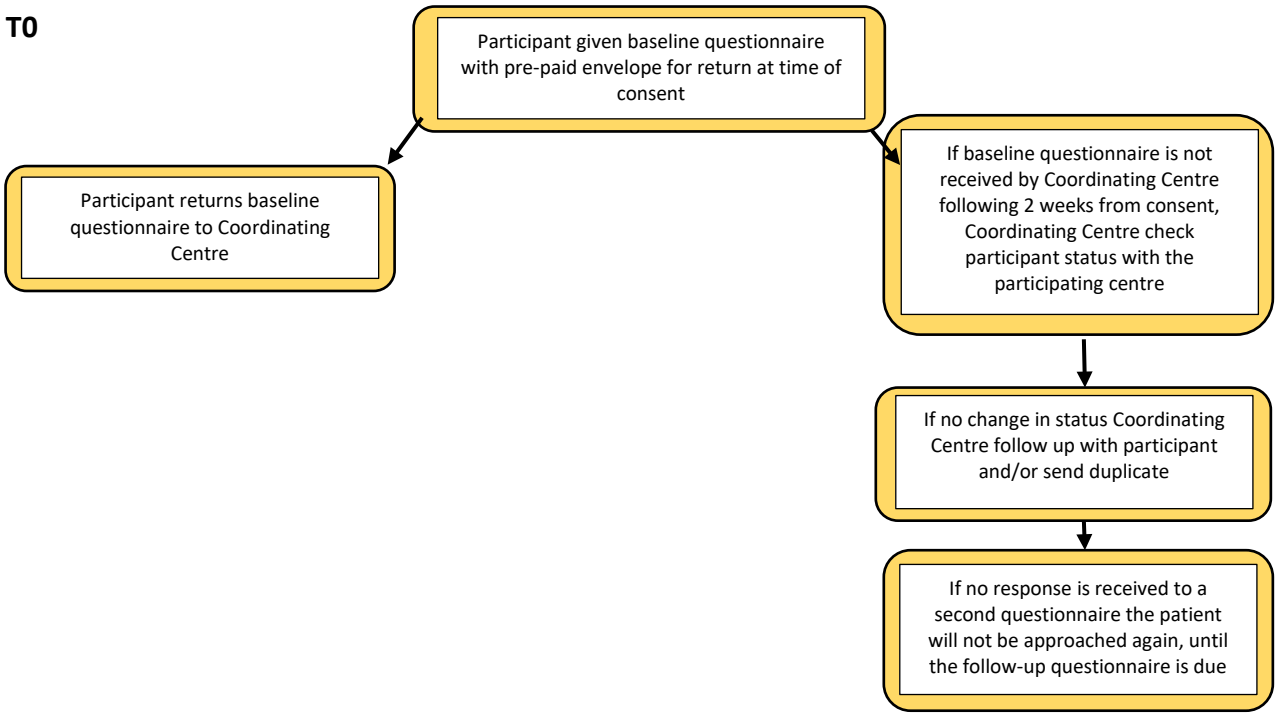
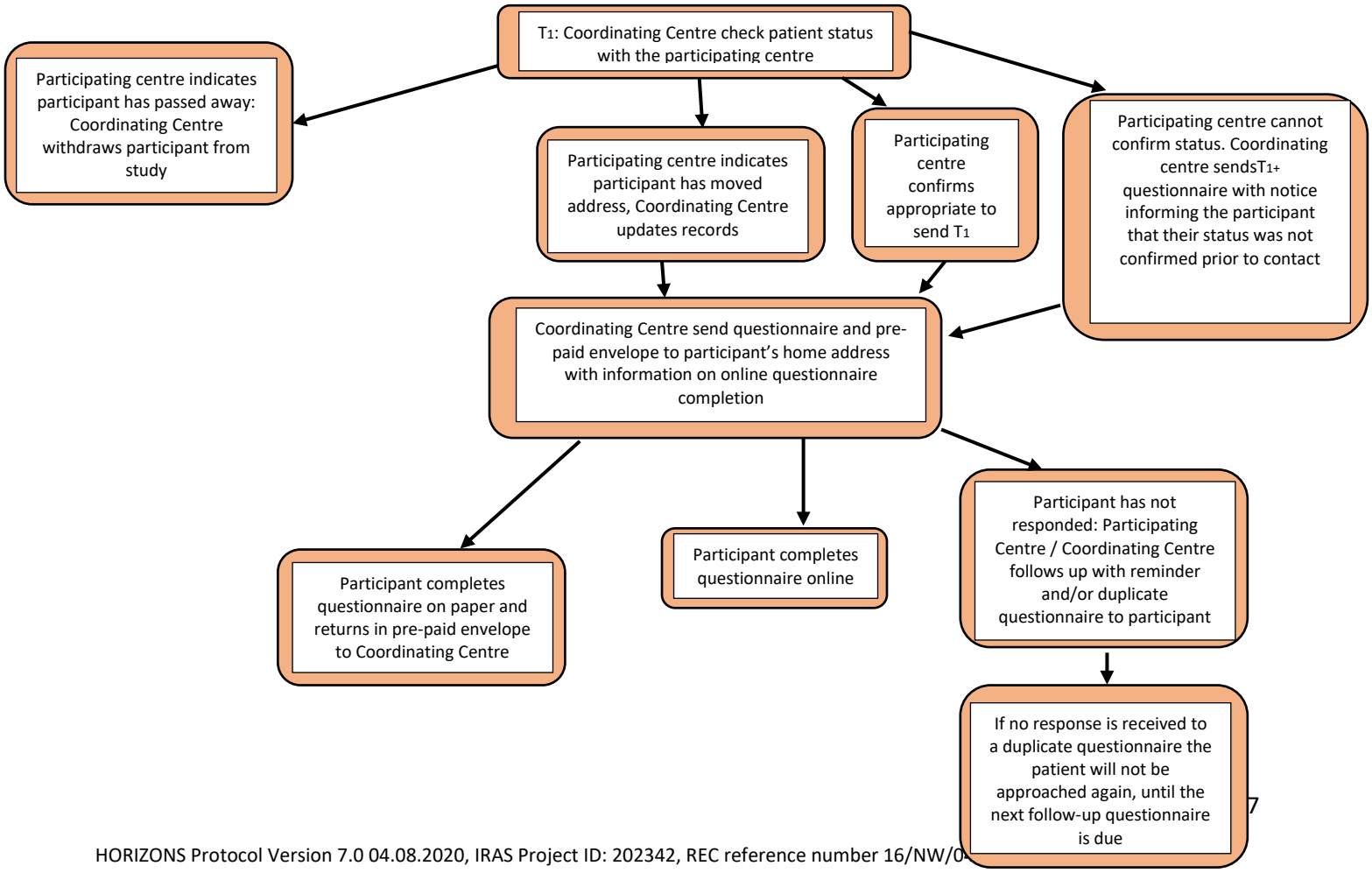


T_{1+} : This follow-up protocol will be followed at each time-point



Time schedule

Programme Plan

Activity	Approvals & set up	Year 1	Year 2	Year 3	Year 4	Year 5
		Jan 16 – Dec 16	Jan 17 – Dec 17	Jan 18 – Dec 18	Jan 19 – Dec 19	Jan 20 - Dec 20
Sign contract, recruit study personnel, agree programme deliverables						
Draft protocol and study documentation						
Ethics and governance approvals & portfolio adoption						
Establish Advisory Groups and Panels						
Develop and launch website, host project launch event						
Build and maintain relationships with participating centres & devolved Nations						
Pilot participating centre approvals, set up and recruitment						
Phase 2 & 3 participating centre approvals and set up						
Recruitment of 3,000 participants						
Questionnaire distribution						
Data collection and management						
Data analysis						
Write up and dissemination of findings						
Strategic Advisory Board meetings		x	x	x	x	x
Tumour expert panel meetings		x	x x x x	x x x	x x x	x x
User reference group meetings and knowledge cafés		x	x x	x x	x x	x x

1 BACKGROUND

Experiences and outcomes of cancer treatment and care are changing. A growing number of people are experiencing cancer not as a life-limiting disease, but as a life-changing and long term condition. There is a growing imperative to understand the changing landscape of cancer and its consequences: as we do so, we will be better able to inform the design and delivery of cost effective interventions that make possible supported self-management, as well as service organisation and delivery. The Macmillan HORIZONS Programme at the University of Southampton will provide the robust and comprehensive data that the patient, clinical, and policy communities need to transform care for people living with and beyond cancer.

The number of people living with and beyond cancer in the UK is set to double, to an estimated four million, by 2030 [2]. Rising survival rates are due to improvements in detection and treatments with many people faring well after treatment. However, cancer and its treatment can have a considerable and long term impact on everyday life [1, 3, 4]. Most cancer diagnoses are in people over 65 years, and with an ageing population (around 23% of the UK population will be over 65 by 2035 [5]), and a stretched health care system, there is growing concern about how best to support cancer survivors (people living with and beyond a cancer diagnosis). Healthcare services need to adapt to the rapidly growing number of people living with or beyond cancer.

2 RATIONALE

Cancer survivors can face a range of challenges following primary treatment that can have a significant impact on all aspects of daily life [6]. Some consequences may resolve in the short term, others may persist for years or arise a long time after treatment [4]. These may require medical management and support as well as self-management. Some people will experience a recurrence following treatment for curative intent (the rate of recurrence varies considerably by cancer and treatment type) and undergo further treatment. Patients have highlighted the need for support in managing the impact of cancer on everyday life [1]. People can be unprepared for the impact cancer and its treatment can have on their lives, may feel vulnerable and experience loss of confidence and may struggle to access care and support [4, 6-8]. This may have serious implications for recovery and the success of self-managed follow-up, and the amount of work survivors are able to undertake to gain timely access to appropriate services.

The National Cancer Survivorship Initiative (NCSI) document *Living with and beyond cancer: Taking action to improve outcomes* [9] and *Achieving world-class cancer outcomes: a strategy for England 2015-2020* [28] describe the urgent need to better understand the survivorship population to identify unmet needs. Data are not routinely collected to determine numbers of people affected by particular consequences and how severely, or who is currently at risk of consequences. Existing studies, such as the national PROMS survey (cross-sectional survey of cancer survivors in England one to five years post diagnosis), demonstrate that many people experience problems, and are useful at highlighting key problems experienced, but often do not provide evidence that consequences of treatment can be directly attributed to the treatment [10, 11]. Cross sectional surveys are also problematic in that those who are experiencing problems are most likely to respond and it is not possible to demonstrate that treatment causes problems or patterns of treatment burden over time (e.g. [12, 13]). Prospective clinical trials are useful but are applicable only to a minority of patients and have high dropout rates [14]. Another problem is that quality of life assessments generally provide a narrow view of symptoms and psychological problems. Looking at quality of life alone does not give a full picture of the impact of consequences on everyday life or how they are managed.

The Macmillan HORIZONS Programme sets out to improve the lives of people affected by cancer by building understanding of the cancer survivorship population and providing a depth of evidence not available through other research. The Macmillan HORIZONS Programme will:

- Use a longitudinal cohort approach involving representative groups of people with a range of cancers and different combinations of: treatment, prognoses, likelihood of recurrence, short term and late effects, co-morbidities, lifestyle and socio-economic profiles.
- Reveal how the consequences of cancer treatment affect people's lives, how consequences are managed in everyday life, including lifestyle changes, role of self-efficacy, social networks, burden of treatment, and experiences of those living with co-morbid conditions, how this changes with time and what influences this.
- Lead the way in understanding complex survivorship experiences and health outcomes from the perspective of thousands of people living with and beyond cancer and how this changes for different groups in the population and across the life-course.
- Provide novel and detailed evidence to inform the national and global movement to transform care for cancer survivors.

3 THEORETICAL FRAMEWORK

Cancer survivorship is a growing global concern. Around 13 million people worldwide are diagnosed with cancer each year. The global figure is expected to triple by 2050 as successful cancer treatments increase longevity. Global initiatives, for example in Canada, USA and Australia, are also exploring ways to improve care for cancer survivors and support for self-management is a key component of these. These initiatives call for high quality interdisciplinary research to provide evidence to inform the most effective ways to support survivors to improve health and well-being.

People diagnosed with cancer increasingly experience personal journeys, relationships and clinical pathways characterised by complexity. Cancer survivors may face a range of challenges that can have a significant impact on all aspects of daily life and may last for years [6]. Some people will experience a recurrence following treatment for curative intent (the rate of recurrence varies considerably by cancer and treatment type) and undergo further treatment. Patients have highlighted the need for support in managing the impact of cancer on everyday life [1]. People can be unprepared for the impact cancer and its treatment can have on their lives, may feel vulnerable and experience loss of confidence and may struggle to access care and support [4, 6-8]. Their experiences frequently include self-management and clinical management of multiple morbidities; multiple cycles of engagement with formal health services (admission; discharge; readmission; follow-up care); and burdens of treatment and symptoms that can have disruptive consequences and involve a wide range of relationships in domestic, community and work settings. We need to understand how patients can best be supported. Consequences may persist and have different implications across the life-course.

Healthcare services need to adapt to the rapidly growing number of people living with and beyond cancer. The current aftercare system does not meet the needs of patients sufficiently [10]. The new cancer strategy [15] recognises the need to support cancer patients better when living with and beyond cancer. It is essential to understand how survivors live with and manage all aspects of their aftercare so that they can be supported optimally, consider their ability to take this on and the implications for their personal networks. Failing to provide adequate support may have serious implications for recovery and the success of self-managed follow-

up, the amount of work survivors are able to undertake to gain timely access to appropriate services and the impact on personal networks. A major source of support for many comes from personal networks of support. Social network members are recognised as having an important role in self-management. Vassilev et al. [16] have identified the substantial involvement of partners and close family in illness management, although other sources of support, e.g. community groups, also have substantial involvement. It is important to consider the impact of consequences of cancer and its treatment on those close to the patient following treatment. A better understanding of the role of social networks is needed to inform the design of effective health care services and the development of resources for patients and caregivers.

There is limited robust evidence to determine how to identify which individuals need more intensive forms of support or how to support self-management. The HORIZONS Programme will reveal experiences across the spectrum from complex cases to those receiving support to self-manage their follow-up. For example, evidence from CREW clearly indicates that there are four recovery pathways (for quality of life, health status and personal well-being) experienced by colorectal cancer patients treated with curative intent surgery and important factors at the time of diagnosis predict who experiences poorer recovery which includes lower confidence to manage illness related problems, living with comorbidities, and deprivation [17].

The current MSRG research programme is underpinned by the conceptual survivorship framework of Foster and Fenlon [6] which has self-management of cancer / treatment consequences as a core component of recovery. The HORIZONS Programme will develop this framework further to assess a broader range of factors that are expected to contribute to recovery of health and well-being and how people manage the consequences of their cancer and its treatment from a personal perspective. We will be able to compare across cancer and treatment types and determine whether there are unique factors that are particularly supportive to recovery and others that put people at risk of poor recovery.

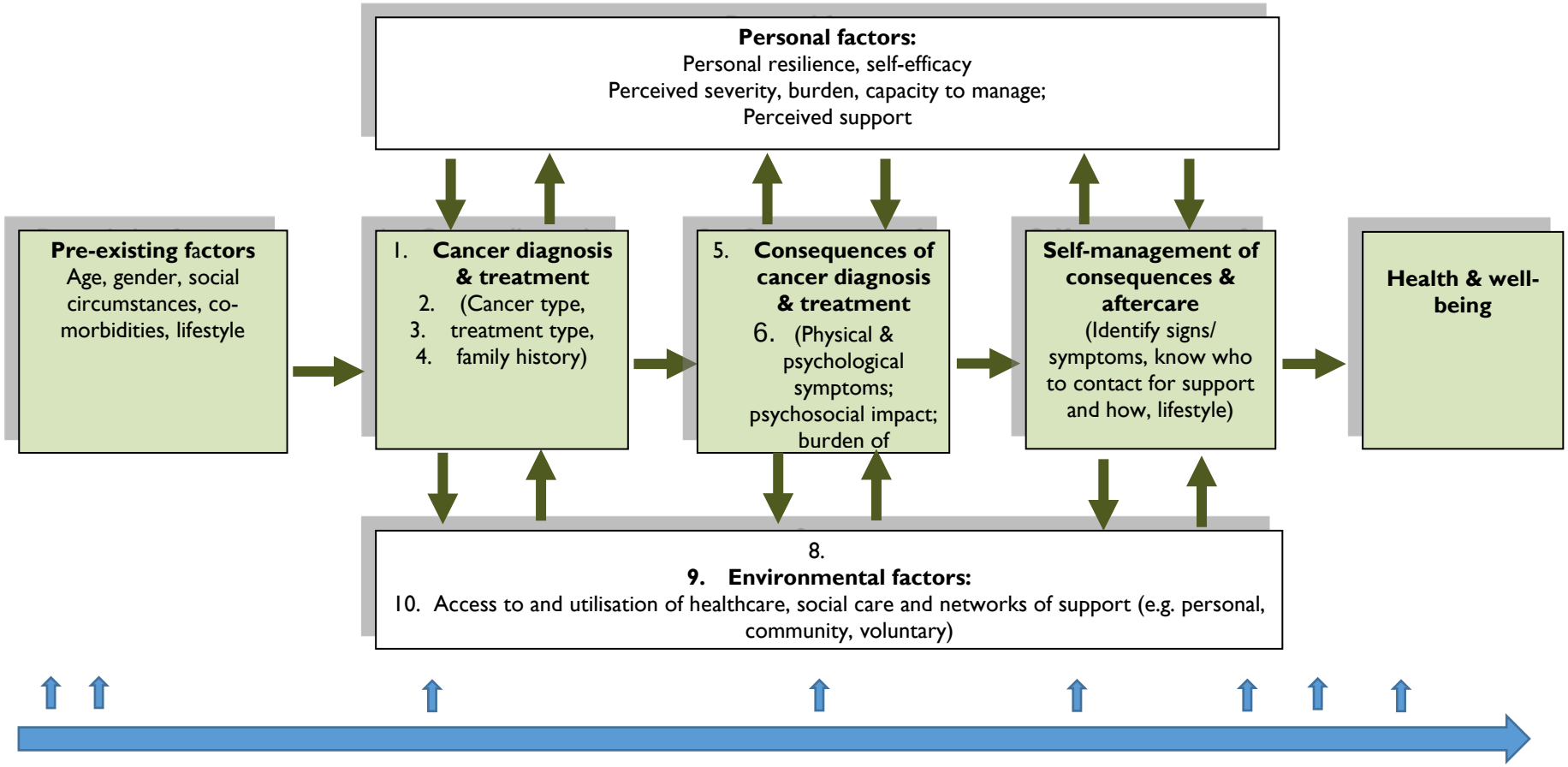
Three important areas of work underpin the HORIZONS Programme:

- Foster and Fenlon's [6] conceptual framework of recovery of health and well-being following cancer treatment hypothesises that health and well-being are positively associated with presence of support for the individual, their confidence to manage problems faced as a consequence of their cancer and negatively associated with problems experienced such as fatigue and pain [18]. This conceptual framework has been explored in the context of the ongoing CREW patients and has highlighted the importance of self-efficacy to manage illness related problems at baseline (pre-surgery for colorectal cancer) in predicting health status, quality of life and personal well-being in the first two years following surgery [19].
- Health services face the challenge of increasing demand from growing populations with long term and life-limiting conditions. They have responded to this by delegating to sick people and their networks work aimed at monitoring and managing symptoms and that is intended to prevent disease progression and identify recurrence. Here, practices of self-care, self-empowerment, and self-actualisation, shifts the work of surveillance and treatment from the clinic into the community or the home. It is important that we understand the dynamics of these processes and their effects on the experiences of cancer survivors, since they shape survivors' capacity for self-monitoring, help-seeking behaviour, and healthcare utilisation. We have two sets of conceptual tools to investigate this problem: Burden of Treatment Theory [15, 17] with its associated Patient Experience with Treatment and Self-management (PETS) instrument [20-22] and Normalization Process Theory [18, 23]. Burden of Treatment Theory is oriented to understanding how survivors' capacity for action interacts with the work that stems from healthcare, and Normalization Process Theory is oriented to understanding how the work of self-care is implemented, embedded and integrated in everyday life. We hypothesise that

there is a dynamic interactional economy here that links the expectations of healthcare systems, the beliefs and behaviours of cancer survivors and their families, and the resources provided by wider social networks. We will use these conceptual tools, along with qualitative investigations, to identify, characterise and explain individual and group mechanisms that promote or inhibit the development of capacity for self-care and self-monitoring in cancer survivorship.

- We will use a network approach to explore self-management support in survivorship conceptualising it as types of illness 'work' undertaken within peoples' social networks [16, 24]. We will use a method previously used with people with long term conditions to identify network members who contribute to illness management. The results are intended to provide an articulation of how social network members are substantially involved in survivorship and the type of work that they undertake [16]. Network mechanisms bring to the fore the close interdependence between social and psychological processes in managing a condition, and the intertwining of practical and moral dilemmas in identifying, offering, accepting, and rejecting support [25]. In terms of mechanisms, we will use as sensitising concepts [16]: *network navigation* (identifying and connecting with relevant existing resources in a network), *negotiation within networks* (re-shaping relationships, roles, expectations, means of engagement and communication between network members) and *collective efficacy* (developing a shared perception and capacity to successfully perform behaviour through shared effort, beliefs, influence, perseverance, and objectives [24]). We will explore the extent to which these are evident in cancer survivorship.

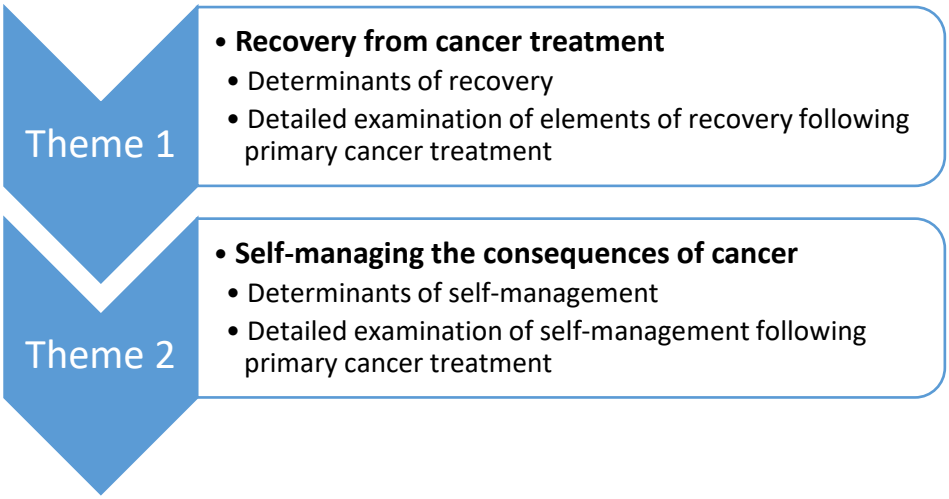
Figure 1: Conceptual framework for the HORIZONS Programme informed by Foster and Fenlon [6], May et al. [15] and Vassilev et al. [16]



Research Themes

Informed by the theoretical framework underpinning the HORIZONS Programme, activity will be structured around two linked research themes which will be developed through the course of the Programme (Figure 2).

Figure 2: Research Themes



Research Theme 1: Recovery from cancer treatment

This theme will address the determinants of recovery following primary cancer treatment. Recovery from cancer and its treatment is a process that takes time and we know little about this, beyond physical, psychological symptoms and quality of life. Some will be living with advanced disease, some will experience a recurrence, and we will investigate the implications of these for health and well-being across the life-course. Our hypothesis is that curative cancer treatment disrupts health and well-being and people require time and support to recover. The cohort data will be examined to address the research questions and determine who recovers health and well-being following their primary cancer treatment and what helps / hinders this. It will also allow the identification of those who do less well and what determines this.

Research Theme 2: Self-managing the consequences of cancer

This theme will examine how cancer and its consequences are managed and how this changes over the life-course. Self-management is a component of recovery but requires a different and particular approach to theory and measurement. For example, in the recovery theme we will explore patterns of recovery of physical, psychological, social functioning and what helps / hinders this. We will also explore who is most at risk of a protracted / complex recovery pathway and examine whether we can characterise those that do well and those that do poorly.

What self-management support looks like needs to be tailored and targeted at those who most need it and we need evidence to inform this. Our hypothesis is that consequences of cancer and its treatment disrupt ways of managing, irrespective of level of health need, although those with complex needs will need most support. Those who feel supported to self-manage will be more able to self-manage. The HORIZONS data will be examined to test this hypothesis and determine the work involved in self-management of consequences of cancer (both for the person diagnosed with cancer and those in their social networks), who is most likely to need support to self-

manage follow-up, what helps / hinders this, when support should be offered and in what form. It will also allow the identification of those who are least likely to self-manage successfully.

4 RESEARCH QUESTION / AIM(S)

4.1 Aims

The aim of the HORIZONS Programme is to:

- Establish a series of cohorts of cancer patients to capture their health related outcomes and experiences from beginning active treatment and regularly over their life-course.
- Maintain and develop the HORIZONS Programme as a national and international resource to explore consequences of different cancer diagnoses and treatments from the individual perspective across the life-course.
- Inform policy and practice based innovative solutions to minimise the health burden and maximise support available to them over their life-course.

The key research questions are:

- What impact does cancer and its treatment have on people diagnosed with cancer in the short, medium and long term?
- What are the health outcomes, experiences and self-management activities over the life-course across different cancer types and what influences these?
- How do people connect with and mobilise resources which enable them to self-manage consequences of cancer and its treatment?

4.2 Key HORIZONS outcomes

By carefully capturing evidence prospectively and over time about cancer survivors' life histories we will be in a position to understand what consequences are faced, when and what can be done to improve the lives of people living with and beyond cancer.

The Macmillan HORIZONS evidence will:

- Improve understanding of the consequences of different cancers and treatments, impact of co-morbidities, impact of recurrence and late effects, characteristics that lead to increased risk of poor recovery, ability to self-manage and what helps or hinders this.
- Enable us to predict who is most likely to need support and what form this should take and when it should be available.
- Help to prepare future patients for likely consequences and how long these might last following treatment so that they know what to look out for and when to seek support. And to support decision making where appropriate.
- Support the transformation of care for people living with and beyond cancer. Better information on short, medium and long term outcomes and experiences across cancer types and treatments will enable

health professionals to provide more personalised care to their patients tailored to their needs and to support people to live as healthy and active a life as possible.

- Inform the development of risk stratification models such as likely proportion of patients in different follow-up pathways across cancer / treatment type.
- Identify areas for service innovation and other solutions to support cancer survivors and their personal networks to manage the consequences of cancer and its treatment across all aspects of their lives.
- Be an important vehicle for the development of further important clinical / research questions and development of theoretical models.

5 STUDY DESIGN, METHODS OF DATA COLLECTION AND ANALYSIS

5.1 Type of design

A series of longitudinal cohort studies will be conducted in cancer survivors using a questionnaire survey, either mailed or completed online.

Qualitative work is planned during the Programme and once details are known will be submitted as a protocol amendment. Patients will give consent to be approached about other related studies at initial consent and those who consent will be contacted to ask if they would like to participate in related qualitative studies. Full information will be given and additional consent to participate in these studies will be taken prior to any data collection.

5.2 Study measures

The validated measures used will be informed by the conceptual framework (Figure 1) and some study-specific questions will be developed. Not all measures will be used at each time-point.

A core set of measures will be administered at each time-point across all cancer types. A small number of tumour-specific measures will be included to capture disease-specific consequences. See Table 1 for proposed measures. Consent will be sought to collect medical details for all participants.

From summer 2020 for a 12 month period, an insert of COVID-19 questions will be included with the next questionnaire booklet each participant receives (at one time point only for each participant). This is necessary to help us understand any differences in responses to the main HORIZONS questionnaires completed before and after the pandemic. In addition, these questions will help us understand the needs of people being treated for and recovering from cancer during the pandemic.

5.2.1 Primary outcome measure

QLACS; [26] will be the primary outcome measure across cancer types and will be included at each time-point. QLACS [26] was developed to assess QoL of adult cancer survivors. QLACS measures 12 domains of cancer survivorship; 7 generic domains (pain, fatigue, positive and negative feelings, cognitive and sexual problems, social avoidance) and five cancer-specific domains (financial problems, family distress, recurrence distress, appearance concerns, benefits from cancer). QLACS has been validated amongst cancer survivors [26] and has good convergent validity with other QoL measures (e.g. FACT and SF36).

Areas under investigation will include (see Table 1 for details):

- Pre-existing factors: including age, gender, social circumstances, co-morbidities.
- Cancer diagnosis and treatment (data collected on medical details form by participating centres).
- Consequences of cancer diagnosis and treatment: including physical symptoms, psychological problems, social implications such as impact on social relationships and networks, practical implications (e.g. work-related problems, everyday chores, travel); perceived impact on everyday life including financial impact, and how this is experienced as burdensome to individuals.
- Self-management of consequences and aftercare: self-management activities.
- Personal factors: Individual characteristics such as reliance and confidence to self-manage; perceived burden of treatment; perceived support and resources that individuals have in order to manage consequences for themselves.
- Environmental factors: access to / utilisation of health and social care and other forms of support, including social support through family, friends, community, healthcare, social care, third sector and social networks
- Health and well-being: quality of life, health status, personal well-being.
- Life events.

***Medical details**:* Clinical information, such as cancer type, stage, treatment, co-morbid conditions, height and weight, will be abstracted from clinical records by the nurse / researcher at the participating centre. Change in health condition and treatment will be monitored through self-report at follow-up and further collection of clinical data from participating centres at regular intervals throughout the Programme.

Table 1: Proposed questionnaire measures according to domains of the theoretical framework

Domain	Areas of assessment	Proposed measures*
Pre-existing factors	Socio-demographic (age, gender, neighbourhood deprivation (calculated from postcode), housing status, vehicle ownership / use, sexual orientation)	
	Educational attainment	Highest level achieved
	Domestic situation (marital status, who lives with participant, number of children / dependents)	
	Caring responsibilities	
	Ethnicity	
	Occupational / economic factors (employment status, household income, weekly hours, sickness leave, history of shift working, receipt of benefits / pension)	
	Access to mental health services	
	Family history of cancer	
	Genetic testing for cancer	
	Co-morbidities	List of current co-morbidities and impact on everyday activities
	Lifestyle:	
	- Exercise	Godin-Shepard Leisure-Time Exercise Questionnaire; Resistance and strength exercise questions

	- Diet	Fruit and vegetables screening log; special diet open-ended question
	- Smoking; including use of e-Cigarettes	Whether current / ex- / non-smoker and amount for current / ex-smokers; similar questions used for e-Cigarette use
	- Alcohol	Frequency of alcohol drinking and number of units
Consequences of cancer diagnosis and treatment	Symptoms, functioning	European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and tumour-specific modules (see Appendix 3)
	Body image	Body Image Scale (BIS)
	Sexual functioning	In EORTC tumour-specific modules
	Sleep problems	
	Anxiety and depression	Hospital Anxiety and Depression Scale (HADS)
	Impact on day to day tasks	Work and Social Adjustment Scale (WSAS); in EORTC tumour-specific modules
	Financial impact	Captured by EORTC QLQ-C30 subscale; self-report on financial cost of accessing health and social care services (e.g. petrol, parking, public transport) and other costs associated
	Burden of treatment	Patient Experience with Treatment and Self-management (PETS)
	Fear of recurrence	Worry of Cancer scale; captured by QLACS subscale
	Unmet needs	Supportive Care Needs Survey (SCNS)
	Positive outcomes / benefits of cancer	Captured by subscale in QLACS part 2

Self-management of consequences and aftercare	Self-management	Health Education Impact Questionnaire (heiQ)
	Use of internet	
	Use of other therapies (including complementary and alternative medicines)	
	Use of follow-up and routine health assessments	
Personal factors	Self-Efficacy	Self-Efficacy for Managing Chronic Disease Scale (Lorig) – Cancer survivors version
	Resilience	Brief Connor-Davidson Resilience Scale (CDRISC2)
	Health literacy	Brief Health Literacy Screen (3 questions)
	Health beliefs	Brief Illness Perception Questionnaire (BIPQ)
Environmental factors	Access to / utilisation of health and social care and third sector; including receipt of advice or information	
	Patient experience of care	
	Social support and social networks	Medical Outcomes Study (MOS) Social support scale; adapted UCNET (mapping tool)
Health and well-being	QoL	QLACS, parts 1 and 2
	Health status and Well-being	EuroQoL EQ-5D-5L and Visual Analogue Scale; SF-12 version 2 (SF-12v2)
Life events	Significant life events	Open-ended question

* Where there is no named questionnaire measure given, study-specific questions will be used that have been developed from existing studies, including others conducted by the MSRG and also utilising national resources, e.g. from the Office for National Statistics (ONS).

5.3 Collection of Data - schedule of data collection

Baseline data will be collected by direct approach to ALL eligible patients from the recruiting clinician / research nurse PRIOR to primary treatment and assigned as time T_0. One of the criteria for selecting participating centres to participate in HORIZONS will be the ability to approach a total sample and prior to treatment commencing. Outcome data will be collected at regular intervals and these timings will be consistent across the different cancer types. Participants will have the option to complete paper-based or online questionnaires. All follow-up questionnaires will be sent to participants from the HORIZONS Coordinating Centre in Southampton.

Timing of assessments will be refined during the set up phase following wide consultation.

Proposed assessment points:

T_0: baseline – following diagnosis but prior to initial curative intent treatment

T_1: 3 months after study entry – to monitor early adaptation and coping and detect initial treatment effects.

T_2: 12 months after study entry – to monitor later adaptation and coping and detect initial treatment effects.

T_3: 18 months after study entry – to monitor further adaptation and early stages of recovery

T_4: 24 months – to monitor consequences in the longer term and how they are managed.

T_5 +: Annual assessments to monitor consequences, emergence of late effects, co-morbidities, lifestyle change and how they are experienced and managed across the life-course.

5.4 Methods of data collection

Data will be collected through:

- Self-report questionnaires over the course of the HORIZONS Programme; prior to treatment and in the months and years beyond.
- Routinely collected medical records data. Medical details will be collected via CRFs at baseline, 6 months, 12 months and then annually by research nurses at the participating centres.

Procedure for Study Questionnaires:

Baseline and follow-up data will be collected using self-report questionnaires. Patients will be given the option of completing the questionnaires either on paper or online (from T_1). The paper baseline questionnaire will be given directly to the patients in clinic to be returned to the HORIZONS Coordinating Centre using the pre-paid envelope provided. A paper copy of the T_1 questionnaire will be mailed directly to participants together with instructions outlining optional online completion using a secure web-portal. Participants can chose to complete subsequent questionnaires online, with email reminders when due. If participants do not respond to email reminders they will be sent a paper copy of the questionnaire. If a participant completes their paper questionnaire at any time-point and returns it using the pre-paid envelope, it will be assumed this is how they would like to receive further questionnaires but the option for online completion will still be offered each time.

The baseline questionnaire will be completed prior to initial primary curative intent treatment (the date of questionnaire completion will be compared to date of treatment to establish this). If the patient is unable to complete the baseline questionnaire then **in exceptional circumstances only,** patients will not complete the

baseline but will be sent follow-up questionnaires if they are willing to participate providing the HORIZONS Coordinating Centre is informed.

On receipt of returned questionnaires these will be checked for completeness. Participants will be contacted by the HORIZONS Coordinating Centre (for example by telephone, email, letter) to ask about whether sections were missed in error and if possible complete missing items in order to reduce the amount of missing data. Mailing of paper questionnaires, or an email reminder to participants electing to complete questionnaires online, will take place within three weeks of the due date of assessment to aim for data collection to be completed as close as possible to the specified assessment date. Participants will be asked to record the date of completion of questionnaires. Prior to contacting participants regarding completion of the next questionnaire the participants' clinical team will be contacted to request confirmation that the participant is alive and the participants' address has not changed. If the clinical team are unable to confirm whether the participant is alive and has not moved by the due date of assessment and all reasonable efforts to acquire this information in a timely fashion have been explored (e.g. GP contact, other hospital sites), the questionnaire will be sent with a notice informing the participant that their status was not confirmed prior to contact. Participants will also be advised to contact the Coordinating Centre if their information has changed or is not correct. The same follow-up protocol for non-response will be followed at each time-point (see consent and non-participation and withdrawal, sections 7.5 and 7.6).

Medical details CRF

The medical details CRF will be completed by the clinical team / researcher at baseline, six and twelve months and then annually for all patients who provided consent. Information including cancer type, stage, treatment, co-morbid conditions, recurrence and survival will be abstracted from clinical records. As part of the extended follow-up, brief medical information will be collected via self-reported medical status questions on follow-up questionnaires.

5.5 Analysis

For Theme 1: Recovery from cancer treatment

Descriptive statistics will be used to characterise the primary outcome of Quality of Life (QLACS) and describe health status (EQ-5D-5L) and symptoms / functioning (EORTC QLQ C30 and tumour-specific modules) over time. Changes in these outcomes over time will be investigated using longitudinal methods including generalised estimating equations, and group-based trajectory analyses will investigate whether there are distinct subgroups of recovery within each cohort. Factors that may influence recovery will be included in the regression models, including cancer and treatment type, socio-demographics, treatment and symptom burden, social support, personal dispositions, self-efficacy, self-management, personal network support, lifestyle, comorbidities, utilisation of health and social services, and recurrence. The varying contribution of these factors will be assessed to determine which have the most influence on the outcomes of quality of life, health status, well-being and symptoms / functioning following treatment. Recurrence and survival (overall and disease-specific) will be analysed using standard methods of survival analysis, such as Kaplan-Meier analysis.

Using data from National Databases

In order to evaluate whether the HORIZONS samples are representative of the national population in terms of sociodemographic and clinical characteristics, we will request data from national cancer registries to allow for aggregate comparisons. Requests will be made to Public Health England, ISD Scotland, Welsh Cancer Intelligence and Surveillance Unit and the Northern Ireland Cancer Registry.

In addition, we will request data at the individual level from the same organisations for participants who provide consent to link the data collected by HORIZONS with the data held on national databases. These data will allow additional clinical information to be collected.

For Theme 2: Self-managing the consequences of cancer

Descriptive statistics will be used to summarise patients' self-management activities, and their capacity and confidence to self-manage problems, and longitudinal analyses as previously described will assess changes over time in the measures of self-management (heiQ). Factors that may influence self-management will be investigated in the regression models, such as capacity to self-manage, social networks and community support, utilisation of health and social services, cancer recurrence and co-morbidities. Analyses will also explore how self-management relates to recovery of quality of life, health and well-being. Self-management activities will be compared across groups including cancer and treatment types using statistical methods already described, and analyses such as group-based trajectory analyses will investigate whether there are distinct subgroups with different follow-up care needs.

Patterns of missing data will be investigated in the analysis.

Quantitative data will be analysed using statistical packages such as SPSS and Stata.

6 STUDY SETTING

We aim to recruit people diagnosed with cancer amenable to treatment with curative intent through their clinical teams prior to primary treatment. Participants will be identified and recruited from NHS treatment centres across the UK, with centres chosen from those who express an interest through the CRN or directly to the HORIZONS Coordinating Centre. Centres will be selected for their proven research capability in these cancer types. Centres will indicate that they can approach a TOTAL SAMPLE of eligible patients and BEFORE TREATMENT begins. Additionally, Centres will be selected to ensure the Study covers a wide range of geographical locations across England, Scotland, Wales and Northern Ireland, ethnically diverse populations and varying-sized hospitals.

7 SAMPLE AND RECRUITMENT

7.1 Eligibility Criteria

For each cancer type, we aim to recruit all newly diagnosed patients who will be treated with curative intent (based on imaging, clinical, cytological or histological diagnosis) for the included cancers through their clinical teams prior to primary treatment. The generic inclusion/exclusion criteria for the Study are below, the specific requirements for each cohort are found in Appendix 4.

Diagnosis may not be confirmed until after treatment has begun (i.e. after surgery), if a participant's status (e.g. staging) changes after confirmed diagnosis they will be reassessed for eligibility. If patients meet any exclusion criteria (e.g. surgery reveals their cancer was from another origin site) they will be excluded and no further data will be collected. Participants will be informed by a member of their clinical team that they are no longer eligible to participate.

7.1.1 Inclusion criteria

To be included, patients must:

- Have a new diagnosis of one of the selected cancer types determined through clinical assessment, cytology, histology or imaging

or

- Have new / second primary cancer at a site previously treated for cancer.
- Be awaiting primary **curative intent** treatment, including neoadjuvant treatment.
- Be ≥16 years old.
- Be able to complete questionnaires in English.
- Be able to provide written, informed consent.

7.1.2 Exclusion criteria

Patients will be excluded if:

- They do not have one of the specified cancer types
- Disease is recurrence / progression (either locally advanced or metastatic) at an existing cancer site.
- They are having treatment for a potentially curative recurrence of disease e.g. locally advanced disease (i.e. they have been previously treated for the same cancer).

- They have metastatic disease from a cancer[1] at another site
- They have synchronous primary cancers involving two or more of the HORIZONS specified cancer types[2]

7.2 Sampling

7.2.1 Size of sample

Sample size calculations are based on the primary outcome measure (QLACS). The mean generic summary score for QLACS is 71.2 (SD 25.6) [26]. A difference of one half of a standard deviation is often quoted as a minimum clinically important difference in sample size calculations: using 80% power to detect a difference of one half of a standard deviation at the 0.05 significance level would require a minimum of 228 participants per cancer type, assuming unequal-sized groups will be compared in the analyses. Assuming an intra-cluster correlation of 0.05 to allow for similarities between participants from each participating centre and an average of 30 participants per participating centre the cluster correction increases this figure to 559 per cohort. Taking into account 10% withdrawal and a range of five year survival rates according to cancer type, and rounding up to allow for some subgroup analyses results in approximately 1,000 participants per cancer type.

The sample size will be sufficient for other continuous measures, assuming the same size of difference (one half a standard deviation). Subgroup analyses within cancer types will be possible, but numbers will be small for some instances, limiting the conclusions that can be drawn from these.

7.2.2 Sampling technique

Patients will be identified at the participating centres via a systematic screening process. Eligibility will be assessed using a standardised procedure and all eligible patients will be invited to participate in the Study over the recruitment period. Screening logs will be maintained at the participating centres, to include anonymised data on eligible patients who were "missed" (not invited to participate (e.g. due to logistical reasons)), as well as those who were invited but declined to take part (with reasons).

7.3 Participating centre selection

HORIZONS has been adopted on to the NIHR CRN Portfolio. An expression of interest form was sent out to potential research sites through the CRN. The participating centres will be selected from those that express an interest in participating.

We will recruit patients from 78 cancer centres across the United Kingdom to cover a range of geographical locations, clinical settings and ethnically diverse populations. Centres will indicate that they can approach a TOTAL SAMPLE of eligible patients and where possible, BEFORE TREATMENT begins. We will start with recruitment of patients with gynaecological cancer, non-Hodgkin lymphoma and breast cancer patients diagnosed under 50 years old. We will preferentially choose the participating centres who have the capacity and capability to recruit to more than one cancer type. Each participating centre will appoint one PI who will be responsible for the participating centre activities and the PI will delegate the lead for overseeing recruitment from the tumour groups outside of their specialty to a lead clinician for the specialty as a Co-investigator.

[1] Previous diagnosis of cancer at any other site would not be grounds for exclusion unless disease was metastatic

[2] Exclude synchronous gynaecological primary cancers, synchronous breast and gynaecological primary cancers, synchronous breast and NHL primary cancers and synchronous NHL and gynaecological cancers

Participating centre initiation and training will be undertaken through study days and / or local training via teleconference, Skype or Webinar, as appropriate.

The Study began with a pilot phase in September 2016. During this pilot phase the HORIZONS Coordinating Centre worked closely with the selected pilot participating centres to conduct feasibility work to assess study set up and training procedures, the recruitment strategy, recruitment rates, representativeness of sample and appropriateness of measures for each of the tumour groups and CRF. Pilot participating centres were selected on the basis of certain characteristics, such as geographical location, previous experience and type of Trust. Including a participating centre, one in a devolved nation, participating centres experienced in working on other MSRG studies, specialist cancer centres and a district general hospital allows us test out our set up and recruitment procedures in different circumstances.

7.4 Recruitment

Within both the pilot phase and full study, there will be variation according to cancer type but in general, eligible patients will be identified by a member of the patient's direct care team through MDT meetings or clinics at each participating centre. The HORIZONS Coordinating Centre staff will work with the participating centre's staff to review local procedures and determine the best method of screening and recruiting potential patients for the Study. All eligible patients will then be given a unique Study ID number and entered onto the eligible patients' log. All eligible patients will be invited to participate in the assessment clinic after their cancer diagnosis and before their first primary treatment by a direct care team research nurse or member of the clinical team. **Care must be taken to ensure all patients are approached, and all groups are represented, in order that the research is generalisable and will improve understanding of who is at risk and may need more support.** Care should also be taken to ensure that patients from ethnic minorities (who speak English) are also approached to participate (numbers of ethnic minorities included will be compared to population norms). The questionnaires used in the study are only validated in English and therefore full study participation is only available to those who can communicate sufficiently in English to complete questionnaires about their health and well-being. **It is also important that patients are invited to participate before their treatment begins so that the baseline data represents a pre-treatment picture. Change over time can then be compared to these baseline data and indicate what has got worse or improved during and after the course of treatment (See exception in Appendix 4).**

Participation in other research studies is not an exclusion criteria for this study, the HORIZONS Coordinating Centre support the NCRI Consumer Forum call to widen patient participation in clinical trials [29] and NIHR's patient empowerment campaign - *It's OK to ask* - and will encourage and support the participating centre's staff to give information to all eligible participants to allow them to choose if they want to participate in the Study. If the patient is participating in, or considering participation in another study, HORIZONS should still be offered to the patient, unless it is an exclusion criteria of another study to which the participant is *already* consented.

7.5 Consent

Given the proximity of the approach to the start of treatment we propose several options of study introduction should be available to the participating centres both to ensure baseline questionnaire data are collected prior to treatment and to minimise patient burden of additional appointments:

- If the patient is interested in taking part in the Study and is returning for a clinic visit prior to their treatment commencing, the member of the research or clinical team making the approach will give the patient a PIS and relevant supporting information for the patient to consider participation and consent at their next clinic visit.

or

- As an alternative to this process, an invitation to participate letter and a PIS may be sent, in advance, to an eligible patient along with their pre-appointment letter to consider their participation in advance of their pre-treatment appointment.

Following the provision of the PIS the clinical team's research staff will discuss with the patient if they wish to participate in the Study. If the patient is interested in participating they will be given an opportunity to ask any questions before being given the consent form and being asked to provide fully informed written consent. At this point they will also be asked to provide their contact details and will be given the baseline questionnaire and a pre-paid envelope for return of the questionnaire.

For patients who do *not* have another clinic appointment prior to the start of treatment the clinical team will give the patient the PIS, consent form, contact details form, baseline questionnaire and pre-paid envelope for return of the questionnaire (Study Pack). In the discussion about the Study the patient will have an opportunity to ask any questions they may have and if the patient would like to take part, they can provide fully informed written consent at that point.

If the patient requires further time to consider participation, they may be given the consent form, contact details sheet, baseline questionnaire and pre-paid envelope to take home. If they choose to participate they may return their completed consent form directly to the HORIZONS Coordinating Centre along with their completed contact details form and questionnaire in the pre-paid envelope. If participants take study information home to consider participation the research nurse / researcher at the participating centres may follow-up with a telephone call to check they do not have any questions prior to signing the consent form. Participants who take documents home should still be recorded on the screening log with the patients initials, the participating centre ID, cohort initial and consective number (for example, AC01B001, BS01B002 etc). The screening outcome should be recorded as documents taken home and the date taken home supplied.

Patients who present as acute admissions (e.g. emergency surgery) will be approached by their direct care team as soon as possible after surgery.

These options have been reviewed by our PPI representatives and the NCRI Consumer Forum and deemed appropriate and in the patients' interests for our study design. The option for approach and consent in the same appointment has also been well received by patients in other questionnaire cohort studies conducted by the HORIZONS Coordinating Centre - CREW cohort (cohort of colorectal cancer patients 10/H0605/31).

Patients wishing to participate in the full study (i.e. completion of questionnaires) will give fully informed written consent and be asked to complete the consent form. The completed consent form will be posted, emailed (using nhs.net accounts and password protected) or faxed (to a secure fax) to the HORIZONS Coordinating Centre by the nurse / researcher. Consent will be sought to access patients' records in order to gain accurate information about disease type and stage, as well as medical information about co-morbidities and any cancer treatments received. In the consent form we will notify patients that we will be informing their GP of their participation in the Study. Patients will be asked to consent to being approached about related future research and consent to their medical details being collected for the duration of the Study.

All eligible patients will be allocated consecutive Study IDs which will consist of participant initials, the participating centre identifier, cohort identifier and consecutive number (for example CF01B001, LC01B002, JH01B003 etc) which will be documented on each participating centre's screening log. If a completed consent form is not received from patients on the screening log who have indicated their interest in the Study, HORIZONS Coordinating Centre staff will contact the relevant participating centre to check latest hospital record of address

and status, and ask the participating centre to follow their usual procedures and contact the patient again to ascertain if they still wish to participate or have any further questions to ask or information required to make their decision, if this is appropriate.

Patients who decline any participation in the Study will be logged on a decliners log containing aggregate data on age, gender, stage of disease and ECOG status of those that decline, in order to monitor that the Study cohort is representative of the relevant population. Patients who decline will have their Study ID revised by the addition of the letter D to the original Study ID on the screening log and their initials will be replaced with XX so no patient identifiers are held by the HORIZONS Coordinating Centre (for example, XX01B004D).

The nurse / researcher will abstract routinely collected NHS data after consent has been received. The CRF will be completed at baseline and a further CRF completed at six months and then annually, to ensure that all relevant medical events are collected for the Study period. This form only uses the participant Study ID as an identifier. The CRF will be faxed to a secure fax by the participating centres, emailed using the nhs.net account and password protected, or posted to the HORIZONS Coordinating Centre.

Checks will be conducted with the participating centres, before follow-up questionnaires are due to be sent, to update records and reduce the chance of inappropriately contacting a patient (e.g. who has recently died).

Participants will be given the option to complete questionnaires online, from three months (T_1) onwards. Paper copies of questionnaires will be returned to the HORIZONS Coordinating Centre in Southampton in the pre paid envelopes provided.

7.6. Non-participation and withdrawal

The right of patients to refuse to participate without giving reasons will be respected. Patients will remain free to withdraw from the Study at any time without giving a reason. At all stages the research team will endeavour to record reasons for non-participation. The participating centre will hold a list of eligible patients (screening log) and supply non-identifiable details of the number of eligible patients to the HORIZONS Coordinating Centre. Where possible, this information will include details of reasons for non-participation. Patients who decline any participation in the Study will have their Study ID amended by the addition of the letter D to the original Study ID, and use of XX in place of initials on the screening log (for example, XX01B004D), and the reason for their decision not to participate (if given) will also be added to the screening log.

All eligible patients should be approached. However, if there is a legitimate reason for not approaching a particular patient, then their Study ID also needs to be amended by the addition of the letter M, and use of XX in place of initials to the original Study ID on the screening log (for example, XX01B005M). The reason for the missed approach must also be added to the screening log. The screening log must be completed and posted / emailed/ faxed (as above) to the HORIZONS Coordinating Centre.

If questionnaires have not been returned following consent, the HORIZONS Coordinating Centre /Participating Centre will contact the patient to remind them about questionnaire completion. A duplicate questionnaire or reminder email will then be sent. If no response is received to a duplicate questionnaire the patient will not be approached again, until the next follow-up questionnaire is due.

At the follow-up time points, if the questionnaire has not been returned after three weeks, a reminder letter and/or duplicate questionnaire will be sent. If no response is received to a duplicate questionnaire the patient will not be approached again, until the next follow-up questionnaire is due.

If a participant wishes to withdraw they will be given the information to contact the HORIZONS Coordinating Centre to discuss their concerns about participation. If the participant would like to withdraw they will be sent a withdrawal form (or this can be completed over the telephone with a participant) which will give them three options for levels of withdrawal:

- No further contact: participant elects to receive no further questionnaires but allows the research team to retain and use information collected previously and to continue to access their medical records for research purposes.
- No further access: participant elects to receive no further questionnaires, nor for the research team to have further access to their medical records, but information collected to date may be retained and used for research purposes.
- No further use: the participant elects to receive no further questionnaires, nor for the research team to have further access to their medical records and for information collected to date to be held only for regulatory purposes and not used for research purposes.

Study participants who develop metastases / disease progresses after consent will remain in the Study.

If, after consenting, it becomes clear that a participant no longer meets the eligibility criteria, the participant cannot be included in the Study. All copies of the participant's personal data and completed questionnaires will be destroyed. A member of the clinical team will inform the participant that they can no longer be included in the Study and that they will not be contacted again to complete questionnaires or to answer any questions.

8 ETHICAL AND REGULATORY CONSIDERATIONS

8.1 Assessment and management of risk

People with cancer are likely to be at a vulnerable time in their lives. The research team has significant experience of working with people who have cancer, and their carers, and have conducted similar studies successfully (CREW cohort, cohort of colorectal cancer patients 10/H0605/31 and Roy Castle Lung Cancer Foundation feasibility cohort studies, 13/YH/0081 and 15/EM/0255). Patients will only be approached by an agreed member of their local clinical team. This person will be a member of the direct care team of this group of patients. A nurse / researcher, appropriately qualified and delegated the task by the the participating centre's PI (using the HORIZONS study signature / delegation log) will fully outline the Study, answering any patient questions in a sensitive manner. All patients will receive a detailed PIS which will include information about the Study and how they might access support if they are experiencing any particular worries or concerns related to their cancer. The PIS will also make clear that the Study is unlikely to have any direct benefit on those agreeing to participate.

Contact with the HORIZONS Coordinating Centre will be via telephone, email or mail, based on the contact details provided by the participant. If the participant has queries about their treatment or needs further support the HORIZONS Coordinating Centre will refer them back to their GP or local specialist team.

We do not anticipate that there will be any risks to participants, but patients will be advised prior to study entry that if they have any concerns about their health as a result of study participation, they should contact their doctor or nurse.

Sometimes people find it difficult to talk or write about their experiences. We will be asking participants about their emotional health, for example, how they are coping. Participants will be advised that they do not have to answer questions in any questionnaire that they would prefer not to answer.

If patients feel they are finding any aspect of their experience particularly difficult the HORIZONS Coordinating Centre staff will also provide them with details of where they might get more support, such as Macmillan Cancer Support (www.macmillan.org.uk), and Maggie's Centres (www.maggiescentres.org). Participants will be advised that they may also want to talk to their GP or hospital clinician if they have any more specific questions. No individual response to questionnaire answers can be made by the HORIZONS Coordinating Centre, and participants will be made aware of this.

8.1.2. SAE monitoring and reporting

In light of the above we will only be asking the participating centres to report SAEs if it is deemed directly related to the person's participation in this study. Depending on the nature of the event, the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the CI in the first instance.

Only SAEs during study participation deemed to be related to the completion of study questionnaires, or due to participation in the Study, shall be reported to the CI within 24 hours of the the participating centre learning of its occurrence. The initial report can be made by telephone notification to the CI followed by completion of the current report of SAE (non-CTIMP) provided by REC. In the case of incomplete information at the time of initial reporting, all appropriate information should be provided as follow-up as soon as this becomes available. Relationship of the SAE to study procedures should be assessed by the PI at the participating centre.

The main REC will be notified by the CI, or a delegated member of the HORIZONS Coordinating Centre (on behalf of the Sponsor), of all SAEs within 15 days of the CI becoming aware of the SAE (unless urgent safety measures are required, in which case initial notification by telephone will be made immediately the CI aware of the SAE, with notice in writing following within three days). SAEs will be reported using the current report of SAE (non-CTIMP) provided by REC.

Local investigators should report any related SAEs as required by their local Research and Development Office.

8.2 REC review and reports

Before the start of the Study, approval was sought from a REC for the study protocol, informed consent forms and other relevant documents e.g. patient facing documents, GP letter, etc.

Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the Study.

All correspondence with the REC will be retained.

The CI, or a delegated member of the HORIZONS Coordinating Centre (on behalf of the Sponsor), will submit annual progress reports to REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the Study is declared ended.

If the Study is ended prematurely, the CI will notify the REC, including the reasons for the premature termination.

Within one year after the end of the Study, the CI will submit a final report with the results to date, including any publications / abstracts, to the REC.

PISs and consent forms for the Study will be designed in accordance with ICH GCP (1996), the HRA Consent and Participant Information Sheet Preparation Guidance and the current guidance from the NHS Executive. Patients' consent to participate in the Study will be obtained after they have been given the PIS, when they understand their role in the Study and when they are happy to take part in it. It will be made clear to patients that participation in the Study is entirely voluntary and declining to take part will not affect the NHS medical care that they receive. The right of patients to refuse to participate in the Study without giving reasons will be respected. Similarly, patients will remain free to withdraw from the Study at any time without giving reasons and without prejudicing their future NHS care.

Collectively the HORIZONS Coordinating Centre team has many years of experience of working with people affected by cancer and life-limiting conditions, including talking about sensitive and difficult subjects. Some participants in the HORIZONS Programme may find completing questionnaires and talking about their problems and concerns upsetting. This is not uncommon. For some it can be therapeutic to have the opportunity to talk to someone outside their care or circle of family / friends. Well established procedures (CREW cohort (cohort of colorectal cancer patients 10/H0605/31) and Roy Castle Lung Cancer Foundation feasibility cohort studies (13/YH/0081 and 15/EM/0255)) are in place to offer support to anyone distressed and the research team have appropriate training and will be appropriately supervised. The URG will inform questions asked and information provided to HORIZONS Programme participants.

Members of the team undertake regular GCP training and hold Research Passports where appropriate. All of the research will meet the ethical requirements of the Research Governance Framework for Health and Social Care. Ethical and Research Governance approvals will be sought through REC and HRA approval at the outset with University Hospital Southampton NHS Trust as the lead centre and sponsor. Anonymity and confidentiality will be assured. Data will be stored in accordance with the current data protection regulations.

8.3 Peer review

An independent peer review of the HORIZONS Programme was carried out, facilitated by the Funder, Macmillan Cancer Support, in October 2013. The reviewers were external to the host institution and Funder and not involved in the Study in any way. Four national / international experts independently reviewed the proposal and comments were sent to the CI for response. All reviewers agreed the Programme fundable following modifications. The CI responded, in collaboration with the Co-applicants, to further successful peer review in November 2013.

8.4 Study Management arrangements and committees

The Study will be managed by the HORIZONS Coordinating Centre in the MSRG, University of Southampton, delegated this task by the Sponsor. Staff within the HORIZONS Coordinating Centre will be responsible for study design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results.

The Programme Director and members of the HORIZONS Coordinating Centre will engage with Macmillan partners on a regular basis through the design, delivery and dissemination of the research programme.

The Director of the HORIZONS Programme will have responsibility for delivery of the Programme. The research team in the HORIZONS Coordinating Centre, wider team of senior academics (including Co-applicants (PMG) and scientific advisors), SAB, TSEPs, DSP and URG includes lay experiences of cancer and professional expertise in psychosocial oncology, clinical oncology, social science, nursing, data management, statistics, epidemiology, health economics, demography and social geography. The HORIZONS Programme is included in the National Institute for Health Research (NIHR) CRN Portfolio, and we will provide monthly anonymised reports on study

accrual to the NIHR CRN office. We will also provide regular reports on study recruitment and progress to Macmillan and the relevant NCRI CSGs and the NCRI Consumer Forum.

Programme and trial managers will support the set up and delivery of the HORIZONS Programme supported by trial coordinators, data manager and administrative staff.

The Strategic Advisory Board (SAB)

The SAB acts as a mechanism to maximise the impact of the Macmillan HORIZONS Programme and to offer advice on its overall progress. The Board meets at least once annually and is chaired by Professor Dame Jessica Corner, membership includes senior clinicians, academics, Macmillan representatives and people affected by cancer as Research Partners. The SAB critically advises on the strategic direction of the HORIZONS Programme; how to develop our strategy to share knowledge, methodological approaches and data for greatest impact.

The Programme Management Group (PMG)

The CI and the PMG including Co-applicants and members of the HORIZONS Coordinating Centre will meet at frequent and regular intervals and oversee the conduct of the Study.

Tumour Specific Expert Panels (TSEPs)

TSEPs inform our methods and involve the disease specific NCRI CSGs. TSEPs include people affected by the cancer type (patient / consumer representatives), oncologists, surgeons, specalist nurses and researchers.

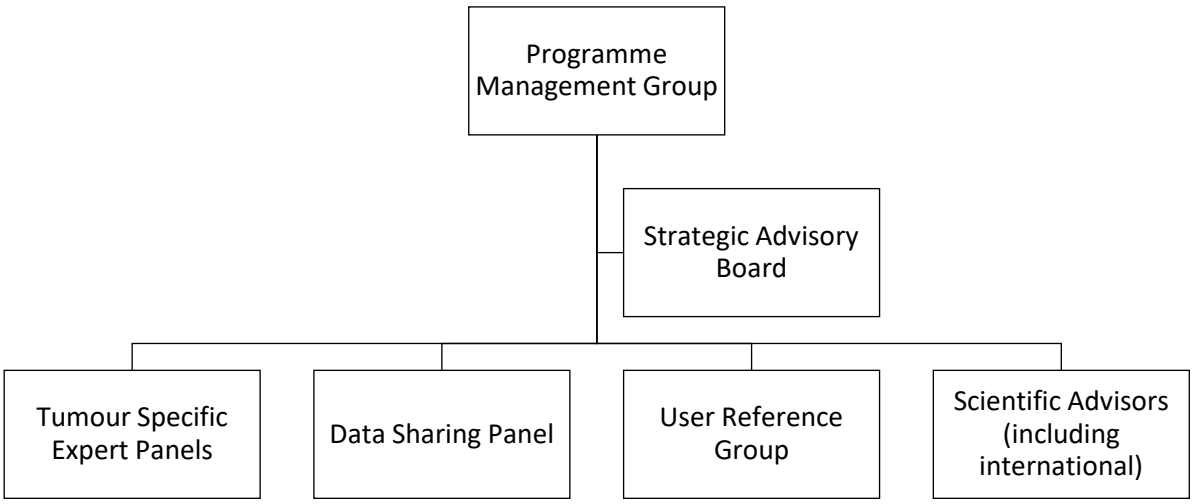
Data Sharing Panel (DSP)

A DSP will be established to to review requests to access study data from outside the HORIZONS Coordinating Centre and advise on data sharing protocols.

User Reference Group (URG)

A URG formed of people closely affected by cancer advises on all aspects of the Programme such as the way participants are recruited, updated and contacted within the HORIZONS Programme. The group also advises on study design, planning and contributes to, and reviews, study documentation and participant burden. We invite our URG members to attend events such as the programme launch, and they are supported by the HORIZONS team to contribute to the programme through means such as Knowledge Café event co-facilitation, data interpretation and paper writing.

Figure 3: Research management structure



Network involvement and participating centre engagement

NIHR portfolio adoption was granted for the HORIZONS Programme. The team will work closely with the CRN to identify suitable participating centres and recruit into the HORIZONS Programme[3].

From our current programme of work (CREW cohort (cohort of colorectal cancer patients 10/H0605/31) and Roy Castle Lung Cancer Foundation feasibility cohort studies (13/YH/0081 and 15/EM/0255), RESTORE (Online intervention to support people with cancer related fatigue 12/SC/0374)) we are aware that participating centre engagement is crucial to the success of large multi-site studies. We have developed excellent links with 45 research participating centres across the UK and have met or exceeded recruitment targets for our current research studies (CREW cohort (cohort of colorectal cancer patients 10/H0605/31) and Roy Castle Lung Cancer Foundation feasibility cohort studies (13/YH/0081 and 15/EM/0255), RESTORE (Online intervention to support people with cancer related fatigue 12/SC/0374) and YoDA BRCA (Genetic testing decision aid for young women 14/SW/1181)). Potential research participating centres will complete an expression of interest form and will be selected to participate on the basis of recruitment numbers and ability to recruit as per the protocol. We will build relationships and engage with the participating centres during set up.

As well as regular communications with the participating centres, we will hold engagement events funded by the Programme to bring together participating centres / research nurses and members of the URG to discuss the Study, identify and solve potential problems and foster a HORIZONS community. The first meeting will be at study initiation; then on an annual basis (unless more regular meetings are required e.g. to resolve recruitment challenges). One PI will be identified at each participating centre although there may be a number of research nurses and clinical team members involved in recruitment.

[3] This has worked well for the HORIZONS Coordinating Centre's (MSRG) CREW cohort study (colorectal) and RESTORE trial (mixed cancers).

8.5 Patient and Public Involvement

The HORIZONS Coordinating Centre research team has a long history of working closely with people living with and beyond cancer to design, develop and deliver research programmes and projects – our PPI Research Partners. We have worked with PPI Research Partners as Co-researchers, for example in the Macmillan Listening Study [1], and work alongside PPI Research Partners in our URGs and Knowledge Café events where we discuss, involve PPI Research Partners and engage the wider public in research ideas and on-going projects.

Involvement of PPI Research Partners and engagement with the wider public will benefit the HORIZONS Programme by enhancing the awareness, relevance and accessibility of the research. This will be achieved by working closely with PPI Research Partners in the HORIZONS URG to develop more effective ways of working. For example, in the design, development and delivery of the HORIZONS Programme alongside other stakeholders.

The URG advises on all aspects of the Programme such as the way participants are recruited, updated and contacted within the HORIZONS Programme. The group also advises on study design and participant burden and contributes to and reviews study documentation. We invite our URG members to attend events such as the Programme Launch, and they are supported by the HORIZONS' team to contribute to the Programme through means including Knowledge Café Event co-facilitation, data interpretation, paper writing and conference presentations.

We will hold Knowledge Café events in the community during the life of the Study to bring together the public and people living with and beyond cancer to support involvement, engagement as well as public awareness and understanding of the HORIZONS Programme. These events will be advertised using various media to ensure that we engage with and involve the public across the UK. We will proactively seek engagement with and involvment of those typically under-represented in research, e.g. younger and older people, black and minority ethnic groups and those with lower health literacy. The purpose of these events will be to critically examine and develop the research methods to broaden the reach of involvement and particiption in the HORIZONS Programme and contribute to the development of new grant applications.

PPI Research Partners will receive training as appropriate for their role within the HORIZONS Programme. This is likely to include Macmillan's *Building Research Partnerships* course designed for professionals and lay people to support PPI in research. PPI Research Partners will also receive programme specific training from the HORIZONS Programme team to support their involvement in the Programme. This will include training in chairing URG meetings. Research Partners will, following INVOLVE guidelines, be paid for their time and reimbursed their expenses (including travel, subsistence and carer costs) for attending meetings and undertaking other PPI activities.

8.6 Regulatory Compliance

Before any participating centre can enrol patients into the Study, the CI / or designee will ensure that confirmation of capacity and capability and agreement to the statement of activities is received from NHS Research and Development.

Substantial and non-substantial amendments will be submitted to HRA for approval with respect to regulatory compliance and will be managed in line with the HRA advice regarding handling of amendments with participating NHS centres.

8.7 Protocol compliance

Accidental protocol deviations will be documented on the relevant forms and reported to the CI and Sponsor immediately.

Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

Steps will be taken to ensure that questionnaires are sent out on time by tracking patients using appropriate software.

8.8 Data protection and patient confidentiality

All investigators and study participating centre staff must comply with the requirements of the current data protection regulations with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

The data will be handled in compliance with GCP guidelines and in accordance with current Data Protection regulations, following procedures as laid out by the Sponsor organisation (UHSFT). All data will remain confidential at all times.

Wherever possible, paper data will be anonymised and stored in locked filing cabinets in secure office premises at the University of Southampton. Only members of the HORIZONS Coordinating Centre will have access to these filing cabinets. Paper forms will be identifiable only by Study ID number. The register of participants' Study IDs and corresponding names and addresses will be stored securely and separately. Clinical and questionnaire data will be stored separately from patient identifiable data and securely stored in locked filing cabinets at the HORIZONS Coordinating Centre. The CI will be the data guardian and will keep a copy of all study documents, patient consent forms and any patient identification lists for ten years from the end of the Study (the HRA define this as the end of collection of all data required to answer the research questions in the protocol). All electronic data will be stored on a secure, password-protected University of Southampton database server, accessible only to the research team. All data will be anonymised prior to leaving the HORIZONS Coordinating Centre premises for data processing and / or statistical analysis. See section 8.12 regarding access to the final study dataset.

8.9 Data Quality

Staff at the HORIZONS Coordinating Centre will be responsible for overseeing the handling and management of all study data. Paper copies of questionnaires and other CRFs will be checked upon receipt at the offices of the HORIZONS Coordinating Centre and any discrepancies or missing data will be queried. Double data entry will be used if possible for entry of the data from paper questionnaires into electronic databases. Electronic data will be checked for accuracy in a random sample of questionnaires, as specified in a statistical monitoring plan.

Missing data

Active steps will be taken to minimise missing data. These will include:

- Obtaining full contact details.
- Reminders to patients via telephone calls, emails or letters.
- Checks with the clinical team to determine if the patient is alive or has changed address.

If questionnaires have not been returned within two weeks, the HORIZONS Coordinating Centre will contact the patient by telephone, email or postal reminder. A second questionnaire or reminder email will then be sent following a further two weeks. If no response to a second questionnaire the patient will not be approached again, until the subsequent annual follow-up questionnaire is due.

Measures to minimise bias

Selection:

- Patients will be identified through a systematic screening process.
- Patients' eligibility to participate will be assessed using a standardised procedure.
- Non-identifiable data regarding reasons for non-entry will be collected on those who choose not to participate.
- Non-identifiable socio-demographic data will be collected (with verbal consent / agreement) on those who choose not to participate in the Study.
- Anonymised data will also be collected for those who were 'missed' i.e. eligible but not invited to participate (e.g. due to logistical reasons).

Outcome measurement and analysis:

- All outcomes are self-rated.
- Strenuous efforts will be made to reduce missing data and maintain subjects in the cohorts, including checks to ensure patients have not moved or died, reminders or repeat questionnaires being mailed on non-response and telephone calls made for missing data.

8.10 Indemnity

UHSFT as Sponsor provides NHS to NHS indemnity. University Staff will be covered by the University of Southampton's Professional Indemnity and Clinical Trials Insurance for the conduct of the research.

8.11 Amendments

If the HORIZONS Coordinating Centre, with the agreement of the Sponsor, wishes to make a substantial amendment to the original application or the supporting documents, the HORIZONS Coordinating Centre will submit a valid notice of amendment to the REC for consideration. The HORIZONS Coordinating Centre will seek confirmation from the Sponsor on whether an amendment is substantial or non-substantial for the purposes of submission to the REC.

Amendments will be submitted in IRAS to the HRA, which will determine whether the amendment requires notification to English participating centres or may be implemented immediately (subject to REC approval were necessary). Amendment processes for participating centres in devolved nations will be followed. The HORIZONS Coordinating Centre will manage amendments in line with the HRA advice regarding participating NHS participating centres.

The amendment history is tracked in this protocol in Appendix 2.

8.12 Access to the final study dataset

The full study dataset will be available to research staff within the HORIZONS Coordinating Centre, including the statistician(s) who will be analysing the data. Participating centres will not have access to the complete dataset while the Study is ongoing and the main results are being analysed and reported. If the participating centres investigators or other researchers wish to access the Study data for the purposes of secondary data analysis then a formal request will need to be made to the HORIZONS Coordinating Centre for consideration. We will design and implement processes to ensure timely open access to the HORIZONS Programme data to a range of communities of research and practice, (e.g. through the ESRC UK data archive http://www.data-archive.ac.uk/). Strict regulations are in place to ensure appropriate use of such archived data. Patients will be asked to consent to the use of their anonymised data in future secondary analyses.

9 DISSEMINATION POLICY

9.1 Dissemination policy

An annual dissemination policy will be agreed with Macmillan (the Funder) to ensure timely dissemination of study findings to change practice and improve patient care. We will engage with our SAB, Macmillan and the University of Southampton to ensure maximum publicity and benefit. Findings will be widely disseminated through Macmillan, high impact publications, conference presentations and stakeholder events. We will make recommendations for where to target services and resources for cancer survivors. We will work with service users through our PPI events to disseminate study findings and discuss the progress of the Study.

We intend HORIZONS to be a high profile resource (e.g. website; regular news reports) and work closely with Macmillan, the University of Southampton and other avenues recommended by the SAB to maximise publicity and dissemination of study outputs. HORIZONS has a dedicated website www.HORIZONS-hub.org.uk.

9.2 Authorship eligibility guidelines and any intended use of professional writers

The MSRG supports the International Committee of Medical Journal Editors (ICMJE) guidelines for authorship, whose recommendation is that authorship be based on the following four criteria:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

The HORIZONS study will adhere to the MSRG publications policy with regards to authorship qualifications.

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11. APPENDICES

11.1 Appendix 1- Required documentation

The local documentation the HORIZONS Coordinating Centre require prior to initiating a participating centre:

- Agreed statement of activities, including agreement of schedule of event.
- CVs of the research team signed and dated, within 12 months.
- GCP certificates, within two years, of the research team.
- All patient facing documents on headed paper.
- Completed local delegation log.

11.2 Appendix 2 – Amendment History

Amendment no.	Protocol version no.	Amendment date	Author(s) of changes	Details of changes made
SA1	1.0	05/07/2016	Becci Petch and Joshua Turner	PIS v1.1 data transfer wording to cover HRA requirements Baseline questionnaires pilot phase submitted to REC
SA2	1.0	21/09/2016	Joshua Turner	3 month questionnaires submitted
SA3	2.0	21/12/2016	MSRG team	Administrative updates to reflect processes Inclusion/ exclusion
SA4	2.0	10/03/2017	MSRG Team	Addition of sites Baseline gynaecological questionnaire divided into the 3 sub groups 9 month questionnaire submitted
SA5	3.0	19/06/2017	MSRG team	Updates to remove reduced consent option and demographics forms for decliners Changes to the questionnaire time points (12 and 18 months) 12 month questionnaires submitted

SA6	4.0	27/11/2017	MSRG Team	Addition of the Vulval cancer sub-cohort (as part of the mixed Gynaecological cancer cohort) Baseline, 3 month and 12 month Vulval cancer sub-cohort questionnaires submitted Study team contacts updated General and specific exclusion criteria updated Patient Newsletter Issue #1 submitted
SA7	4.0	13/02/2018	MSRG team	18 month questionnaires submitted
SA8	4.0	08/06/2018	MSRG team	24 month questionnaires submitted
SA9	5.0 5.1	29/11/2018 21/01/2019	MSRG team MSRG team	Study team updates Removal of references to a short version of the HORIZONS questionnaires. Changes to patient facing documents which improve clarity Changes to reflect the introduction of the General Data Protection Regulations (GDPR) Removal of the NOMAD tool as a proposed questionnaire measure Change in the number of recruiting centres from 50 to 78 Addition of an Appendix containing the protocol for the qualitative phase of the HORIZONS study Addition of documents designed to boost retention of participants at follow-up points MODIFICATION OF AMENDMENT 9 Removal of HORIZONS Qualitative Decliner Form v1.0 12.09.2018 Removal of reference to use of a Decliner Form in supporting documents

SA10	5.1		MSRG Team	Annual Questionnaires submitted including the 36, 48 and 60 month follow ups Changes to the qualitative reply slip
SA11	6.0	10/10/2019	MSRG team	Study team updates Changes to the Data Monitoring Committee name and function Changes made to participant status check and sending of the follow-up questionnaires processes Changes made to processes in the event of no response Amendment made to follow-up questionnaire letter Amendment made to follow-up reminder letter Notice informing participant that their status was not confirmed prior to contact submitted Patient Newsletter Issue #2 submitted
SA12	6.1	11.03.2020	MSRG Team	Change of wording relating to using Public Health England (PHE) databases. The wording relates to a change in PHE policy not a change in study procedure.
SA13	7.0	23.07.2020	MSRG Team	Addition of a COVID-19 questionnaire insert Addition of an Appendix 7 containing the protocol for a qualitative COVID-19 sub-study

List details of all protocol amendments here whenever a new version of the protocol is produced.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee.

11.3 Appendix 3 - Proposed tumour-specific measures for each cohort

Domain	Areas of assessment	Breast	NHL	Gynaecological
Consequences of Cancer Diagnosis and Treatment	Symptoms, functioning, short and long-term adverse effects	EORTC QLQ-BR23	EORTC QLQ-NHL-HG29 (NHL high grade) and QLQ-NHL-LG20 (NHL low grade)	EORTC QLQ-CX24 (cervical), QLQ-EN24 (endometrial), QLQ-OV28 (ovarian), QLQ-V31 (vulval)
	Additional adverse effects not captured on EORTC tumour-specific modules, such as:	Neuropathy (use items from other tumour-specific modules)		
		Radiotherapy-specific adverse effects Sleep problems Fertility problems Urinary and bowel problems Osteoporosis		

11.4 Appendix 4 - Detailed inclusion/exclusion criteria for each cohort

Tumour Specific Inclusion and Exclusion Criteria

Breast

Inclusion:

- Women aged <50 years old
- Stage 1, 2 or 3 invasive breast cancer
- Have no distant metastases
- Patients due to undergo neoadjuvant treatment should be approached before this starts

For those whose core biopsy shows DCIS only but post-excision biopsy pathology confirms invasive cancer, approach should be made as soon as possible following diagnosis and completion of the baseline questionnaire should be prior to the start of adjuvant treatment.

Exclusion:

- Confirmed diagnosis of CIS (ductal or lobular) only
- Men

Non-Hodgkin Lymphoma

Inclusion:

- Any pathological diagnosis of Diffuse Large B Cell lymphoma (DLBCL) including;
    - Secondary transforming or transformed DLBCL which has transformed from an indolent/low grade lymphoma (most commonly Follicular Lymphoma) as long as the low grade lymphoma was not treated and this is a recent transformation for which curative intent treatment has not yet started.
    - Rare sub-types of DLBCL such as T cell rich Large B Cell Lymphoma and primary mediastinal (thymic) large B-cell lymphoma

Patients who have started steroid pre-phase treatment are eligible for approach before the start of chemotherapy.

Gynaecological cancers

ALL GYNAECOLOGICAL CANCERS

Gynaecological Cancer Exclusion criteria

Synchronous gynaecological primary cancers. For example, synchronous ovarian and endometrial primary cancers.

OVARIAN

Ovarian Inclusion criteria:

Have a confirmed diagnosis either from cytology, histology, imaging or diagnostic primary surgery of either;

- Epithelial ovarian cancer;
    - primary peritoneal cancer
    - fallopian tube cancer
- Ovarian carcinosarcoma
- Granulosa tumour of the ovary

Patients should be entered prior to any treatment including surgery. However, where the diagnosis is only made at the time of surgery, these women may enter the study following surgery. Approach should be made as soon as possible following diagnosis and completion of the baseline questionnaire should occur prior to the start of adjuvant treatment.

FIGO stage
Stage IA
Stage IB
Stage IC1
Stage IC2
Stage IC3
Stage IIA
Stage IIB
Stage IIIA1

Ovarian Exclusion criteria:

- Borderline ovarian cancer
- Germ cell tumour
- Sarcoma

ENDOMETRIAL

Endometrial Inclusion criteria:

Have a confirmed diagnosis either from cytology, histology or imaging of;

- endometrial cancer
- endometrial carcinosarcoma

  Patients should be entered prior to any treatment including surgery. However, where the diagnosis is only made at the time of surgery, these women may enter the study following surgery. Approach should be made as soon as possible following diagnosis and completion of the baseline questionnaire should occur prior to the start of adjuvant treatment.

FIGO stage
Stage IA
Stage IB
Stage II
Stage IIIA
Stage IIIB
Stage IIIC1
Stage IIIC2

Endometrial Exclusion criteria

- Choriocarcinoma
- Germ cell tumour
- Sarcoma

CERVICAL

Cervical Inclusion criteria:

Have a confirmed diagnosis either from cytology, histology or imaging of;

- Cervical cancer

FIGO stage
Stage IA2
Stage IB1
Stage IB2
Stage IIA1
Stage IIA2
Stage IIB
Stage IIIA
Stage IIIB

Cervical Exclusion criteria:

- FIGO stage IA1
- Cervical carcinoma in situ (CIS)
- Sarcoma
- Small cell cancer of the cervix

VULVAL

Vulval Inclusion criteria:

Have a confirmed diagnosis either from clinical assessment, cytology, histology, imaging of;

- Vulval cancer

FIGO stage
Stage IA
Stage IB
Stage II
Stage IIIA
Stage IIIB
Stage IIIC

Vulval Exclusion criteria:

- Basal cell carcinoma
- Melanoma
- Sarcoma
- Vulval intra-epithelial neoplasia (VIN)

11.5 Appendix 5 – protocol for HORIZONS qualitative work

1 Background

As length of survival following treatment is increasing, a growing number of people are living with cancer as a long term condition. However, cancer survivors are often left with symptoms, side effects and psychological consequences of their treatment which can impact on their daily lives and which may require support (1).

The Macmillan HORIZONS Programme at the University of Southampton is established to improve the lives of people affected by cancer by building a depth understanding of the cancer survivorship population. The Programme addresses the linked themes of recovery of health and wellbeing following cancer treatment and self-management of the consequences of treatment. The Programme assumes that recovery from cancer treatment takes time and support, and that a key element in the process of recovery is access to and utilisation of healthcare, social care and networks of support.

To date, the HORIZONS Programme has established a longitudinal cohort study of people with Non-Hodgkin's Lymphoma (NHL), young women with breast cancer and women with gynaecological cancers. Alongside this, the Programme will conduct qualitative work to investigate an aspect of self-management and recovery in more depth. This appendix describes this qualitative work, which addresses one of three HORIZONS research questions: How do people connect with and mobilise resources which enable them to self-manage consequences of cancer and its treatment? The work is located within the conceptual framework developed for the HORIZONS Programme.

2 Rationale

There is growing emphasis on the role of patient self-management, both during cancer treatment and into the post-treatment phase (2). In the United Kingdom, care for those who have completed primary treatment has shifted in recent years from a clinically led approach to supported self-management, with the aim of empowering individuals to take responsibility for their condition alongside appropriate clinical assessment, support and treatment (3). The nature and duration of follow-up care is decided through individual assessment of various factors such as risk of recurrence, degree of resolution of consequences of the cancer and its treatment, and patient preference (3).

Self-management, in essence, involves the transfer of tasks from the healthcare service to the patient and their social network (4). For cancer survivors, these tasks will likely include arranging and undergoing tests and investigations for disease surveillance, self-monitoring for signs of recurrence in-between times, finding ways to improve quality of life in the context of residual symptoms, actions to manage and/or minimise long term consequences of treatment, improving lifestyle to reduce chances of recurrence, and knowing when and where to seek support (5, 6). In addition, self-management and recovery of health and well-being might entail dealing with uncertainty and rebuilding confidence (7).

A transition from treatment to self-management focussed follow-up care involves a change in expectations of patient interactions with health care services, with a reduction in contact with specialist services and an expectation that a person will seek help and support from healthcare services and wider community resources when needed and as appropriate (4). Health Education England's Workforce Planning for 2014-2029 designates "patients as 'members of a community of health', where qualified/paid staff may be one of, rather than the sole source of, advice and support

to a person" (8). A reduction in scheduled contact with services can result in feelings of abandonment for the individual (9).

There are a range of supportive services and resources available to cancer survivors, in addition to formal healthcare services, including provision by charity providers, community resources and online resources. However, some people may struggle to access such supportive services and resources and this may impact on self-management ability and recovery (7). Poorer health related quality of life is associated with low levels of social support (10).

There is recognition that self-management draws on a range of skills and abilities, including those required to identify, connect, and engage with self-management resources. Resource utilisation and formation of a patient/health care provider partnership are recognised as core self-management skills (11). People's skills and abilities will, however, vary, and people will engage with supportive services and resources to a greater or lesser degree (4).

We know relatively little about the process of supportive resource use among cancer survivors (12). Quantitative studies among people with various cancers suggest that awareness and use of available services is low (13, 14), that use often results from referral rather than being sought out by an individual (14), and that those most in need may be the least likely to seek support (13). Qualitative accounts have added to understanding of the barriers to resource use, including lack of awareness (15), problems with access (15, 16), mental images of the services (15), personal barriers, such as being too busy returning to normal and feeling a lack of entitlement once treatment is finished (16), and the context of everyday lives (16).

Given the long-term consequences of cancer treatment and the increasing emphasis on self-management throughout the cancer trajectory, it is important we understand in more detail the processes of seeking and utilising supportive services and resources, the value and importance of these for cancer survivors, the challenges of getting the right support at the right time, and the interaction of these resources with formal health care services. Improvements in provision and accessibility of services and resources are likely to impact on recovery of health and wellbeing.

This qualitative element of the HORIZONS programme will take this forward, focussing on the post-treatment phase, when formal, scheduled support lessens and expectations of self–management increase. The work will consider use of a wide range of supportive services and resources, including informal health care, community resources, online resources, self-help resources and groups. The study will not focus on personal social networks as sources of support, as these are being studied within the cohort study, but the role of personal social networks in helping to access and use supportive services and resources will be included.

3 Theoretical framework

The qualitative element will locate self-management tasks within the HORIZONS framework of recovery of health and wellbeing, informed by Foster and Fenlon's conceptual model (7), in order to sensitise the research to the types of challenges people might face and need help or support to manage.

Engagement and utilisation of supportive services and resources involves effort on the part of the cancer survivor and their social network. The effort involved in managing illness was originally defined within Strauss and Corbin's illness trajectory model as 'work' (17-19). The model offers three types of work: 'illness work', 'everyday work' and 'biographical work' (19). The model has been recently adapted for the work of transitional cancer survivorship (6), which remains substantial after

primary treatment has finished and includes adherence to secondary and adjuvant therapies, dealing with treatment related symptoms and late effects of treatment, continued adherence to surveillance, coming to terms with the implications of cancer and survivorship, and managing uncertainty. Other authors have offered understanding of different types of work involved in chronic illness management, including: contingency/improvisation work, translation/mediation work, coordination work, advocacy work, emotional work (20), information work (21), biographical work (22) and communication work (23). Burden of treatment theory (4) furthers this by indicating how people's capacity for action interacts with the work they must undertake and with their utilisation of health services. The theory delineates the qualities of social skill, social capital and structural resilience, which patients and their relational network must possess if they are to exploit health care opportunities.

These theoretical approaches help to sensitise the current study to these different categories of work and to the influences on the capacity of individuals to undertake that work. Drawing on these bodies of work, it is anticipated that: i) there is an interaction of cognitive, emotional, relational and behavioural work within the process of engagement and utilisation of supportive services and resources; ii) that people's capacity to undertake the work varies, and iii) the work is undertaken within the interrelated contexts of beliefs, understandings and norms about recovery of health and wellbeing after cancer treatment and about the use of services, and within the context of an individual's everyday life

4 Aims and objectives

4.1 Aims

The HORIZONS qualitative work will address the third of the HORIZONS key research questions. It will seek to understand, characterise and explain how people connect with and mobilise supportive services and resources to help them to self-manage the consequences of cancer and its treatment and to promote recovery of health and wellbeing.

4.2 Objectives

i. To understand the work involved for cancer survivors and their supportive others in the process of seeking and utilising supportive services and resources for self-management and recovery of health and wellbeing post cancer treatment.
ii. To characterise influences on cancer survivors' capacity to seek and utilise supportive services and resources for self-management.
iii. To provide a theoretical explanation of how cancer survivors connect with and mobilise supportive services and resources to support self-management and recovery, and how this has implications for their use of formal health care services.
iv. To provide recommendations for improving the relevance and accessibility of supportive services and resources for cancer survivors.

5 Design and methods

5.1 Design

This work will elicit greater understanding of cancer survivors' experiences of seeking resources and support for post-treatment self-management and recovery. The study uses qualitative methodology to offer participants opportunity to give detailed accounts of their experiences and understanding of seeking supportive services and resources for self-management and recovery.

5.2 Study setting

The HORIZONS cohort study is currently recruiting people diagnosed with cancer amenable to treatment with curative intent (people with NHL, women with gynaecological cancers and young women with breast cancer) from around 70 participating centres across the United Kingdom. The cohort is recruited at diagnosis and followed up at regular intervals. The anticipated sample size is 3,000 participants. Participants for the qualitative work will be drawn from cohort study participants who have indicated through the consent process that they would be happy to be contacted about other research.

5.3 Eligibility

People will be eligible for the study if:

- they are cohort study participants who have given consent to be contacted about other studies and are still participating in the HORIZONS cohort study
- they are between 12 and 18 months beyond the end of their primary treatment
- and they are not having second line treatment nor have had a relapse or recurrence

End of primary treatment is defined as follows:

- for NHL patients: the first out-patient appointment following completion of chemotherapy or radiotherapy
- for breast cancer patients: after completion of primary treatment (surgery, chemotherapy or radiotherapy)
- for gynaecological cancer patients: completion of surgery or completion of adjuvant radiotherapy/chemotherapy

5.4 Sampling

Patients in the HORIZONS cohort study are asked as part of the consent process to the study whether they are happy to be approached about other related studies. The sample for the qualitative element will be drawn from those who have given a positive response to this. Because of the practicalities and resource issues of conducting face-to-face interviews, we will restrict selection to patients from sites in England and Wales, and to sites clustered within a small number of geographical areas, while ensuring diversity of rural and urban areas and socio-economic factors. The cohort study collects clinical data for each participant from the study sites at 6 months and 12 months post baseline, using a Case Report Form (CRF). These data include start and end dates of any treatment. We will use the CRF data to identify people who have finished their primary treatment in the 12 to 18 months prior to their interview.

We will identify all those who are eligible at the selected sites and will then draw the sample using purposive sampling, selecting participants according to a number of variables known to influence self-management: gender, socio-economic status (SES), age, density of social network and self-efficacy. Selection of those to be approached for interview from those eligible will be random. Qualitative studies have small samples and a sample of up to 32 interviews is felt to be adequate for this study to cover a range of variables and to give an in-depth understanding.

5.5 Recruitment

Prior to contacting the potential respondent, we will check with staff at the hospital that they have not had a recurrence or relapse, whether there is any other reason they should not be contacted, and to check that their address is correct.

If it is okay to make contact, potential participants will be sent a letter of invitation, participant information sheet, reply sheet and a pre-paid envelope. They will be asked to return the reply slip to

the university if they are interested in taking part in an interview. Those who return a reply slip will be contacted by telephone/email to arrange a suitable date and to confirm the place of interview. At this point, a check will again be made that they are not having any further primary treatment.

If no response has been received after three weeks, a second interview pack will be sent. After that, no further contact will be made.

5.6 Data collection

Data will be collected by in-depth interviews at one point in time, when participants are between 12 and 18 months post end of treatment. Participants will be offered a face-to-face interview at their home or another place of their choosing.

To aid recall of use of supportive services and resources, participants will be invited, in advance of the interview, to complete a network visualisation exercise known as the egocentric sociogram (24), to map past and present supportive service and resource contacts (see example figure below). This type of approach is commonly used in social network analysis and increasingly in combination with qualitative interviews (24). The sociogram consists of concentric circles and participants are asked to indicate their contacts within those circles, with closeness to the centre indicating importance.

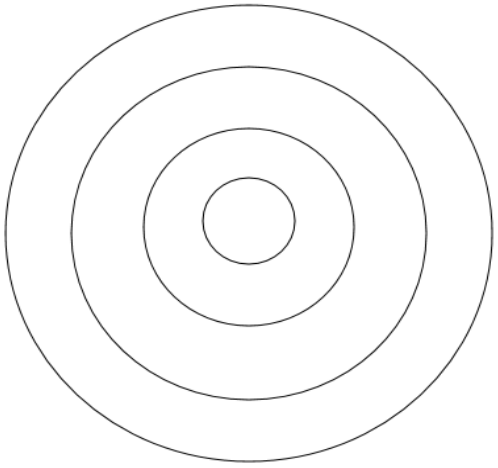

Figure 1: example of a sociogram template

A sociogram is often constructed during an interview, through dialogue between interviewer and participant. In this study, to aid recall and because much of self-management is undertaken by the individual along with members of their social network (20) , participants will be invited to complete this in advance of the interview, with the assistance of family and friends if helpful. The egocentric sociogram template along with instructions for its completion will be introduced to the participant during the telephone call to arrange the interview, and a copy will be sent by post/email at that point. Interviewees will be invited to plot any supportive services or resources they have used since their treatment finished, following the criteria that the more important or helpful they were to them, the closer to the centre of the circles they are placed.

The interview will last no longer than 2 hours. It will follow an open-ended interview schedule and will be structured around the information provided in the sociogram. This type of combined approach has been successfully used in the study of social networks, facilitates the process of remembering resource contacts and the context in which they occur (25) and allows for understanding of the meaning of the supportive services and resources within the person's overall network (26). The interviews will focus on the meaning of the supportive service or resource to the interviewee, the process of making contact and engaging with the service or resource, and any constraints to the process. Should the

participant choose not to complete the sociogram in advance of the interview, this process will be undertaken at the beginning of the interview.

A draft interview schedule is included in appendix 11.6. In order to provide a background to the use of supportive services and resources, the interviewer will ask the interviewee to describe any cancer related problems or issues they have had since their diagnosis. The interviewer will ask them to describe their completion of the sociogram (e.g. did anyone help them) and then to talk about the supportive services and resources they have added, starting from wherever they like. The interviewer will also have a list of questions to use as the participant talks, in order to explore use of services and resources in depth.

The study will be led and managed on a day to day basis by a senior researcher who has considerable experience of conducting interviews and interviewing about sensitive and emotional issues. Interviews may also be conducted by other named members of the HORIZONS team. Training and support will be provided to less experienced interviewers, and all interviewers will be provided with support via debriefing. The University of Southampton's risk assessment and lone worker policies and procedures will be followed.

At the start of the interview, the participant will be given the opportunity to ask any questions about the study. If happy, they will then be asked to sign a consent form. Participants will be told that they can stop the interview at any point, without giving a reason. If this happens, the interviewer will discuss with the participant whether they are happy for the data that have been collected to be included in the study, explaining briefly the reasons why this would benefit the study.

Cancer survivors may have enduring emotional and psychological issues. Some may find being asked to revisit their cancer experience upsetting. Should the participant become upset, the researcher will ask if they would like to take a break and, when they have recovered, whether they wish to continue.

Should the participant raise any questions about their cancer, treatment or current health, they will be advised to contact a health professional as appropriate. Details of community based supportive services and resources will be offered by the interviewer at the end of the interview as appropriate.

5.7 Consent

Consent for the interview will be taken immediately before the start of the interview. Two copies of the consent form will be completed, with one copy being kept by the research team and the other copy given to the interviewee.

Participants will be asked to consent separately (i.e. for all or some of the following) as they wish:

- to take part in the study
- for the interview to be audio recorded
- for direct quotes to be used
- for questionnaire and CRF data to be used to describe the participant
- for use of the data for secondary analysis
- to be contacted about further work related to the study

It will be made clear to cohort study participants that participation in the study is entirely voluntary and declining to take part will not affect the NHS medical care that they receive. The right of patients to refuse to participate in the study without giving reasons will be respected. Similarly, patients will remain free to withdraw from the study at any time without giving reasons and without prejudicing

their future care. Participants will be asked at the end of the interview whether they are still happy to consent to the study.

5.8 Ethical considerations

People with a recent cancer diagnosis are at a vulnerable time in their lives. The research team has significant experience of working with people who have cancer, and have conducted other qualitative studies successfully.

5.9 Data protection and patient confidentiality

The study will comply with current data protection regulations, and follow University of Southampton guidance. The data will be handled in compliance with Good Clinical Practice (GCP) guidelines and all interviewers will be trained in GCP.

All data will remain confidential at all times.

- Audio recorders will be password protected. Audio files will be downloaded to the University network as soon as possible after completion of the interview, and the file deleted from the recorder.
- Audio files will be transcribed by University approved transcribers who have signed a confidentiality agreement. Audio files and the resultant transcriptions will be sent to transcribers and returned via the secure University drop off system.
- Interview transcripts will contain a study ID number rather than the respondent's name. Should the respondent mention a person or organisation by name, these will be removed and a descriptor (e.g. 'participant's husband'; 'name of hospital') added instead.
- Audio files will be destroyed once transcripts have been verified.
- Any paper copies of transcripts will be stored in a locked cabinet in secure entry offices at the University of Southampton. Electronic copies will be stored on the University of Southampton server with password protection. Interview audio files and transcripts will be stored separately from the participant's contact information.
- Study data will be kept for 10 years from the end of the study, in accordance with University of Southampton policy.

6 Analysis

The main source of data for the analysis will be the in-depth interview. The sociogram will be used to summarise the number of supportive services and resources reported by each of the participants. HORIZONS questionnaire data and CRF data will be accessed, with participant consent, in order to describe the clinical and socio-demographic characteristics of the sample.

Each audio transcription will be transcribed verbatim and the transcript checked against the recording. Transcripts will be anonymised at this point. Data will be uploaded to the NVivo qualitative analysis package for data management.

A thematic approach to analysis will be used (27). The analysis will take a team approach to development and refinement of the coding frame and to advance tentative explanations (28). A small number of interviews will be selected for preliminary analysis by at least two researchers. The transcripts will be read several times by the researchers to gain familiarity and to identify important ideas and patterns in the data. In undertaking this process, the researchers will be sensitised to the theoretical frameworks mentioned above, though will not be constrained by these and will be looking for other ideas outside of these frameworks. Each researcher will independently mark up the

transcript with emerging codes. The researchers will then meet in order to discuss and agree the coding.

Agreed concepts or ideas will form the coding frame that will then be applied to the interviews through line by line coding, possibly by several different researchers. Where several researchers are working on the analysis, the reliability of the individual coders will be established by comparing coding over a small number of transcripts. As coding progresses, any new codes will be agreed by the team and then applied to all transcripts.

Analysis will involve the constant comparison of data within and across transcripts, with close attention to deviant cases. Regular team meetings, which will include people from a range of disciplines (for example, sociology, psychology, nursing) and people with experience of cancer, will be held to discuss and interpret emerging themes and findings.

7 Ethics review and governance

The protocol for the qualitative work will be submitted to the North West – Lancaster Research Ethics Committee (REC) as a substantial amendment to the HORIZONS cohort study (ref 16/NW/0425), as agreed through review of the HORIZONS protocol. Research Governance approvals will be sought through the HRA. The University Hospital Southampton NHS Trust is acting as sponsor.

8 Management and oversight

This plan for the qualitative element of the HORIZONS study has been reviewed by members of the Project Management (PMG) and User Reference Groups (URG) for the HORIZONS study.

9 PPI involvement

The work will be conducted in close collaboration with the HORIZONS URG. Members have been involved in discussion of the focus of the research and have commented on the protocol. Members of the group will be invited to work closely with the team, for instance in reviewing and assessing study paperwork and in piloting of interviews, in discussing themes in the data and commenting on results and conclusions. Implications of the research and how to take them forward will be discussed.

The HORIZONS Tumour Specific Expert panels (TSEPs), which include members who are cancer survivors, will also be consulted regarding any tumour specific issues.

10 Time plan

Activity	**Year 1**	**Year 2**	**Year 3**
	Mar 18 – Dec 18	Jan 19 – Dec 19	Jan 2020– Aug 2020
Draft protocol amendment and study documents			
Respond to comments on protocol amendment from PMG and URG			
Ethics and governance approvals			
Select sample			
Interviewing			
Transcription of interviews and verification of transcripts			
Data analysis			

PPI consultation exercise												
Write up and dissemination of findings												
Planning next steps in light of findings												
Strategic advisory board meetings				X				X				X
Programme Management meetings	X	X	X	X	X	X	X	X	X	X	X	X
User reference group meetings				x		x		x	x			x

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11.6 Appendix 6 – interview schedule for HORIZONS qualitative work

Interview schedule

This interview schedule is intended as a guide and offers broad questions to be covered along with suggested ways of asking. The exact way questions are asked may differ in order to explore and probe the individuals' experience

Consent

1. Information sheet – check they have read it and understand it
2. Reinforce: you can ask me to stop at any time, confidentiality
3. Sign consent form and leave them with a signed copy to keep
4. Start recorder and check it's recording

Introduction

We want to talk about any supportive services or resources you have used since you completed your main cancer treatment, and the work or effort that you put in to accessing and using these. If you have not used any supportive services or resources, we will talk about your views and why that is. We asked you to complete the circle exercise, if you were able to do this we will talk about it during the interview.

Background information

- **Before we do that, could you start by telling me how you have been since your main treatment finished?**
  - *When was this?*
  - *Probe any problems or issues: physical, psychological, social, financial, work, any other*

- **And could you tell me about the contact you have had with the hospital where you had your treatment since your main treatment finished?**

- **If consent is not given by this interviewee to access HORIZONS questionnaire and medical record data then ascertain the following about the patient**

  - Sociodemographic details: age, employment status, marital status, living arrangements, ethnicity, highest educational qualification
  - Medical characteristics: type of cancer, date of diagnosis, treatment received, date of end of main treatment, any adjuvant treatment(s).

Sociogram

Could we now look at the circle diagram and talk about the supportive services/resources you have put on it. First check they are all supportive service/resources used since they finished their main treatment.

Completing the circle diagram

a) Did anyone help you to complete the circle diagram?
b) Was contact with any of the supportive service/resources made before you finished your main treatment? Which ones?
c) Was contact with any of the supportive service/resources made since you finished your main treatment? Which ones?
d) If no supportive service/resources are listed – talk this through with the person to check this is correct, then move to the next section

IF THE INTERVIEWEE HAS USED ANY SUPPORTIVE SERVICES/RESOURCES, ask them to talk about each, starting wherever they like. For each service/resource, cover the following stages of using. The emphasis of the interview should be on the work or effort that they needed to put in to achieve the support they seek. The interviewer will ask: what was their experience of each stage, what did they need to do, how did each stage go, what challenges did they face, how did they feel about it:

- Details of the supportive service/resource
  - Description of what the supportive service/resource was
- Deciding to seek support
  - What issue was it that made you decide to seek help from that supportive service/resource
  - Why decided to use that particular service/resource
  - When was contact with the supportive service/resource made?
- Finding out where to access supportive service/resource:
  - What hoped to get from it?
  - How did you go about finding out about it?
- Making contact
- Using the supportive service/resource
  - How did that go?
- Evaluating the supportive service/resource
  - How did you find using the supportive service/resource?
  - Did you get what you hoped from it?
  - What were the challenges in accessing this supportive service/resource?
  - Is it ongoing, or when and why finished?
- Did you have any problems or issues for which you did not seek help or support?
  - Would you have liked any help or support for this problem or issue?
  - If so, what stopped you from finding help or support?
  - What might have helped you to seek help or support?
  - How did you feel about seeking help and support for this issue?

IF THE INTERVIEWEE HAS NOT USED ANY SUPPORTIVE SERVICES/RESOURCES, talk through any problems or issues they have reported to the interviewer, asking:

- Would you have liked any help or support for this problem or issue?
- Did you try to find any help or support for this problem; how did you go about this?
- What happened?
- What stopped you from finding help or support?
- What might have helped you to seek help or support?
- How do you feel about seeking help and support for this issue?

Evaluation of support overall

- How did you find seeking out and using help overall?
- Was there anything that you would have liked (more) support with but didn't get? Why not?

Evaluation in relation to NHS care

Ask person to add to their circle diagram if not included, in relation to how important they have been:

- *Contact with specialist cancer care*
- *Contact with GP*
- *Contact with any other NHS services*

Ask about how they have accessed them and their experience and how these services relate to their other supportive service/resource use.

Ending the interview

- Is there anything else that I haven't asked you about in relation to accessing supportive services/resources which is important?

Interview close

- recheck consent
- give thanks
- what happens now
- any questions

11.7 Appendix 7 – protocol HORIZONS COVID-19 qualitative study: Understanding experiences of the COVID-19 pandemic on the care and support of people who have completed treatment for cancer

Background

COVID-19 has the potential to disproportionally affect the lives of people living with and beyond cancer (LWBC), including those who have completed treatment and those who are living cancer free (1). As lockdown in the UK is beginning to ease and cancer care services and wider supportive services are moving to the next phase of response, including restarting services, it is important to include the voice of people LWBC in terms of understanding the impact of COVID-19 on them, their continuing challenges and support needs, and experiences of the rapid changes to their clinical and supportive care that were necessitated by the pandemic.

People treated for some cancer types (e.g. lymphomas) and with some long-term effects of treatment (e.g. immunosuppression) are at increased risk and have been advised to shield. Shielding leads to reliance on others for errands outside of the home; loss of access to usual face-to-face supportive resources, such as support groups; restrictions to usual support from personal social networks; and potentially to increased anxiety, isolation and/or depression. As shielding measures continue beyond the initial 12 weeks and as they begin to be eased, it is important to understand in detail the experiences, challenges and concerns of this group and their supportive needs.

As well as those who are shielding, there are potential disruptions and concerns that could impact the whole of the LWBC group and which may lead to new/increased supportive care needs. Psychosocial issues such as depression, anxiety, low confidence to manage health and limited social support can affect cancer patients' wellbeing following treatment, and such associates to wellbeing may be worsened by the impacts and uncertainties of the pandemic. Some people LWBC have unique health anxieties related to their cancer experience which may be exacerbated by the additional threat of COVID-19; for others, the impact of social distancing measures on their usual forms of support may be a significant challenge (1).

In addition, those who are beyond their cancer treatment are likely to have experienced changes to their follow-up care during the pandemic. Services have had to rapidly change their delivery, to release capacity for treating COVID-19 patients (2) and to protect patients from possible infection. Much attention has been on changes to screening and treatment for cancer (2), but post treatment follow-up care has also had to be rapidly remodelled in order to keep patients safe. Service delivery changes have been focussed on limiting face-to-face appointments: postponement of appointments and surveillance imaging/physical examinations and a move to remote (telephone or online) appointments (3). While remote methods of follow up are becoming the norm for a few cancer types (such as breast and prostate cancer), as a way to address both service capacity issues and patient need (4), they are not common across all cancer types. This is therefore an important opportunity to understand the experiences of services changed in this way, which may be positive for some but challenging for others, as an opportunity to inform and develop remote follow-up care across cancer types going forward.

The Macmillan Survivorship Research Group (MSRG) at the University of Southampton has an ongoing cohort of more than 3,000 people diagnosed with cancer amenable to treatment with curative intent (people with NHL, women with gynaecological cancers and young women with breast

cancer) recruited from around 110 participating centres across the United Kingdom. The cohort was recruited at diagnosis and is followed up at regular intervals. Most participants are currently around 18-24 months post treatment. The qualitative sub-study described here allows for understanding of experiences of the COVID-19 pandemic to be sought.

Aim

The HORIZONS cohort study of people living with breast cancer (under 50-years-old), Non-Hodgkin Lymphoma, and gynaecological cancers offers an important opportunity to understand experiences and needs resulting from the pandemic for a diverse group of people LWBC.

This qualitative sub-study aims to:

i) understand the impact of COVID-19 on the supportive care needs of people LWBC including those who are/have been shielding;
ii) elicit patient experiences of changes to post-treatment follow-up care;
iii) provide feedback to cancer care services and other supportive services, to inform the development of services going forward.

This will provide an opportunity to feed the patient voice into the restarting/development of health care and supportive services going forward.

Design and methods

Design

The study will use qualitative methods to offer participants an opportunity to give detailed accounts of their experiences.

Study setting

Participants for the current study will be drawn from HORIZONS cohort study participants. **Eligibility**

People will be eligible for the study if they are cohort study participants who have given consent to be contacted about other studies and are still participating in the HORIZONS cohort study.

Sampling

A sample of up to 60 people will be sought.

Purposive sampling will be used to select participants according to variables potentially related to their experiences of COVID-19, which are likely to include

a. cancer type
b. sex (NHL)
c. ethnicity
d. area of UK
e. household status (lives alone/with someone)
f. people who were shielding
g. those with caring responsibilities
h. people who experienced changes to follow-up care

Recruitment

Potential participants will be selected from cohort participants who have indicated through the questionnaire consent process that they would be happy to be contacted about related research. We will also advertise the study to HORIZONS participants in a number of ways, such as using flyers, newsletters, social media and websites (see text for this purpose in appendix 11.7.2)

Prior to sending an invitation for interview to the former, the participants' clinical team will be contacted to request confirmation that the participant is alive and the participants' address has not changed. If the clinical team are unable to confirm and all reasonable efforts to acquire this information in a timely fashion have been explored (e.g. GP contact, other hospital sites), the invitation will be sent with a notice informing the participant that their status was not confirmed prior to contact.

Potential participants will be sent an invitation pack either by post (where there is access to University office facilities – this will be on University approval and following a risk assessment process) or by email (should office access not be possible). The former is our preference as we do not have email addresses for all cohort members.

The invitation pack will contain a letter of invitation, participant information sheet, and a consent form (with pre-paid envelope for return if sent by post). Participants will be asked to return the consent form if they are interested in taking part in an interview. They will be able to do this in a number of ways:

1. to return the signed consent form by post in the pre-paid envelope provided
2. in case it is not possible to return documents by post, participants will be given an email/telephone number which they can use to indicate their interest in taking part in the study. Those who contact by email or telephone will be asked to provide consent by one of the following methods:
    a. to sign and scan the consent form and return via the University of Southampton SafeSend system (which incorporates in-transit and at-rest encryption)
    b. to fill it in electronically (by typing in their responses and full name) and return it to the research team at the University of Southampton via SafeSend
    c. an audio recording of consent will be taken at the beginning of the interview. Consent will be recorded separately to the interview recording (two separate recordings).

If no response has been received after three weeks, a second interview pack will be sent. After that, no further contact will be made. Once consent to take part has been received, the person will be contacted by telephone/email to arrange a suitable date and to confirm arrangements for the interview.

Data collection

Data will be collected by semi-structured telephone interviews (see interview schedule in appendix 11.7.1) at one point in time. The interview will last no longer than 1 hour and will be **audio** recorded. The interviews will be conducted by researchers employed by the University of Southampton, either from home, or from the office at UoS .

At the start of the interview, the participant will be given the opportunity to ask any questions about the study. If happy, they will be taken through their consent form to re-confirm that they are still happy to take part (this will be recorded at the start of the interview, as a separate recording).

Participants will be told that they can stop the interview at any point, without giving a reason. If this happens, the interviewer will discuss with the participant whether they are happy for the data that have been collected to be included in the study, explaining briefly the reasons why this would benefit the study. People LWBC may have emotional and psychological issues from their experience of cancer and from living through COVID-19. Should the participant become upset, the researcher will ask if they would like to take a break and, when they have recovered, whether they wish to continue. Should the participant raise any questions about their cancer, treatment or current health, they will be advised to contact a health professional as appropriate. Details of community based supportive services and resources will be offered by the interviewer (to be sent by post or email) at the end of the interview as appropriate.

Consent

As interviews will be conducted by telephone, written consent will be sought at point of recruitment (as described in recruitment section above). Consent will be re-affirmed at the start of the interview, by taking the participant through the consent form verbally. The participant will be sent a copy of their signed consent form.

Participants will be asked to consent separately (i.e. for all or some of the following) as they wish:

- to take part in the study
- for the interview to be **audio** recorded
- for anonymised direct quotes to be used
- for use of the data for secondary analysis
- to be contacted about further work related to the study

It will be made clear to study participants that participation in the study is entirely voluntary and declining to take part will not affect the NHS medical care that they receive. The right of patients to refuse to participate in the study without giving reasons will be respected. Similarly, patients will remain free to withdraw from the study at any time without giving reasons and without prejudicing their future care. Participants will be asked at the end of the interview whether they are still happy to consent to the study.

Ethical considerations

People with a recent cancer diagnosis are at a vulnerable time in their lives. The research team has significant experience of working with people who have cancer and have conducted other qualitative studies successfully. If the participant raises any specific health queries they will be advised to

contact a relevant Health Care Professional. Participants will be given details of other sources of information, advice and support (such as Macmillan Cancer Support) as appropriate.

Study management

The study will be led and managed on a day to day basis by a senior researcher who has considerable experience of conducting interviews and interviewing about sensitive and emotional issues. Interviews will be conducted by members of the HORIZONS team. Training and support will be provided to less experienced interviewers, and all interviewers will be provided with support via debriefing.

The study plan and interview schedule have been reviewed by members of the Project Management (PMG) and User Reference (URG) Groups for the HORIZONS study.

Data protection and confidentiality

The study will comply with current data protection regulations and follow University of Southampton guidance. The data will be handled in compliance with Good Clinical Practice (GCP) guidelines and all interviewers will be trained in GCP.

All data will remain confidential at all times.

- Audio files will be uploaded to the University network as soon as possible after completion of the interview, and the file deleted from the recorder. Electronic copies will be stored on the University of Southampton server with password protection. Audio files will contain a study ID number rather than the respondent's name.

- Audio recordings will be transcribed by University approved transcribers who have signed a confidentiality agreement. Audio files and resultant transcripts will be sent to and returned by transcribers using the secure University online drop off system. Interview transcripts will contain a study ID number rather than the respondent's name. Should the respondent mention a person or organisation by name, these will be removed and a descriptor (e.g. 'participant's husband'; 'name of hospital') added instead.

- Audio files will be destroyed once transcripts have been verified.

- Any paper copies of transcripts will be stored in a locked cabinet in secure entry offices at the University of Southampton. Electronic copies will be stored on the University of Southampton server with password protection. Interview audio files and transcripts will be stored separately from the participant's contact information.

- Study data will be kept for 10 years from the end of the study, in accordance with University of Southampton policy.

Analysis

Each audio transcription will be transcribed verbatim and the transcript checked against the recording. Transcripts will be anonymised at this point. Data will be uploaded to the NVivo qualitative analysis package for data management. A thematic approach to analysis will be used (5). The analysis will take a team approach to development and refinement of the coding frame and to advance tentative explanations (6). A small number of interviews will be selected for preliminary analysis by at least two researchers. The transcripts will be read several times by the researchers to gain familiarity and to identify important ideas and patterns in the data. Each researcher will independently mark up the transcript with emerging codes. The researchers will then meet in order to discuss and agree the coding.

Agreed concepts or ideas will form the coding frame that will then be applied to the interviews through line by line coding, possibly by several different researchers. Where several researchers are working on the analysis, the reliability of the individual coders will be established by comparing coding over a small number of transcripts. As coding progresses, any new codes will be agreed by the team and then applied to all transcripts.

Analysis will involve the constant comparison of data within and across transcripts, with close attention to deviant cases. Regular team meetings, which will include people from a range of disciplines (for example, sociology, psychology, nursing) and people with experience of cancer, will be held to discuss and interpret emerging themes and findings.

Ethics review and governance

The protocol will be submitted to the North West – Lancaster Research Ethics Committee (REC) as a substantial amendment to the HORIZONS cohort study (ref 16/NW/0425). The University Hospital Southampton NHS Trust is acting as sponsor.

Management and oversight

This plan for the COVID-19 substudy has been reviewed by members of the Project Management (PMG) and User Reference Groups (URG) for the HORIZONS study and by Macmillan Cancer Support.

PPI involvement

The work will be conducted in close collaboration with the HORIZONS User Reference Group. Members have been involved in discussion of the focus of the research and have commented on the interview schedule. Implications of the research and how to take them forward will be discussed.

Qualitative study timeline

Activity	Jul 2020	Aug 2020	Sept 2020	Oct 2020	Nov 2020	Dec 2020	Jan 2021	Feb 2021	Mar 2021	Apr 2021	May 2021	Jun 2021	Jul 2021	Aug 2021	Sept 2021
Draft protocol amendment and study documents															
Ethics and governance approvals															
Sample selection and recruitment															
Interviewing															
Transcription of interviews and verification of transcripts															
Data analysis															
Write up and dissemination of findings															
Strategic advisory board meetings				X											
User reference group meetings			X						X						

Appendix 11.7.1 : INTERVIEW SCHEDULE

Interview schedule

This interview schedule is intended as a guide and offers broad questions to be covered along with suggested ways of asking. The exact way questions are asked may differ in order to explore and probe the individuals' experience

Introduction to interview

- Thank you for agreeing to take part in the interview
- We are interested in the experience of the COVID-19 pandemic among people who have been treated for cancer
- Before we start that, we need to check consent
- Reiterate confidentiality/anonymity etc

1) **Exposure to COVID-19**
   - Did you have or suspect that you had COVID-19?
   - Did anyone in your household have or suspect that they had COVID-19?
   - Were you/they tested to confirm?
   - What were your/their symptoms?
   - Did you/they need any treatment for symptoms, outside of the home?

2) **COVID-19 precautions**
   - How concerned have you been about COVID-19?
   - Could you describe to me the precautions you have taken in response to COVID-19? (shielding, self-isolating, social distancing)
   - For those who describe taking shielding precautions:
     - Were you specifically advised to shield? Check: reason for shielding (cancer or other condition); who advised by?; For how long?
     - If chose to shield without this advice, why was this?
     - How did/do you manage shielding within your household?
   - What have been the impacts on you of taking these precautions?
   - What have been the challenges for you in taking these precautions?
   - Have there been any positives in taking these precautions?
   - What precautions are you currently taking?
   - How are you approaching the easing of restrictions?
   -

3) **Information about cancer and COVID-19**
   - Have you been able to find all the information you needed about COVID-19 for people who have been treated for cancer? If not, what was missing/confusing?
   - Where did you get information from? HCPs, government, media, social media, charities?
   - What did you have to do to get/find the information you needed?

4) Support needs during the pandemic

- Could you tell me about any usual sources of support that were not available to you because of the pandemic?
    - from friends/family etc
    - from supportive services, such as charities
- Could you tell me about any additional support you needed because of the pandemic? (e.g. support for practical tasks/for emotional needs)?
- What did you have to do to get/find the support you needed?
- Was there any support you would have liked during the pandemic but were not able to access? Why was this?

5) Impact on health care services for cancer related needs

- Could you tell me about any changes to your care from your cancer care team because of COVID-19?
    - Have you had any appointments that were changed?
        - In what way were they changed?
        - How were you informed about this?
        - What did you feel about this? (were there things about it that were positive or negative for you?)
    - Have you had any scans or tests that were changed?
        - In what way were they changed?
        - How were you informed about this?
        - What did you feel about this? (were there things about it that were positive or negative for you?)
    - Have you had any treatment that was changed?
        - In what way was it changed?
        - How were you informed about this?
        - What did you feel about this? (were there things about it that were positive or negative for you?)
- Have you felt able to contact your cancer care team with queries during the pandemic?
- Have you felt able to contact other health care services (e.g. GP) with queries during the pandemic?

Appendix 11.7.2 Wording for advertising COVID-19 sub-study

This text might be used in a number of ways, such as in a flyer to send to the cohort study participants, on our website/in newsletters and in social media.

Alongside our HORIZONS questionnaire study, we are currently conducting interviews about participants' experiences of the COVID-19 (coronavirus) pandemic. This will help us to understand the needs of people who have been treated for cancer and allow us to make recommendations about support.

We are seeking up to 60 participants. We are sending out invites to questionnaire participants who said they are happy to be contacted about other research, so you may hear from us. In addition, if you are interested in taking part you can let us know by emailing us at HORIZONS@soton.ac.uk or telephoning us on 023 8059 6885.

Sharing your stories matters to us! Anything you tell us will be of benefit and will help us towards improving the lives of other people going through similar experiences. All information which is collected during the research will be kept strictly confidential.

Thank you to those who have already taken part in an interview!

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