

# INDIGO Community

## INvestigating DIGital Outcomes

Participant led electronic completion of PROMs and PREMs for patients  
living with and beyond cancer in the community

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## Funder

Brain Tumour Research Campaign

This protocol describes the INDIGO Community study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the UK Policy Frame Work for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act, and other regulatory requirements as appropriate.

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## GLOSSARY OF ABBREVIATIONS

BDAU	Big Data and Analytical Unit
CRN	Clinical Research Network
DARS	Data Access Request Service
EAG	Expert Advisory Group
ICS	Integrated Care System
NCRN	NIHR Clinical Research Network (CRN)
NHSE	NHS England
NIHR	National Institute for Health and Care Research
PCRN	Primary Care Research Network
PGI	Patient Generated Index
PID	Personal Identifiable Data
PREM	Patient Reported Experience Measure
PRO	Patient Reported Outcome
PROMs	Patient Reported Outcome Measure
SDI	Social Difficulties Inventory
TMG	Trial Management Group
WSIC	Whole Systems Integrated Care

## KEYWORDS

Cancer  
 Community  
 Digital clinical trial  
 EORTC QLQ-C30  
 EQ-5D-5L  
 Long term outcomes  
 Patient Generated Index  
 Patient Reported Experience Measurement  
 Patient Reported Outcome Measurement  
 Service use  
 Social Difficulties Inventory  
 Value based healthcare

## STUDY SUMMARY

<b>TITLE</b>	INDIGO Community [INvestigating DIGital Outcomes in the community]
<b>DESIGN</b>	Research administering questionnaires in a mixed methods study
<b>AIMS</b>	To understand more about the long-term outcomes and service use of patients living with and beyond a diagnosis of cancer
<b>OUTCOME MEASURES</b>	<p><b>Co-primary outcome measures</b></p> <ol style="list-style-type: none"> <li>1. To assess the feasibility of recruiting to a self-enrolment community digital Patient Reported Outcomes Measures (PROMs) study via participant self-identification or contact from the primary care research network.</li> <li>2. Feasibility of linking participants PROMs to regional and national data sets.</li> </ol> <p><b>Secondary outcome measures</b></p> <ol style="list-style-type: none"> <li>1. Feasibility of different methods of communication to trigger participant self-identification and self-enrolment into a digitally administered community cancer PROMs study.</li> <li>2. To assess which of three PROMs participants identify as most useful to them in combination with EQ-5D-5L.</li> </ol> <p><b>Tertiary outcome measures</b></p> <ol style="list-style-type: none"> <li>1. The feasibility of collecting, filtering, grouping, and interpreting free text responses in the context of a digital community-based PROM study.</li> <li>2. The feasibility of developing a national cohort of people living with and beyond cancer with linked registry datasets who can be followed longitudinally with repeat sampling.</li> <li>3. The feasibility of administering PGI digitally with no help from NHS staff and research team.</li> </ol>
<b>POPULATION</b>	Patients who have received a diagnosis of cancer in England.
<b>ELIGIBILITY</b>	All people over the age of 16 who have been diagnosed with cancer and completed their initial treatment (if any was received) more than 12 months ago. Patients receiving subsequent treatment or maintenance therapy are eligible to participate
<b>DURATION</b>	24 months recruitment, 12 months follow-up

## 1. INTRODUCTION

### 1. BACKGROUND

It has been estimated that in 2020 there were 2.4 million people in the UK living with or beyond a diagnosis of cancer <sup>1</sup>. There have been studies that have sought to develop and optimise Patient Reported Outcome Measures (PROMs) in cancer care <sup>2-6</sup>. Patient reported outcome collection to date has almost universally been in the context of clinical trials assessing treatment or in the early period after cancer treatment has been completed <sup>7-11</sup>. This means that there is a gap in our knowledge when we consider outcomes and service use for the large number of people who are long term cancer survivors (both cancer free and living with cancer) who are not utilising secondary care cancer services. The purpose of this study is to explore the feasibility of collecting patient reported outcomes and service use in people who are living with or beyond cancer and who are not receiving routine care from their treating centre. By doing this we hope to improve our understanding of health-status related quality of life outcomes for people following treatment for cancer.

PROMs are tools which help to translate a patient's quality of life and results of their treatment into categories that clinical teams can measure and act upon <sup>2,4,5</sup>. Most PROM studies in cancer care have been part of clinical trials. Clinical trials do not include all 'types' of patients which means that they are limited in how much they can tell us about the 'real world' experiences of patients <sup>12-15</sup>. Clinical trials tend to recruit younger and fitter patients, with a disparity in gender <sup>16-18</sup>. There have been studies looking at long term outcomes, but these studies have limitations. For example, they recruited only patients with one cancer type <sup>19,20</sup> or they recruited patients who were still under the period of cancer follow up, 1-5 years from diagnosis <sup>7,19,20</sup>. These studies yielded response rates of 54-66% using paper-based methodologies. Reaching patients who are no longer receiving treatment or hospital follow-up for their cancer has been a barrier to research in this area. We are aiming to explore outcomes in the longer term, 5 to 10 years following a diagnosis of cancer. In addition to PROM collection there have been very few large-scale studies exploring which healthcare services patients use in the long term as they live beyond their cancer diagnosis and its treatment. Those that have been performed often focus on costs not qualitative measures <sup>21</sup>.

Historically PROM studies involved paper-based questionnaires. This methodology is associated with significant costs especially in terms of administration and data processing. Secure digital platforms are being increasingly used due to the opportunity they offer to reduce costs <sup>22-25</sup>. Furthermore, they also offer an ability to edit, update, and share questionnaires much more easily allowing iterative approaches to questionnaire design to maximise utility and minimise responder burden. NHS England have commenced PROM collection for all patients 18 months after a diagnosis of cancer utilising two PROM questionnaires <sup>26</sup>. Their methodology involves using the national cancer registry to identify potential participants who are invited in writing to participate in an online study (or paper based if the participant prefers). Initial analysis demonstrated a 52% response rate and most respondents opted for online questionnaire completion. The focus of this rolling programme was initially breast, colorectal and prostate cancer and now other cancer patients are being offered the opportunity to participate <sup>27,28</sup>.

The National Disease Registration Service (NDRS), now part of NHS England, collects patient data monthly from English NHS providers, focusing on secondary care (inpatient and outpatient admissions, and Accidents and Emergency (A&E)) visits are recorded in the Hospital Episode Statistics (HES) dataset; the anti-cancer treatments, in the Systemic Anti-Cancer Therapy (SACT) data set; all the radiotherapy treatments, in RadioTherapy DataSet (RTDS); and the imaging data, in the Diagnostic Imaging Dataset (DIDs)). Patient demographics and tumour details are captured in the national cancer registry <sup>29</sup>. Although clinical and NHS administrative data are widely collected, PROMs data are largely missing even with the National Cancer Patient Experience Survey (NCPES) <sup>30</sup>. Indeed, the sending of

the NCPES is triggered in all adult NHS patients (aged 16 and over), with a confirmed primary diagnosis of cancer, discharged from an NHS Trust after an inpatient episode or day case attendance for cancer related treatment over a 3-month period each year. Therefore, patients who did not use healthcare services during that time are not sampled. Furthermore the survey is paper-based and can be complex as the respondents must understand the logic of the questions by themselves although telephone helpline support is available.<sup>31</sup> Although the survey focuses on the use of healthcare services, it does not use well validated questionnaires (e.g., EQ-5D-5L). However, Public Health England has successfully linked patients between the survey and the national cancer registry with patients' year of birth, sex, ethnicity and post code<sup>32</sup>. By being able to link patients' PROMs data to the cancer registry, we then link symptoms and side effects to clinical data on a national scale without relying on clinical trials data which is usually subject to selection bias. This can help clinicians and patients to improve their understanding of treatments and overcome the bias in clinical trial recruitments. This then reduces the patients' burden to find clinical information and exact dates to help researchers.

Our ambition is to develop a firm, pragmatic evidence based to support the collection of patient reported data for people living in the community who have previously been treated for cancer.

INDIGO Community is an innovative pan-cancer trial, in line with NHS plans to transform digital health data collection<sup>33</sup>. INDIGO Community intends to recruit people who have been diagnosed with any type of cancer, who are aged over 16 and who are able to manage written English and with minimal online screen-access (via any device). It will initially run in Northwest London and then subject to satisfactory performance it will be scaled nationally.

This study does not impact treatment. No changes to a participant's care or treatment will be made as a result of the study. Participants can select to receive a copy of their response via email. Seven days after completion of the questionnaire, where a participant consents, we will send a very short follow up questionnaire. This will check for any service use or issues following participation in the study e.g., distress, service utilisation, that may have occurred because of the study. A 24-hour a day helpline is offered by a cancer charity to support any participant who is distressed by considering their quality of life beyond their cancer diagnosis and treatment<sup>34</sup>.

## 2. RATIONAL FOR CURRENT STUDY

The rationale for this study can be best understood by considering the problems we intend to address:

1. PROMs which assess the long-term outcomes (>18 months post diagnosis) for patients living with and beyond cancer in the community have not been collected at scale.
2. Service use has not been explored at scale for patients living with and beyond cancer in the community.
3. Cancer registries do not have PROMs data and most PROMs studies lack cancer registry data to contextualise the PROM scores of participants compared to their cancer pathway.
4. It is unknown which PROM tools achieve highest sustained participation, completion rates and value to the participants when added to EQ-5D-5L in the context of a community-based digitally administered cancer patient PROMs study.
5. It is not known which methods best drive recruitment and how different patient groups may respond to these methods in the context of a living with and beyond cancer study.

Considering these problems provides the rationale for the choices we have made in designing the study. The large gaps that exist in our knowledge in this field mean that this is a feasibility study that will also allow us to capture useful and actionable information.

We have chosen a secure digital platform (“Qualtrics” <https://www.qualtrics.com/uk>) in order to address the first two problems above, with the explanation below.

- We hope it will allow high volume PROMs collection for minimal cost. If successful, this methodology will significantly lower the barrier to large scale PROMs collection in terms of costs.
- It will allow iterative development of the questionnaire in response to randomisation outcomes at minimal cost and minimal effort.
- It will allow rapid national scaling.
- A secure digital platform allows us to use patient self-identification as a route to recruitment. It offers the opportunity to capture outcomes from groups who may not be accessible via paper-based studies using the postal service e.g., sofa surfers, younger population, people who relocate after completing their cancer follow up and don’t have an updated address on the cancer registry.
- We can utilise conditional questioning to minimise participant burden. This can allow content to be presented in a more user-friendly manner than with paper-based questionnaires.
- We will be able to administer and modify, if required, questions assessing participants’ service use.

We have chosen to explore participants willingness to consent to linkage of their responses to registry data that is held about their cancer care to address the third problem above, with the explanation below.

- By exploring the acceptability of linkage to national cancer registries we will identify if the burden on participants can be reduced. If participants consent to linkage in future studies some of the fields in the cancer diagnosis and treatment domain will not be needed as this data is within the cancer registry data (e.g., year of diagnosis, first treatment).
- This would allow the generation of an extremely rich dataset of long-term PROMs in cancer care and the clinical pathways associated with those outcomes which provides context to the reported PROMs.
- If participants are willing to consent to linkage of their PROMs responses to the national cancer registry dataset, this offers a new method to create data sources for research and service development by going directly to patients rather than via healthcare providers.
- It will allow us to collect this information at scale and across multiple providers from participants who have been cared for by multiple different service providers over time, as well as understand how the results may vary across multiple parameters (i.e., patient groups, geography).

We have chosen to explore the value of different PROM tools by completion rates and at the level of value to the participant to address the forth problem above, with the explanation below.

- EQ-5D-5L will be administered to all participants. This has been chosen as it is used in many cancer outcome studies and has been chosen by NHS England for its cancer outcomes studies at 18 months following diagnosis and treatment of cancer <sup>26</sup>. Using the EQ-5D-5L allows us to compare our results to those of other studies.
- In addition to the EQ-5D-5L we want to compare three other PROMs tools: EORTC QLQ-C30, Social Difficulties Inventory (SDI) and a Patient Generated Index (PGI).

- The EORTC QLQ-C30 is being used by NHS England for its 18-month cancer patient PROM study<sup>26</sup>. Therefore, selecting this tool allows comparability with their study.
- The Social Difficulties Inventory has been chosen as it looks beyond physical symptoms and functioning so providing a more holistic overview of a patient's life. Therefore, we wish to explore if this performs better than EORTC QLQ-C30 when considering long term outcomes.
- There is evidence that Patient Generated Indexes, where patients record the aspects of their life they most value, and the aspects most impacted by their illness can be powerful tools. Use of PGI has been limited until now as participants have required someone to support them with completing this on paper. However, we believe that a digital platform can support the self-administration of this tool. Our secure digital platform offers a way for us to explore PGI in comparison to more traditional PROMs tools.
- By exploring different questionnaires via randomisation, we hope to identify which questionnaires are associated with the greatest completion rates and are perceived by participants to be of the most value, do the participants feel that the PROM allowed them to 'describe' their quality of life?

We have chosen to explore different communication strategies to drive recruitment as we do not know the best channels of communication through which to drive awareness and participation in the study. This will address the fifth problem above, with the explanation below.

- We will explore traditional and novel strategies by assessing which channels are associated with sign up by which demographic groups. We will advertise the study via the Primary Care Research Network utilising social media platforms and via cancer charities and support groups.
- We do not have any evidence on which to base assumptions regarding reach and inclusivity of using a secure digital platform to administer cancer related PROMs in the community. Therefore, we are exploring this aspect within the trial. It will be possible to track how participants access the study by having different survey links for PCRN driven enrolment and for the different communication channels (e.g., via QR codes, links, URLs).
- From the participants' point of view and to encourage recruitment, participants will be able to share their answers with friends, family, and healthcare professionals. They will also be offered to being updated of the progress of the study and its aggregated results.

We have chosen to stage the study (stages described in 3.3 - Study stages) so we can utilise data we can access easily which describes cancer prevalence in North West London (via the Whole Systems Integrated Care (WSIC)<sup>35</sup>). This will allow us to understand the response rate and demographic spread of the participants compared to the population data. This will support the Expert Advisory Group (EAG) and trial management group to consider if the questionnaire and methodology are performing sufficiently well in the first stage to open the second stage. If we omitted the first stage in the design, then in order to assess the participant population as being representative, we would require national cancer registry data of all patients diagnosed and treated for cancer over many years. For many reasons this is not feasible or appropriate. Using a two-stage approach minimises costs, facilitates rapid assessment and amendment of the questionnaire. All amendments will be subject to the standard HRA/REC substantial amendments process.

The study has been developed with an EAG from the fields of PROMs, healthcare, and data science research. There has been continuous PPI input into the study from members of the public and patients representatives who have been treated for cancer and who have previously participated in PROMs study development.

There will be regular meetings of the EAG who will review participation and completion rates. Questions with poor completion rate may be withdrawn from the questionnaire.

Once the EAG has assessed the returns from the Northwest London population, and if they are satisfied with the performance of the study, we will start scaling the study nationally. This is technically straightforward as the digital platform is designed to scale. We will not have such strong links into community services nationally as we do within Northwest London so the impact that this has on participation rates and demographics of participants can be assessed. Although Northwest London does not statistically represent the British population, we assume that the sample size will be powerful enough to draw interim conclusions to determine if any amendments are required prior to scaling up to other regions.

## 2. STUDY OBJECTIVES

Our main objective is to assess the feasibility of mass recruitment to a community cancer survivor study via a large-scale online platform using participant self-enrolment. Our ambition is to develop a firm, pragmatic evidence based on how to collect patient reported data for people living in the community who have previously been treated for cancer.

### 1. OBJECTIVES AND REASONS BEHIND THE SELECTION AS AN OUTCOME

#### 1. Recruiting cancer patients and linking their data to cancer registries

- a. To assess the feasibility of recruiting to a self-enrolment community digital Patient Reported Outcomes Measures (PROMs) study via participant self-identification or contact from the primary care research network.

No evidence exists as to using this approach in the context of a digital tool capturing long term PROMs data in patients living with and beyond cancer.

- b. To assess the feasibility of linking participants' PROMs responses to multi-geographical data sets.

No evidence exists of the feasibility of using this approach to obtain consent to generate a linked dataset and whether it is in fact possible to link PROMs data from the community to regionally and nationally held cancer registry datasets.

#### 2. Communicating with patients and understanding the most efficient and preferred PROMs questionnaires

- a. To assess the different methods of communication to trigger participant self-identification and self-enrolment to a digital community cancer PROMs study.

Explore the impact on participation rate in a PROM study across demographic groups by different communication methods will provide evidence which is missing from the literature to date.

Communication channels will be assessed in a step wise manner:

- i. We shall use PCRN methods of approach e.g., charity sector, secondary care cancer information hubs.

- ii. Once recruitment plateaus, social media will be opened to trigger enrolment – for example Facebook, Twitter, TikTok, Instagram, charity web pages, with snowballing into other channels to maximise dissemination.
  - iii. The digital platform can provide real time data on recruitment. Recruitment rate will be plotted weekly and the TMG will determine when recruitment appears to be plateauing in order to trigger the next stage of recruitment.
  - b. To assess which of three PROMS performs best in combination with EQ-5D-5L.  
The use of EQ-5D-5L is common in studies of cancer populations, however, this is often supplemented with a second PROMs tool. We do not know which PROMs tools are most acceptable or helpful to this population in the context of a long-term community-based study. The use of a digital platform allows us to trial PROMs that traditionally require support to facilitate completion.
- 3. Analysing, linking PROMs data, and following up patients**
- a. To assess the feasibility of collecting, filtering, grouping, and interpreting free text responses in the context of a digital community-based PROMs study.  
No evidence exists of the feasibility of collecting large scale free text responses in the context of PROMs collection in patients living with and beyond cancer. If we can classify the free text responses into categories that permit an analysis, this methodology will be valuable for future PROM studies which can more deeply explore the use of free text responses to questions in this population.
  - b. To assess the feasibility of developing a national cohort of people living with and beyond cancer linked to their cancer registry records and who can be followed longitudinally with repeat sampling.  
Patient registries with patient-level data have traditionally been built from the perspective of secondary care or nationally for epidemiologic purposes. This methodology does not work for all types of disease or patients. Therefore, we will explore if asking patients directly to join a repository is a feasible way of constructing a cohort of patients. It will allow us to assess the feasibility of linking patients captured data to electronic healthcare records using the patients' name, date of birth, sex assigned at birth and/or gender. This data set should allow longitudinal follow-up of disease in secondary care and treatment outcomes. Linkage to primary care is at the moment not possible but it may be available at the time of completion of the data.
  - c. The feasibility of administering PGI digitally with no help from NHS staff and research team.  
PGI have always been administered face-to-face with a research team member explaining and helping participants how they must answer the various section. We aim to understand if this is feasible with pre-built online validation or if participants can complete the questionnaire just by following guidelines.

### 3. STUDY DESIGN

We aim to create a cohort observational trial exploring the feasibility of performing a pan-cancer community based randomised trial to explore and improve methodology around collecting long-term cancer outcome data and service use for people living with and beyond cancer.

This observational study contains randomised questions relating to both the methodology and to questionnaire content. It is a multi-phase feasibility study with regional and national components.

As this is a novel approach to capturing long-term quality of life outcomes in people previously diagnosed with cancer, there is not a strong evidence base upon which to develop the trial. For that reason, we believe this is a series of feasibility trials as there are differing dimensions within this trial (e.g., age at diagnosis, age at enrolment, gender, time since end of treatment, ethnicity). However, to maximise the utility of the study, we will have a core component which runs through the study to develop a large dataset whilst simultaneously randomising and exploring distinct aspects of QoL assessment using a secure digital platform assessment.

This is a single time point study which will recruit for 24 months from September 2023 and follow up for 12 months. The study should end in September 2026. If a large cohort of respondents provides consent to ongoing contact for PROM measurement, the standard HRA/REC process for substantial amendments will be followed to seek permission to continue the study beyond 36 months.

The assessment of maximum recruitment in the first stage might be approximately 16,000 participants per year, based on an estimation of a 45% response rate from the 37,000 patients with a known diagnosis of cancer on the regional database based up the NHS England 18-month cancer follow-up study (45-55%)<sup>27,28</sup>. There are differences in methodology and populations between their study and ours, but it is the most appropriate benchmark we have been able to identify.

The minimum response rate that would be accepted to allow progression to the second stage would be 5% (equivalent to 1,850 adult cancer patients). Whilst this is a small number, and a concern would exist regarding bias in the sample, this response rate nationally would yield over 100,000 responses delivering valuable insights into PROMs and service use even accepting the risk of selection bias. It may yield benefit to patients whilst also allowing us to improve and develop the study in order to obtain wider participation.

## 1. SURVEY

The survey ([https://imperial.eu.qualtrics.com/jfe/form/SV\\_20kfPG0ye1UOYMS](https://imperial.eu.qualtrics.com/jfe/form/SV_20kfPG0ye1UOYMS)) is composed of a succession of questions and validated PROM questionnaires and should take around 30 minutes for participants to complete. Consent is obtained from participants at 3 points in the survey. An initial consent at the start for participation and then on two further occasions in the survey here it is immediately prior to the relevant question the participant will view (described in Figure 1).

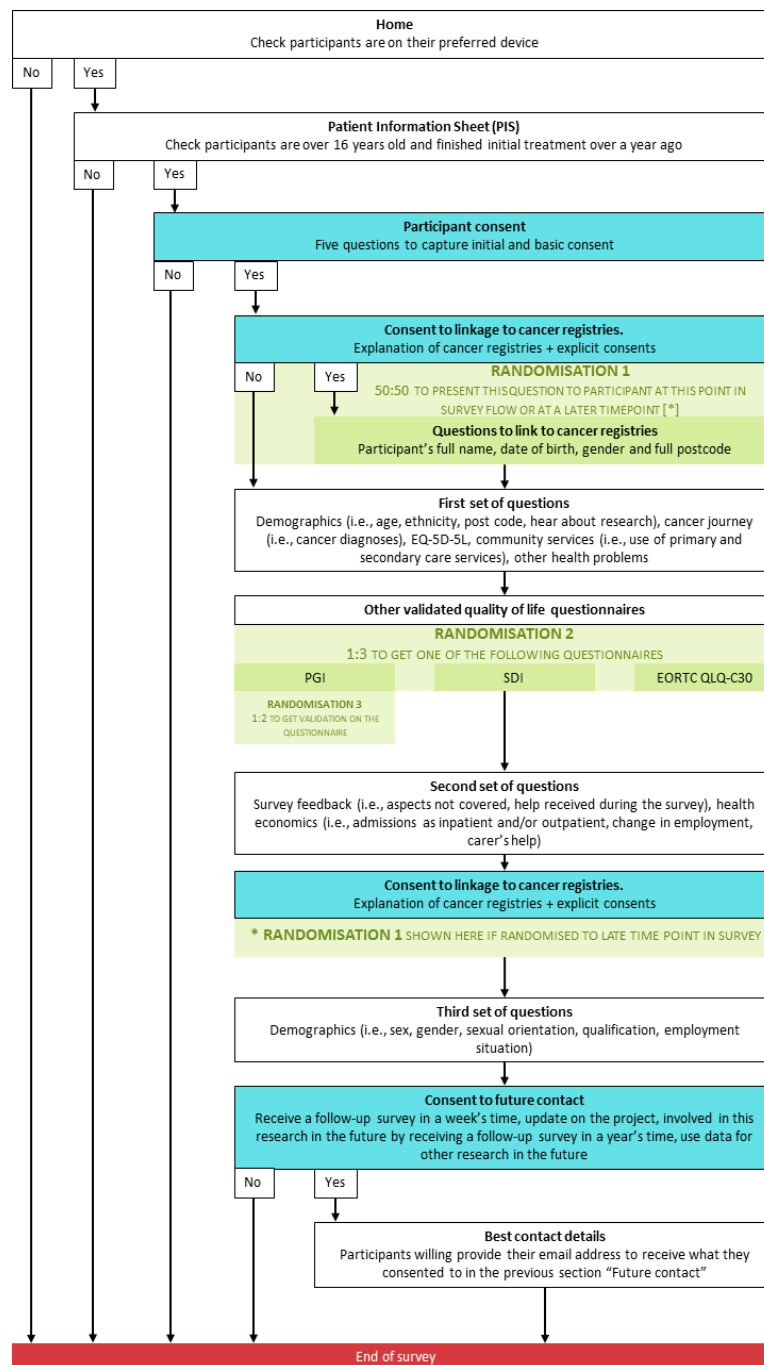


Figure 1: Survey flow with the options participants will have to choose from

Participants are welcomed with a question checking they are on their preferred digital device (phone, tablet, computer) as they cannot change device in the middle of the survey. They are then shown the online patient information sheet, (this can be reviewed at any point in the survey via an external link on every page). The first block of consent questions is then shown where participants must accept the basic conditions of the survey. Following the consent to participate, participants are presented with blocks of validated questionnaires and a set of two randomisations:

1. Randomisation 1: Is the consent to linkage to national datasets affected by when in the survey the question is asked?

2. Randomisation 2: Which quality of life questionnaire is associated with the highest completion rates and participant satisfaction (Comparison of the Patient Generated Index (PGI), Social Difficulties Inventory (SDI) and EORTC QLQ-C30).
3. Randomisation 3: Participants will be shown the PGI either with strict numerical validation included on the platform (e.g., they must indicate five things that have a negative impact on their life) or with no validation (e.g., they can provide zero up to five areas that impact their life). PGIs have never been administrated digitally and this randomisation will help to understand how much participants may need help. The use of numerical validation does have a potential downside as participants cannot skip pages if they don't understand or don't want to complete the page so there may be an impact upon completion rates).

At the end of the survey, participants are asked if they consent to being contacted in the future using their preferred email address regarding updates on this project and follow-up surveys. Consent is explicitly asked for each potential future contact.

## **1. Case scenarios of PID captured and held**

In each of the case scenario presented below, and when applicable, we assumed that participants are presented with the questions about linkage to cancer registries at the beginning of the survey.

**Case 1:** Member of the public declined to consent to participate. Their non-consent is recorded, and this is the only data captured about them.

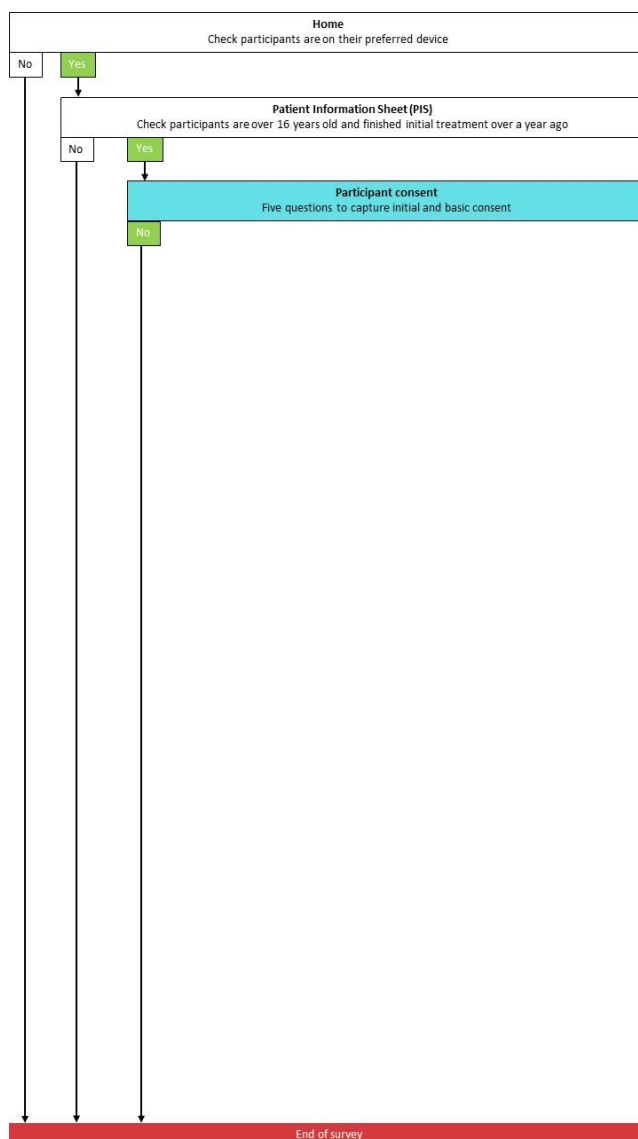


Figure 2: As consent to participation withheld no questions are shown and therefore, no data is captured. Responses are anonymous since no metadata is recorded (e.g., IP address, location).

## Case 2: Participant consented to all aspects of the survey

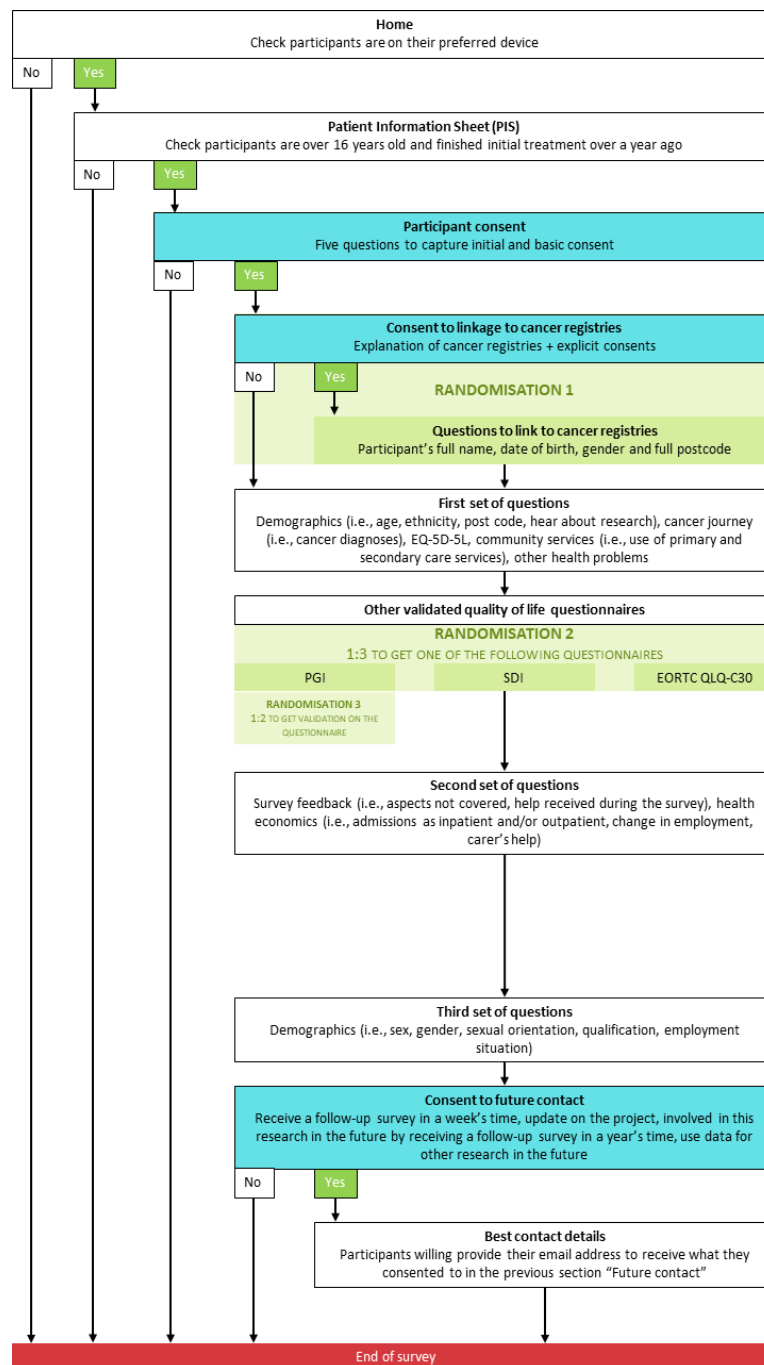


Figure 3: Participant consented to participate in all aspects of the trial and therefore they will have provided their PID to allow linkage to cancer registries. They followed on to consent to be contacted in the future and provided their preferred email address.

**Case 3:** Participant consented to participate but withheld consent to provide PID for cancer registry linkage. Consent was given for future contact.

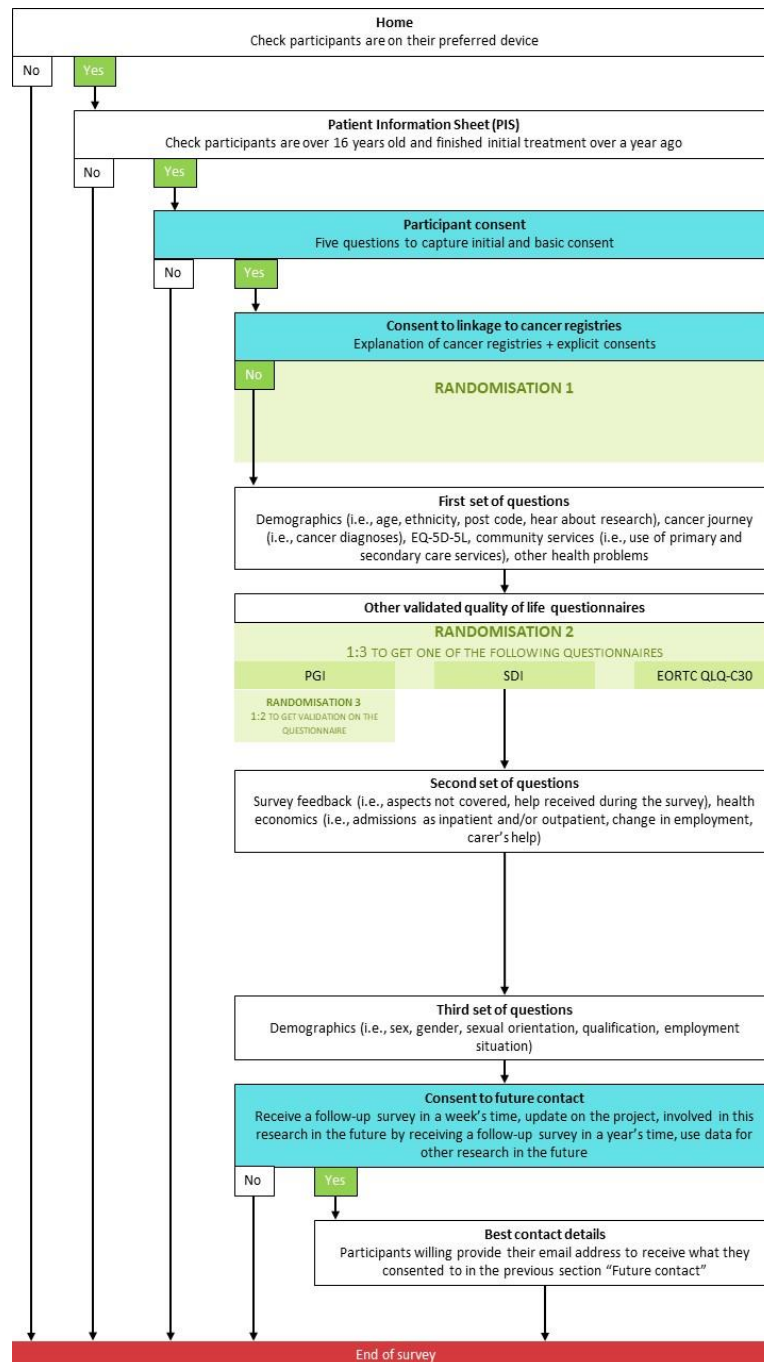


Figure 4: Participant consented to the basic questions, decline to provide their full name and date of birth to have their answers linked to the cancer registries, but consented to be contacted in the future by providing their preferred email address. Therefore, only PID held would be their email address.

**Case 4: Participant answered the survey anonymously without providing any extra information**

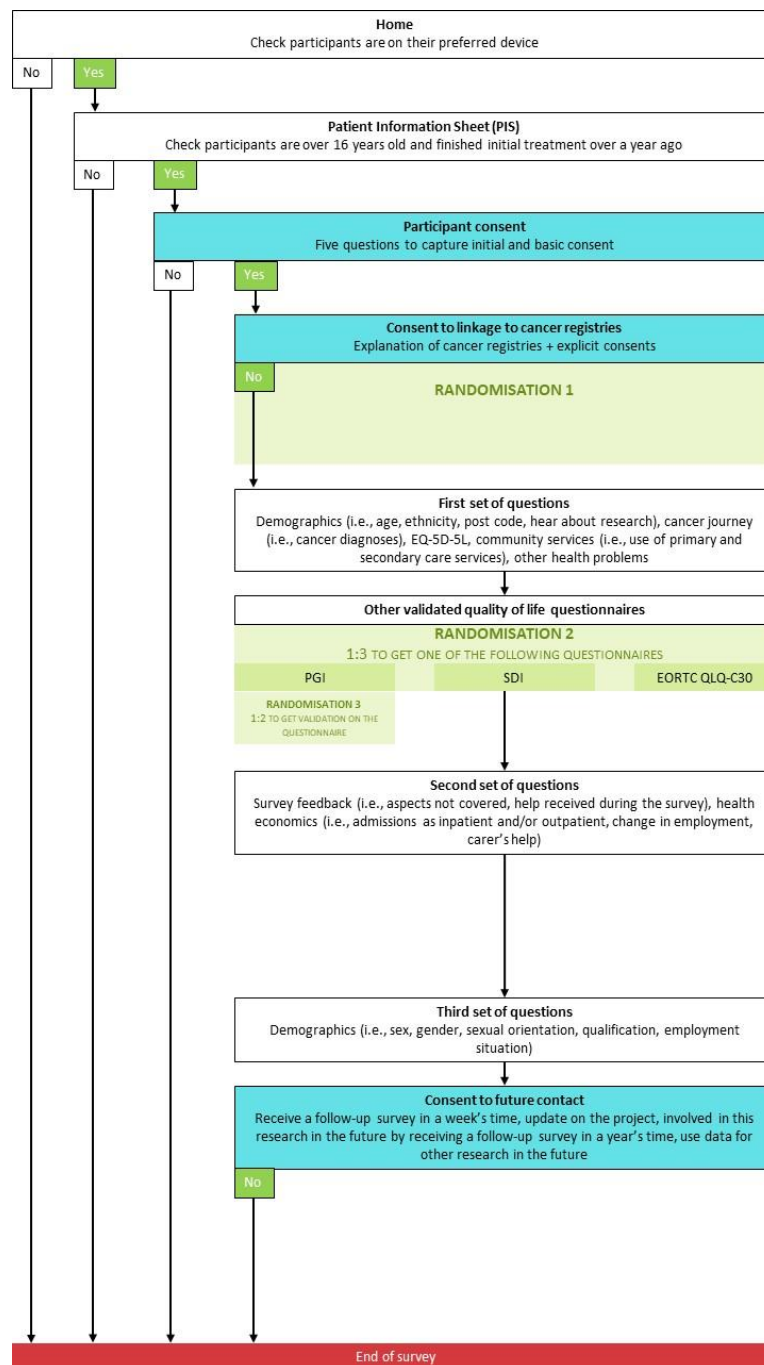


Figure 5: Participant consented to answering the questions but withheld consent to link to cancer registries and withheld consent to be contacted in the future. Therefore, only their answers to the validated questionnaires have been recorded. No PID will be held.

## 2. Data held based on different cases

	CASE 1: “NO CONSENT”	CASE 2: “FULL CONSENT”	CASE 3: “CONSENT TO PARTICIPATE AND FUTURE CONTACT”	CASE 4: CONSENT TO PARTICIPATE ONLY
<b>PARTICIPANT CONSENT</b>	No	Yes	Yes	Yes
<i>AGE *</i>	No	Yes	Yes	Yes
<i>ETHNICITY *</i>	No	Yes	Yes	Yes
<i>OUTWARD POST CODE *</i>	No	Yes	Yes	Yes
<i>SEX RECORDED AT BIRTH *</i>	No	Yes	Yes	Yes
<i>GENDER *</i>	No	Yes	Yes	Yes
<i>SEXUAL ORIENTATION *</i>	No	Yes	Yes	Yes
<i>QUALIFICATION *</i>	No	Yes	Yes	Yes
<b>CONSENT TO LINKAGE</b>	No	Yes	No	No
<i>FULL NAME</i>	No	Yes	No	No
<i>DATE OF BIRTH</i>	No	Yes	No	No
<i>GENDER (SEX RECORDED IN NHS RECORDS)</i>	No	Yes	No	No
<i>FULL POSTCODE</i>	No	Yes	No	No
<b>CONSENT TO FUTURE CONTACT</b>	No	Yes	Yes	No
<i>PREFERRED EMAIL ADDRESS</i>	No	Yes	Yes	No

\* PARTICIPANTS ARE NOT REQUIRED TO ANSWER THESE QUESTIONS, THEY CAN LEAVE THE SPACE BLANK

Table 1: Summary of data captured depending on each case presented in the previous figures

## 2. CONSENT

In the context of this project, we will use electronic consent. Participants will have the possibility to contact a member of the study team via email if they have any questions before consenting.

As per the HRA-MHRA guidance on e-consenting, we will use “simple electronic signatures” at initial enrolment<sup>36</sup>. Potential participants will be provided with information which they can review online or download. The participant will indicate consent on a digitally administered form. As this is a low-risk study which does not change treatment, participants will be allowed to read the information on the

study, consent and participate in the same sitting. We believe this will minimise a potential barrier to participation that will exist if participants are forced to return to the platform later to participate.

If participants want a cooling-off period, this will be possible. They will be able to read the information and return to consent later or consent and then return to complete the questionnaires up to a week later. We do not have a fixed time point for completion but there will be a point in time when the links and surveys are closed at the end of the study.

During completion the participant will be free to cease completion at any point without giving reasons.

Participants who refuse to e-consent to the study will not have access to the questionnaires. They will have the opportunity to tell us why they declined, should they wish. This question will not be mandatory, and participants can leave the page without giving reasons.

### 3. STUDY STAGES

#### 1. First stage: regional study in North-West London

There are methodology and content randomisations.

Patients will be recruited first via the Primary Care Clinical Research Networks. We discussed the possibility of physical advertising in the community including community healthcare settings with the PCRN team, but they advised against as it was proved in previous studies the lack of engagement from patients with physical posters.

Once recruitment plateaus we will then push information about the study via social media (e.g., Facebook, Twitter, TikTok, Instagram) simultaneously.

There are then content randomisations. These are not related to cluster randomisations as the randomisation is built into the questionnaire platform and randomisation occurs at every individual enrolment.

There are 37,000 people in Northwest London with a coded diagnosis of cancer in their primary care records. To show a 20% difference between arms of the trial 80% (+/- 3%) vs 60% (+/- 3%) in terms of agreement to linkage to cancer registry data or completion of questions, we will require 300-500 subjects per randomisation. Therefore, to allow for drop out of completed questionnaires we will aim for 500 participants as a minimum before any interim analysis is undertaken into the utility and performance of the different randomisation questions. A 100% participation rate will yield 37,000 participants. Using the NHS England figure of 45-55% participation rate we would have approximately 16-21,000 participants. If we have a very low participation rate, as low as 5%, we will recruit 1,850 participants.

The first randomisation relating to content is the positioning of the question asking for consent to link the questionnaire responses to NHS data. The participants will be randomised to being asked this question early in the questionnaire or at the end. The aim of this is to answer:

- a) Does asking participants for consent to link their responses to local and nationally collected cancer registry data affect participation rates or questionnaire completion rates?
- b) Within the questionnaire, does the positioning of the question asking participants for consent to link their responses to nationally collected cancer registry data, affect participation or questionnaire completion rates?

The second randomisation relates to the validated PROM questionnaire they are shown. All patients will receive the EQ-5D-5L and will then be randomised to one of EORTC QLQ-C30, SDI or PGI. The

point of this randomisation is to answer how the choice of PROMs (in addition to EQ-5D-5L) affect participation and completion rates and participant satisfaction.

For the 33% of participants who are randomised to receive the PGI there is a third randomisation. The third randomisation relates to how the PGI is delivered. This PROM has usually been delivered by a researcher in conversation with a participant as it involves giving numerical weights to aspects of the person's life. We wish to explore if presenting this PROM on a digital platform is possible. The digital platform allows validation measures (ensuring the numerical answers fall within the bounds of the PROM) to be embedded in the PROM which may help the participant. However, these same validation measures mean that a participant cannot skip a page if they wish and so there is a risk that validation increases the number of incomplete surveys as participants drop out as they cannot bypass the page. To explore this, we will therefore randomise the participants who have been randomised to receive the PGI (33% of all participants) to receive a PGI with answer validation and a PGI without answer validation (50:50 split therefore 16.5% of total participants in each arm).

## **2. Second stage: national study**

Outcome from the first stage's randomisation questions regarding linkage, PROMs content and triggers to enrol will be reviewed. The intention is to use the same questions and randomisations in the second stage of the study. However, the content of the questionnaires may be updated via the EAG to reduce participant burden. The EAG will consider removal of core questions which are felt by its members to be of low utility either by completion rate or nature of responses. If there is clear evidence of a definitive answer to the randomisation questions, then the randomisation may cease. All amendments proposed by the EAG will be subject to the standard HRA/REC substantial amendments process.

Once an assessment of feasibility, question utility and randomisation process has been made by the trial management group and any proposed amendments from the EAG considered, it is intended that if appropriate there will then immediately follow a national study (once HRA/REC substantial amendments process completed if appropriate). A secure digital platform enables the study to scale nationally via regional CRN, in addition to communication channels which have been found to be helpful in driving engagement.

Nationally there are 2.4 million people with a previous diagnosis of cancer. Therefore, our sample size will vary from 2.4 million with 100% participation, to 1.2 million with a 50% participation rate or approximately 125,000 participants with a 5% participation rate. We believe that recruitment rates will be very likely be above these worst-case scenarios. Feedback from the PPI team and testing the questionnaire has not given reason to think the rate will be significantly different to the NHS England recruitment rate. If the worst-case scenario recruitment rate occurred, this will still be the largest real world cancer patient PROM study in a community setting and as such will yield data on what worked and didn't work with the study methodology and the data on service use can be shared to help design and deliver services for those living with and beyond cancer.

a. Process from the enrolment to the follow-up questionnaire



Figure 6: Process of the INDIGO Community clinical trial

Potential participants will be made aware of the INDIGO Community trial either via the PCRN, physical media in their GP or social media (through a randomisation). A link to the secure online platform [Qualtrics <https://www.qualtrics.com/uk>] will be accessible to potential participants so they can review the Participant Information Sheet (PIS). It will include details of trial's staff to contact if they have any questions. Given the low-risk nature of the study, in-line with HRA advice, patients may enrol either when they are given the PIS, or later.

Once the participant has decided to participate, they self-enrol into the study, using the secure online platform ("Qualtrics" <https://www.qualtrics.com/uk>), and provide online informed consent. It is acceptable to get help from their friends or family to sign-up. The participant will be required to enter demographic data (e.g., sex, gender, age, employment status, outward postcode) then a core set of questions will follow and focus on their cancer diagnosis, treatment, service use, and quality of life. The participant will not be identifiable from the information collected in the core questions.

A set of randomisations relating to content will be presented to the participants, which are handled by the secure online platform. First, to assess their willingness to consent to the linkage of their PROMs data to the national cancer registries. This question will be randomised either at the beginning or at the end of the survey. Patients will not be aware that they were randomised to early or late presentation of this question as that would contaminate the randomisation. If the participant consents to linkage, they are asked to provide personal identifiable data to facilitate linkage. Participants are informed of this transition from not being identifiable to being identifiable.

The second randomisation of content relates to the second quality of life questionnaire which is presented to the participant after the EQ-5D-5L. They are randomised to EORTC QLQ-C30, SDI or PGI. The participants are told that they will be shown one of three possible questionnaires and that this is random.

The third and last randomisation concerns the PGI, with or without electronic validation. On the secure online platform, it is possible to guide participants to avoid mistakes when they answer questions. In the case of the PGI, it has never been delivered online. Traditionally it is delivered by a researcher with a participant. Participants are not aware of this randomisation. Validation may help participants to complete the PROM correctly. However, it means that it is not possible for the participant to skip a

section if they wish therefore validation may increase or decreased completion rates hence inserting this randomisation.

At the end of the questionnaire, participants will be asked three questions about future contact and their willingness to receive a short follow-up questionnaire a week after the completion of the first survey. This follow-up survey aims to check for any unintended consequences of completing the survey. The two other questions will ask if they would like to hear the results of the study and if they consent to be contacted via email to participate in ongoing questionnaire studies. If they approve of any of the three questions, they will be asked to enter a valid email address. It can be theirs, a friend's or a family member's.

After the submission of their answers, participants will get a copy of all the questions and their answers directly on the "thank you" page where online resources will be displayed, in case they have cancer-related questions to the cancer community. If they choose, they can bring a copy to their GP, keep a record of it, or send it to their healthcare professionals.

## 4. STUDY OUTCOME MEASURES

### 1. Primary objectives

- a. To assess the feasibility of recruiting to a self-enrolment community digital Patient Reported Outcomes Measures (PROMs) study via participant self-identification or contact from the primary care research network.
  - i. Participation and survey completion rates as proportion of the denominator of all people over the age of 16 diagnosed and/or treated for cancer.
  - ii. Assessments broken down by different demographic groups.
- b. To assess the feasibility of linking participants' PROMs responses to multi-geographical data sets.
  - i. Number of study participants in North-West London and nationally who agreed to have their responses linked to national cancer registries as a proportion of study participants. The numbers will be captured from the first and second stages of the study.
  - ii. Using participants' answers (i.e., first name, surname, date of birth, sex), is it technically possible to link their PROMs answers to clinical data recorded in the local and/or national cancer registries?

### 2. Secondary objectives

- a. To assess the effectiveness of different methods of communication to trigger participant self-identification and/or self-enrolment to a digital community cancer PROMs study.
  - i. Participation rates and survey completion rates as proportion of the denominator of all people over the age of 16 diagnosed and treated for cancer.
  - ii. Recruitment and completion rates from different communication channels for demographic groups.
  - iii. Number and type of communication channels used until recruitment plateaus. The digital platform provides real time recruitment rates. These will be reviewed weekly by the TMG. When the TMG determine that recruitment has plateaued the next communication channel will be opened.
- b. To assess which of three PROMs performs best in combination with EQ-5D-5L.
  - i. Completion rates of the three PROMs questionnaires.
  - ii. Correlation of PROMs responses to EQ-5D-5L responses.

- iii. Qualitative measure of participant satisfaction with the three PROMS (EORTC QLQ-C30, SDI, PGI).

### 3. Tertiary objectives

- a. To assess the feasibility of collecting, filtering, grouping, and interpreting free text responses in the context of a digital community-based PROMs study.
  - i. Completion rate of free text responses.
  - ii. Ability to group responses into categories.
  - iii. Ability to undertake an analysis on the responses.
  - iv. Link those to demographic or cancer type / treatment details.
- b. To assess the feasibility of developing a national cohort of people living with and beyond cancer linked to their cancer registry records and who can be followed longitudinally with repeat sampling.
  - i. Number of participants who agreed to be contacted for future sampling.
  - ii. Number of participants who responded to a follow-up survey 12 months after completion of the initial survey.

## 4. PARTICIPANT ENTRY

There are no physical or psychological screening tests prior to enrolment. Participants will self-enrol into the study which uses a secure digital platform. There will be two routes that may trigger enrolment. As participants are being made aware of the study, either because they have previously consented to be contacted by the PCRN to take part in research or they have self-identified as interested in participating, we do not think there are any significant ethical issues with regards participant enrolment.

Routes to participation are:

1. The PCRN will send a link to patients on their database with a previous diagnosis of cancer and who have previously consented to be contacted by the PCRN to participate in research.
2. Direct patient self-enrolment having become aware of the study via one of the communication methods being used in the study e.g., community centres, social media, local media, relevant medical charities making their members aware of the study.

### 1. INCLUSION CRITERIA

1. Anyone over the age of 16 who has been diagnosed (receiving treatment is not an inclusion criteria although we expect as this is a long-term survivorship study all participants will have received treatment) for any type of cancer in the past (> 12 months) can participate.
2. Participants who self-identify as having previously (time unlimited) received a diagnosis of cancer, based on histological, radiological, or clinical grounds (primary and/or metastatic cancer). Current treatment is not a barrier to participation, but the emphasis is on patients who have completed treatment.  
Participants need to be able to access the secure online platform, using a mobile device or computer.
3. Have capacity and be able to provide informed consent via the online platform.
4. To be able to understand, read and write English, with or without support from a trusted individual e.g., friends, family, carer.

## 2. EXCLUSION CRITERIA

1. Participants recently diagnosed with cancer (less than 12 months ago).
2. Participants unable to access secure online platform.
3. Participants who do not have sufficiently good understanding of written English to complete the PROMs and are unable to be supported by a trusted individual to complete the questionnaire.
4. Participants lacking capacity and unable to give informed consent.

## 3. WITHDRAWAL CRITERIA

1. For participants who want to cease participation during the initial questionnaire they can leave the survey site. No specific action is required other than this. They can return within a week to complete if they wish. The time limit of a week was proposed by our PPI group as they felt fluctuation in symptoms can occur over longer periods which may affect responses. Thereafter, their responses up until the point they discontinued will be submitted and utilised.
2. For participants who had consented to ongoing questionnaire administration the withdrawal criteria are:
  - i. If the participant withdraws consent.
  - ii. If a participant dies during the trial.
  - iii. In all these cases, the participants responses up until the time of withdrawal from the study will be kept and utilised for the purposes of analysis, including their consent if given to the linkage question.
  - iv. If the study team are made aware that a participant lacked capacity at that time they enrolled or has lost capacity during the trial, their responses to the trial will be deleted and excluded for analysis.

## 5. ASSESSMENT AND FOLLOW-UP

There are different triggers to follow up. The participant will be able to choose what, if any occurs.

For participants who decline any of the questions relating to further contact, this will be a single point in time study with regards the PROMs questionnaire and there will be no follow-up with regards any service use triggered by the study.

If participants consent to being contacted in the future, to receive a one-week follow-up survey and/or to have an ongoing involvement, they will be asked to provide their email address.

Participants will be offered a copy of their PROMs results after the submission of their answers. This summary can also be sent by email if they agreed to provide an email address. Being sent a copy of their results does not trigger any further involvement in the study. Participants are also offered a summary of the questions and their answers on the "Thank you" page at the time of their submission so they do not have to share their email address in order to receive a copy of their responses.

Participants who agreed to provide an email address for a one-week follow-up questionnaire will receive a link to a very short follow up survey. This survey will identify if there have been any impacts on their physical or mental health and if they had communication with anyone about problems with their health because of the study. There will be no further involvement in the study after that questionnaire. If participants decline the opportunity to provide an email address and be contacted a

week after the completion of their questionnaire, they will still be able to contact Tenovus Cancer Care in case of mental distress.

Participants who agreed to ongoing involvement beyond the 1 week follow up will be contacted by email with a follow-up questionnaire 12 months after initial questionnaire completion.

Any participation beyond 12 months will be part of a separate study which will require ethical approval and re-consenting the participants with regards ongoing involvement.

## 6. STATISTICS AND DATA ANALYSIS

There is a paucity of evidence in this area on which to base statistical calculations. There are very few digital PROMs studies, and we are not aware of any self-identification/self-enrolment community PROMs studies.

Therefore, our recruitment is based upon the following considerations.

To show a 20% difference between arms of the trial 80% ( $\pm 3\%$ ) vs 60% ( $\pm 3\%$ ) in terms of agreement to linkage to cancer registry data or completion of questions, we will require 300-500 subjects per randomisation.

Therefore, to allow for drop out of completed questionnaires we will aim for 500 participants as a minimum before any interim analysis is undertaken into the utility and performance of the different randomisation questions.

In the possible, but unlikely, situation where there is an overwhelming difference between arms of the randomisation, the EAG will conclude if there is evidence on which to accept or reject the null hypothesis. The questionnaire will then be adapted to remove that randomisation. If there is no clear difference at interim analysis, the trial will continue recruiting with the TMG determining the next analysis point based upon recruitment rates and initial completion metrics.

This study will be NIHR-badged and will be supported by the local primary care NIHR research nurses with regards identifying potential participants from the PCRN database and posting of physical media. Data will be provided and entered directly by patients onto the secure platform. Data will be extracted at regular intervals to be analysed and aggregated by the data analyst from the TMG. The anonymised results will then be discussed by the EAG.

For participants who agree to linkage once the study has run to the point of plateaued recruitment a request will be made to NHS England for the national cancer registry data so linkage can be performed. This has been discussed with NHS England who have agreed in principle, and we have experience of such applications, but it will require formal application and approval at the appropriate point in time.

All analyses will be conducted between Imperial College Healthcare NHS Trust and Imperial College London. All data will be handled in accordance with data protection and information governance guidance.

We will seek explicit consent to store the enrolment log, consent form and coded data for 10 years following completion of the study. This will mean that participant data is stored for a maximum of 12 years if they are recruited at the very start of the 2-year recruitment period. The data will initially be analysed with conventional statistical methods (e.g., descriptive statistics and repeated measures multilevel modelling) which will inform machine learning methods to be employed.

As computational techniques improve, there is the potential to develop novel techniques to improve our analysis of such data. We expect such data to become increasingly important over the next 5 - 10 years, and therefore having a validated linked dataset is important for technical developments and further research in monitoring physical activity.

## 7. REGULATORY ISSUES

### 1. ETHICS APPROVAL

The Study Coordination Centre has obtained approval from the London - Surrey Research Ethics Committee (REC) and Health Research Authority (HRA). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18<sup>th</sup> World Medical Assembly, Helsinki 1964, and later revisions.

### 2. CONFIDENTIALITY

Pseudonymised data is data that can be linked back to a person (e.g., coded data). It is considered both personal and identifiable data. Anonymised data is data that has no code and cannot be linked back to a person (e.g., aggregated data for publication, data without a code that cannot be linked back to a person).

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act. Data will be anonymised and pseudonymised when applicable. Identifiable data will be transferred to NHS England where participants have given their consent.

#### 1. Data management

We detail below the data management for data captured and laid out in section 3.1 (pages 13-21), Table 1, Figure 1, Figure 2, Figure 3, Figure 4 and Figure 5.

Participants will be asked to provide demographic data which does not contain individual patient identifiable data (i.e., sex assigned at birth, gender, age, sexual orientation). For this group of participants, we will not hold data that could breach their confidentiality (see Figure 1 and Table 1).

Participants will be asked if they consent to linking their responses to national cancer registries. If they agree to this, then they will be asked for their name and date of birth to allow us to undertake the linkage via NHS England. This will mean that for this group we will hold data that can identify them and any breach of this could potentially threaten their confidentiality (see Figure 3 and Table 1).

Participants will also be asked in a non-randomised manner if they consent to receiving a one-week follow-up survey, to keeping updated on the results of the study or to having a 12-month follow-up survey. If they consent, they will be asked to provide an email address for contact (see Figure 3, Figure 4 and Table 1). We will hold that email address securely. It will not be shared with third parties.

At a participant level we have empowered people to take an approach that they are comfortable with regarding identifiable data and its use by allowing the participant to opt in or out of providing identifiable data and consenting to linkage with national cancer datasets.

This study has been developed in partnership with members of a PPI group with experience in PROM and data research in cancer care. They supported the approach we have adopted whereby participants can decide how much of their data they are happy to share.

## 2. Storage arrangements

Data will be collected using Qualtrics for which Imperial College London has a license. Qualtrics is a secure online platform and data will not be physically collected, recorded, and kept in a physical place. Qualtrics is already used by Epsom and St Helier University Hospitals NHS Trust<sup>37</sup> and was used during the coronavirus pandemic in 2020 by universities<sup>38,39</sup>.

## Indigo Community

INVESTIGATING DIGITAL OUTCOMES

## DATA FLOWCHART

VERSION 1.0 - 10/02/2023 - IRAS: 324034

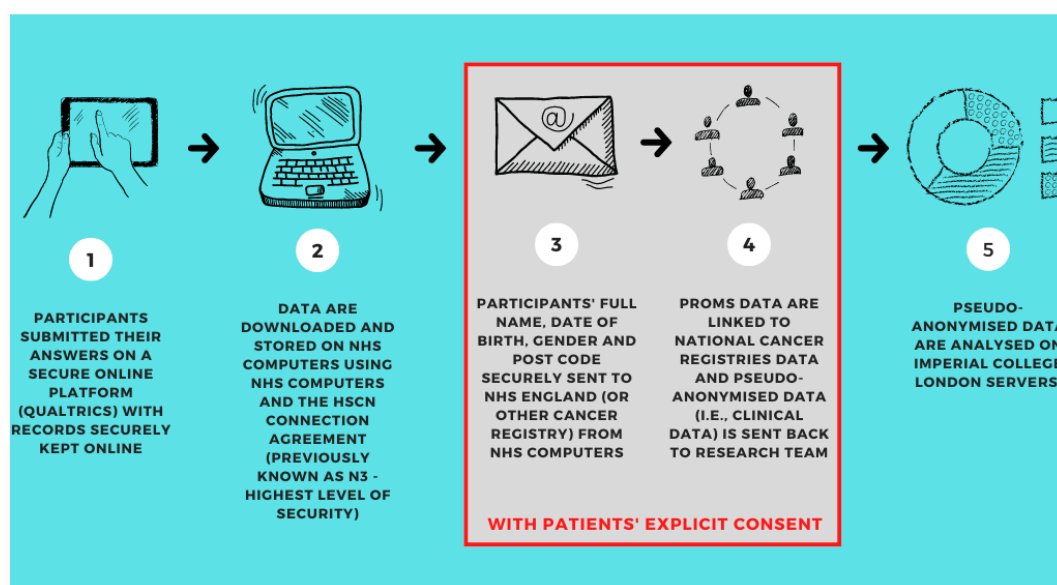


Figure 7: Data flowchart between Qualtrics, HSCN, cancer registries and Imperial College London

When enough participants have taken part in this trial, we shall download their consent and data on NHS servers and within a secure environment using the Health and Social Care Network (HSCN – previously known as N3). Personal identifiable data and anonymous data will be stored with the same levels of security. For patients who agreed to have their data linked to cancer registries, their data will be shared with NHS England using HSCN and NHS.net environments.

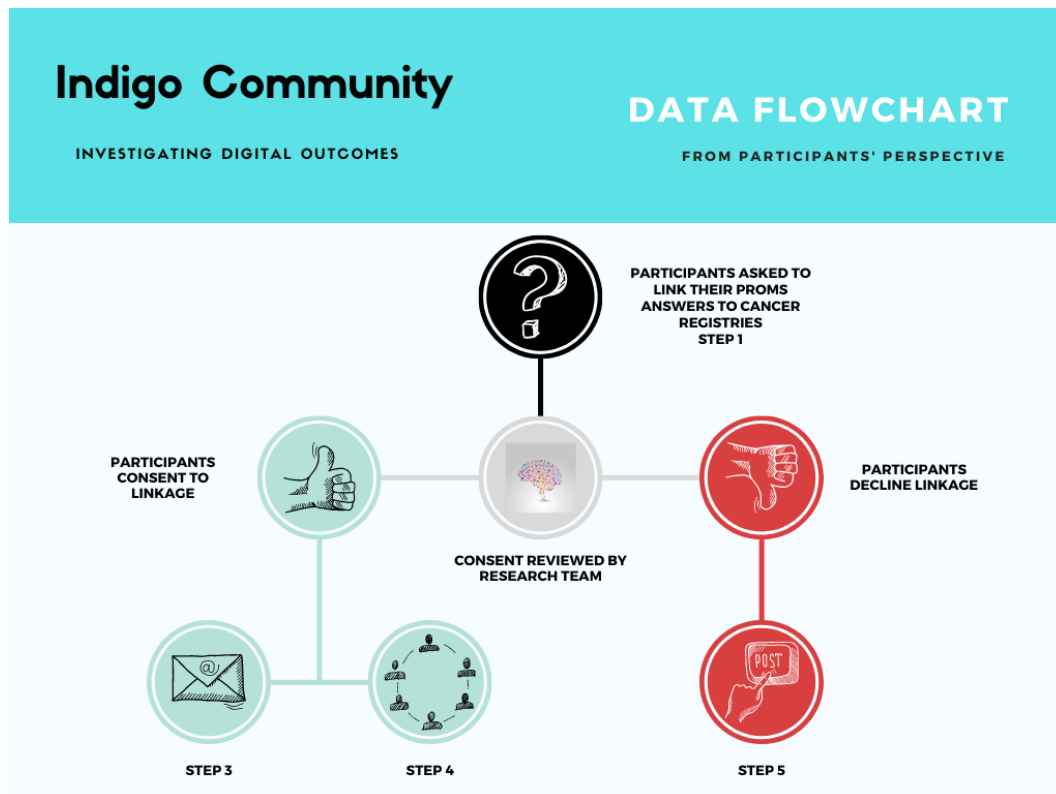


Figure 8: Data flowchart from the participants' perspective for the actions following the consent to linkage to national cancer registries. Participants can review what data are captured by national cancer registries before they consent.

A trial number will be randomly assigned to patients who consented to have their data linked. This will allow us to receive participants' pseudo-anonymised health records on ISO-27001:2013 certified research environment at Imperial College London and compliant with NHS England Data Security and Protection Toolkit (EE133887-BDAU).

The regional and national cancer registries had an active input in the creation and editing of the consents requested throughout the questionnaire and ensure they will accept the data reception at the time of linkage. To receive the data (Step 5 on Figure 7), a separate data application through NHS England's DARS will be started once enough participants have enrolled in this study.

### 3. INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

### 4. SPONSOR

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS Trusts taking part in this study.

### 5. FUNDING

The Brain Tumour Research Campaign is funding this study.

## **6. AUDITS**

The study may be subject to audit by Imperial College London Trust under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Framework for Health and Social Care Research.

## **8. STUDY MANAGEMENT**

The day-to-day management of the study will be co-ordinated through Imperial College Healthcare NHS Trust and the Computational Oncology Laboratory (Imperial College London).

## **9. PUBLICATION POLICY**

The study will be registered through publication of the study protocol in an open access journal, highlighting on our public webpage and publicising the study aims and objectives before we have results through conference presentation.

The results will be reported and disseminated through blog posts, social media, publications in peer reviewed scientific journals and conference presentations.

Where patients consent, the PROM data will be given to NHSE for linkage and further use. However, where possible, we will provide summarised and aggregated data to support our published work.

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