A **S**tudy within a trial of electronic versus paper based **P**atient **R**eported o**U**tcomes **C**oll**E**ction

PROTOCOL

Version: 5.0
Dated: 03/01/2023

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Sponsor:	The Institute of Cancer Research
Coordinating Trials Unit:	ICR Clinical Trials and Statistics Unit (ICR-CTSU) The Institute of Cancer Research

REC Reference Number:	21/WM/0223
IRAS Project ID:	295218
ICR-CTSU Protocol Number:	ICR-CTSU/2021/10074
Sponsor Number:	CCR5447
SWAT Repository Number:	169

The SPRUCE study is part of the National Institute for Health Research Clinical Research Network Trial Portfolio

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Every care was taken in the preparation of this protocol, but corrections or amendments may be necessary. Protocol amendments will be circulated to participating sites as they occur, but sites entering patients into the study for the first time are advised to contact ICR-CTSU to confirm they have the most recent version.

HISTORY OF PROTOCOL AMENDMENTS

PROTOCOL VERSION AND DATE	SUMMARY OF CHANGES
Version 2.0 03/03/2022	A number of changes have been made for alignment with current processes. Major changes are detailed below: Removal of timeframe for consideration of the Participant Information Sheet. Update to study entry contact details. Update to information required at study entry. Measure of impact of SPRUCE on the host trial added. If necessary, ICR-CTSU may ask sites to administer the questionnaire for the first post-intervention time point. Addition of patients' site transfer process. Addition of remote consent process.
Version 3.0 23/05/2022	Addition of PIVOTALboost as a host trial.
Version 4.0 21/10/2022	Addition of demographics questionnaire. Addition of guidance for participants completing their questionnaires electronically. Minor changes for clarification/consistency throughout.
Version 5.0 03/01/2023	Change of Chief Investigator Addition of PACE-NODES as a host trial.

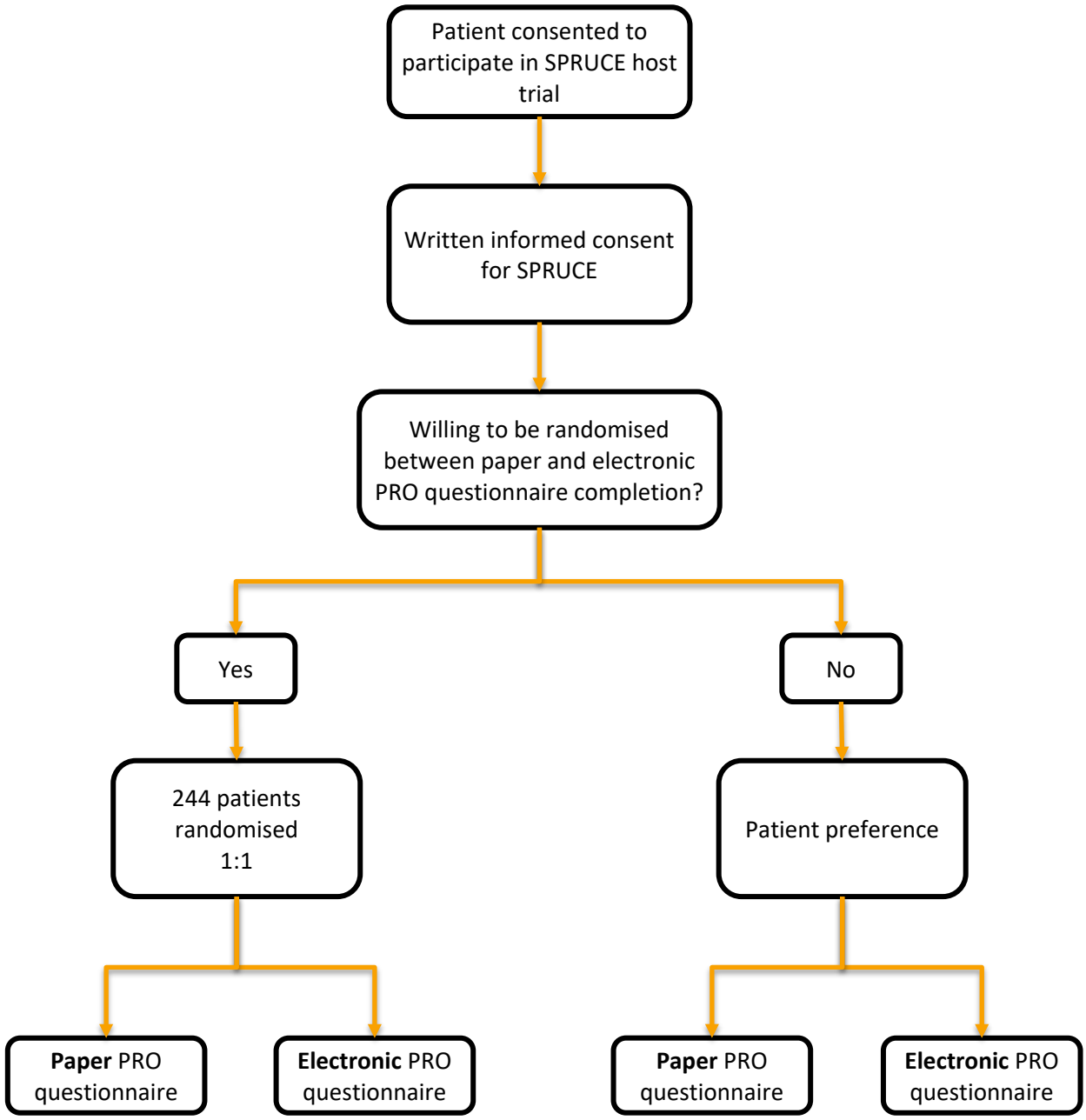
CONTENTS

SPRUCE SUMMARY

PROTOCOL TITLE	A **S**tudy within a trial of electronic versus paper-based **P**atient **R**eported o**U**tcomes **C**oll**E**ction
STUDY OBJECTIVES	Primary • To assess whether there are differences in return rates (compliance) between electronic and paper patient reported outcome (PRO) questionnaires at the first post intervention time point. Secondary • To investigate whether there are differences in response scores between the two modalities (electronic and paper) at key time points. • To assess whether there are differences in return rates (compliance) between paper and electronic questionnaires at later time points after the first post intervention questionnaire. • To investigate whether there are differences in number of items completed within a questionnaire (completeness) between electronic and paper questionnaires. • To investigate whether there are differences in satisfaction between participants filling out electronic or paper questionnaires • To investigate whether there are any demographic differences between people who agree to be randomised and those who choose to complete questionnaires electronically or on paper • To investigate whether changes in response scores from baseline (paper questionnaire) to follow-up vary according to modality of follow-up questionnaire completion. • To investigate the time taken to distribute paper questionnaires compared to electronic questionnaires. • To assess the requirement to remind patients to fill in paper and electronic questionnaires.
STUDY DESIGN	Partially randomised patient preference study within a trial (SWAT).
STUDY POPULATION	Participants in ICR-CTSU oncology trials which are hosting the SWAT (see appendices).
RECRUITMENT TARGET	Two-hundred and forty-four participants are required for the randomised comparison. An estimated 366 participants, including those in the patient preference cohort, will be enrolled.
STUDY INTERVENTION	Modality of PRO questionnaire – electronic or paper.
PRIMARY ENDPOINT	Compliance with questionnaire completion, defined as the percentage of patients returning a questionnaire out of those expected (i.e. not withdrawn or died) at the first questionnaire time point after an intervention within the host trial.

SECONDARY ENDPOINTS	• Domain scores and item responses at key QoL host trial time points. • Compliance with questionnaire completion at all further time points of QoL collection within the host trial. • Completeness of data (% of questions filled in within the questionnaire) in the host trial's primary QoL questionnaire. • Patient satisfaction with electronic and paper questionnaires. • Patient demographics in each group • Change in response scores from baseline. • Time taken (minutes) to prepare a paper questionnaire for distribution compared to electronic dispatch. • % of patients sent reminders to complete questionnaires for paper and electronic questionnaires.
FEASIBILITY ENDPOINTS	• The proportion of participants opting for a preference rather than randomisation after 50 participants have been enrolled. • The number of participants recruited after 6 months.
FOLLOW UP	Follow up questionnaires will be administered at time points determined by the host trial. Questionnaires will be administered for the purposes of the SPRUCE study up to 12 months post study entry, after which PRO data will continue to be collected within the host trial as appropriate. Data collected within SPRUCE will be shared with the host trials for the purposes of trial specific PRO analyses. Participants will be sent a demographics questionnaire for completion after study entry in their chosen/allocated format. SPRUCE participants will receive a paper questionnaire regarding satisfaction with questionnaire method 14 months after study entry.

STUDY SCHEMA



1. INTRODUCTION

Within healthcare and clinical trials, questionnaires can be used to collect information directly from patients on the impact that treatment and health conditions may be having upon their quality of life. These data are known as patient reported outcomes (PRO) and are defined as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else"(1). A wide range of validated questionnaires are used to collect PRO, covering general health items as well as more disease specific factors.

Within oncology trials, the patient perspective and survivorship effects are crucial factors to consider in evaluation of new treatments (2). Quality of life (QoL) information is thus a key factor to consider in their adoption and implementation. At many clinical trials units, including the Institute of Cancer Research Clinical Trials Statistical Unit (ICR-CTSU), QoL information is currently captured with paper PRO questionnaires to inform primary and key secondary end points of clinical trials. Collection of PROs is a time consuming and laborious process requiring significant input from both patients, hospital staff and clinical trials units often over an extended period of time. Streamlining this process with the use of technology in the form of electronic PRO (ePRO) questionnaires has the potential to increase patient convenience, improve patient experience, reduce administrative burden, save costs, increase patient compliance and avoid secondary data errors including those due to data transcription, leading to more accurate and complete data (3)(4).

Over the past decade, advances in information technology and improved access to the internet have led to a rapid increase in the use of electronic devices including smartphones, tablets and laptops. In 2019 91% of adults in the UK had regular use of the internet (5), with the over 65s having a striking increase in internet use from 2011 to 2019. The effect of the COVID-19 crisis is likely to have increased internet exposure further and it has already been shown that the proportion of online adults aged over 65 who make a least one video-call each week increased from 22% in February 2020 to 61% by May 2020 (6).

Although ePRO questionnaires have been widely studied in the general clinical setting it is yet to be proven that they are as effective as paper PRO questionnaires at collecting data within clinical trials where there are additional research ethics, research governance and regulatory requirements to comply with. Our study will pilot implementation of ePRO collection within ICR-CTSU trials and generate evidence regarding its equivalence to paper-based collection. This research will investigate whether ePRO questionnaires can be used within multicentre clinical trials and reduce the burden of clinical trial follow up on patients, allowing patients to participate in quality of life follow up with the minimum possible inconvenience at a time when the patient is already under the stress of being unwell. If this is the case the impact could allow for more comprehensive quality of life study recruitment and responses, helping ensure the patient experience is captured as accurately as possible over the appropriate duration of time.

1.1. BACKGROUND

There has been extensive work conducted across different medical specialities to establish the intra-patient equivalence of paper and electronic based questionnaires within participants and their validity for data collection in a clinical setting. Muehlhausen et al (7) conducted a systematic review and meta-analysis of the equivalence of patient reported outcome measures administered by electronic and paper formats. The review included 72 studies, showing overall equivalence between the two formats when completed by the same patients. This was an update of a previous review by Gwaltney et al conducted in 2008 (8), which also showed equivalence within participants. Following on from these two meta-analyses, further studies have added weight to the finding of equivalence of data following migration from original paper to electronic format. Participants of these studies had the equivalence

of scores compared between their completion of both paper and electronic questionnaires, with a paper test retest arm as the control (9) (10).

Patient compliance with ePRO questionnaires and the completeness of data returned is essential for clinical trials. One factor that may increase questionnaire return rates and improve the patient experience is to reduce the amount of time required to complete. Park et al showed within the clinical outpatient setting that time taken to complete the electronic form was significantly shorter than that required for the paper version (11). Some studies have shown 83% compliance with ePRO questionnaires in the clinic, with between 76 and 95% of patients finding the system usable and recommending it to others (12)(13). On the other hand, studies in a surgical setting found poor uptake of ePRO questionnaires amongst participants offered the option. In a recent report from 2019 only 12% of 642 participants opted for completion of e-PRO in one study and 34% of 1296 participants opted for it in another. Overall, 280 of ~5700 (~5%) questionnaires were completed electronically, with the remainder completed by post or in clinic(14).

There are two significant limitations of literature published to date. Firstly, although ePRO questionnaires are becoming increasingly popular for use in clinical trials, there is limited evidence of patient uptake and compliance in this setting, and none from randomised studies. One trial including rheumatoid arthritis patients within two randomised control trials asked patients to fill in electronic diaries. This study showed high compliance of up to 93% of patients over 12 weeks, however there was the lack of a control group filling out paper questionnaires, meaning it is not possible to be sure the compliance was non-inferior to paper diaries (15) .

The second limitation is the lack of information as to whether completeness of data is equivalent or superior in the electronic format. One recent study in a healthy university undergraduate population (16) did assess data capture in electronic and paper versions with participants of a prospective study being given the opportunity to choose the format for completion of a food intake based questionnaires at baseline and 10 year follow up. The results were mixed, with increased missing data in some subsections in the electronic version with improved data levels in other subsections. The paper concluded that data capture was equivalent. However, these results may not be applicable in a patient population, particularly in oncology where patients can be unwell and more likely to be in the older section of the population. There are a limited number of other studies that performed randomised group studies but these again are largely in either the mental health, general healthy or paediatric population (17)(18) and therefore not directly applicable to oncology patient population.

1.2. DESCRIPTION OF POPULATION

The study population includes all patients recruited to an ICR-CTSU host trial within which SPRUCE is embedded. All participants will be UK cancer patients aged at least 16 years old.

1.3. STUDY RATIONALE

The proposed study aims to assess the effectiveness of using electronic questionnaires to collect PROs, exploring the potential for improving collection of PROs for future assessment of impact of health interventions on trial participants.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective is to assess whether there are differences in return rates (compliance) between electronic and paper PRO questionnaires at the first post intervention time point.

2.2. SECONDARY OBJECTIVES

- To investigate whether there are differences in response scores between the two modalities (electronic and paper) at key time points (e.g. due to convenience of returning ePRO questionnaires more severe PRO issues may be identified electronically).
- To assess whether there are differences in return rates (compliance) between paper and electronic questionnaires at later questionnaire time points.
- To investigate whether there are differences in number of items completed within a questionnaire (completeness) between electronic and paper questionnaires.
- To investigate whether there are differences in satisfaction between participants filling out electronic or paper questionnaires
- To investigate whether there are any demographic differences between people who agree to be randomised and those who choose to complete questionnaires electronically or on paper
- To investigate whether changes in response scores from baseline (paper questionnaire) to follow-up vary according to modality of follow-up questionnaire completion.
- To investigate the time taken to distribute paper questionnaires compared to electronic questionnaires.
- To assess the requirement to remind patients to fill in paper and electronic questionnaires.

2.3. FEASIBILITY OBJECTIVES

- To assess patient acceptance of randomisation between questionnaire modalities.
- To assess feasibility of recruitment**.**

3. STUDY DESIGN

This is a study within a trial (SWAT) which will be run in multiple ICR-CTSU trials to include participants affected by a range of cancers representative of those in ICR-CTSU's trial portfolio.

SPRUCE is a partially randomised patient preference study investigating electronic versus paper PRO collection.

Following enrolment into a host trial, eligible participants will be approached regarding taking part in the SPRUCE study. Patients who provide written informed consent to join SPRUCE will either be:

- Randomised 1:1 between electronic and paper PRO questionnaire completion

OR

- Registered for electronic or paper PRO questionnaire completion

Whether a participant is randomised or registered will be determined by patient preference.

The study has two formats depending on the host trial within which it is embedded:

- Format A:

  Applicable where a host trial does include patient reported outcome measures within the approved trial protocol. The instrument used to capture the host trials' primary PRO endpoint will be the key questionnaire of interest in SPRUCE. PRO data for host trial participants who are also participating in SPRUCE will be collected within SPRUCE (and not within the host trial)

and the questionnaire schedule and content will follow that of the host trial. Data will be shared with the host trial for the purpose of the host trial's PRO analysis. Details of each host trial will be set out in an appendix to this protocol.

- Format B:

  Applicable where a host trial does not include patient reported outcome measures within the approved trial protocol. The EORTC QLQ-C30 will be administered at time points selected to fit the host trials' patient pathway. Details of each host trial will be set out in an appendix to this protocol.

4. STUDY ENDPOINTS

4.1. PRIMARY ENDPOINT

Compliance with questionnaire completion, defined as the percentage of patients returning a questionnaire out of those expected (i.e. not withdrawn or died) at the first quality of life assessment time point after completion of the host trial's study intervention.

4.2. SECONDARY ENDPOINTS

- Domain scores and item responses at key QoL host trial time points.
- Compliance with questionnaire completion at all further time points of QoL collection within the host trial.
- Completeness of data (% of questions filled in within the questionnaire) in the host trial's primary QoL questionnaire.
- Patient satisfaction with electronic and paper questionnaires.
- Patient demographics in each group
- Change in response scores from baseline.
- Time taken (minutes) to prepare a paper questionnaire for distribution compared to electronic dispatch.
- % of patients sent reminders to complete questionnaires for paper and electronic questionnaires.

4.3. FEASIBILITY ENDPOINTS

- The number of participants opting for a preference rather than randomisation after 50 patients have enrolled.
- The number of participants enrolled after 6 months.

5. PATIENT SELECTION & ELIGIBILITY

5.1. NUMBER OF PARTICIPANTS

Two-hundred and forty-four randomised participants are required to detect non-inferiority of electronic PRO questionnaires compliance compared to paper with a 10% non-inferiority margin i.e. at most 10% worse compliance. We have assumed that approximately two-thirds of patients entering the SWAT will agree to be randomised thus anticipate needing to recruit approximately 366 patients overall.

5.2. SOURCE OF PARTICIPANTS

Participants will be recruited from ICR-CTSU clinical trials hosting the SWAT from participating NHS sites in the UK. Potential participants will be identified by their clinical care/research teams during the process of assessment for eligibility for an ICR-CTSU host trial.

5.3. INCLUSION CRITERIA

1. Participation in a host trial
2. Participation in host trial's QoL/PRO sub study (if applicable - format A only)
3. Informed consent for participation in SPRUCE

4. Ability to read English

5.4. EXCLUSION CRITERIA

None

5.5. PROCEDURE FOR OBTAINING INFORMED CONSENT

The Principal Investigator (or designated individual) must ensure that each study participant is fully informed about the nature and objectives of the study and possible risks associated with participation. Participants should be given the current ethics approved SPRUCE patient information sheet for their consideration. Patients should only be asked to consent to the study after they have had sufficient time to consider the information, and the opportunity to ask any further questions.

Patients who are unwilling to be randomised should be offered participation in the patient preference cohort. Refusal to participate in the SPRUCE study will not result in ineligibility to participate in the host trial.

Confirmation of the patient's consent and the informed consent process must be documented in the patient's medical notes. A copy of the signed consent form should be provided to the patient and the original retained in the investigator site file, which must be available for verification by ICR-CTSU study staff or for regulatory inspection at any time.

5.6. PARTICIPATION IN OTHER CLINICAL TRIALS

As SPRUCE is a SWAT participants in SPRUCE will already be enrolled in a host ICR-CTSU trial. Participants in ICR-CTSU host trials will be able to participate in further clinical trials in accordance with the host trial protocol.

6. STUDY ENTRY

Patients must be centrally enrolled onto the study by the trials unit (ICR-CTSU) following informed consent.

Patients should be enrolled onto the study by emailing ICR-CTSU on:
randomisation-icrctsu@icr.ac.uk
and requesting a call back
09.00-17.00 (UK time) Monday to Friday

Patients will either be randomised between paper and PRO completion or registered to complete questionnaires in their preferred format. A study entry checklist must be completed prior to randomisation.

The following information will be required at study entry:

- Name of hospital, consultant and person registering patient
- Confirmation that patient has given written informed consent for study
- Confirmation that patient is eligible for the study
- Whether the patient has consented to being randomised to either paper or electronic questionnaires
- Preferred modality of PRO completion if patient has not consented to be randomised
- ICR-CTSU host trial name, host trial ID and date of enrolment onto the host trial
- Host trial treatment start/end date (if available)
- Patient's full name, postal address, email address (if applicable/available), sex and date of birth

The caller will be given the patient's unique study number (study ID) and questionnaire format allocation.

ICR-CTSU will send confirmation to the recruiting site to confirm patients' entry into the study.

Participants completing their questionnaires electronically will be provided with participant electronic questionnaire guidance for using the electronic system.

7. STUDY ASSESSMENTS

7.1. PRIOR TO STUDY ENTRY

All participants should complete their baseline questionnaire booklet on paper.

For format A studies the host trial's approved baseline booklet should be completed by SPRUCE participants as part of the host trial entry procedure and in accordance with instructions in the host trial's protocol.

7.2. FOLLOW UP

Follow up questionnaires will be administered at time points determined by the host trial for format A and B, as described in the trial specific appendices.

Questionnaires will be administered for the purposes of the SPRUCE study up to 12 months post study entry, after which PRO data will continue to be collected within the host trial as appropriate.

7.3. DEMOGRAPHICS QUESTIONNAIRE

Participants will be sent a demographics questionnaire after study entry in their chosen/allocated format.

7.4. POST-QUESTIONNAIRE FOLLOW UP

Participants will receive a paper questionnaire regarding satisfaction with questionnaire method at 14 months after study entry.

7.5. DISCONTINUATION OF PARTICIPATION

Participants may discontinue from participation in SPRUCE at any time at their own request. Participants who cease participation will continue to be followed up in the QoL sub study within the host trial for format A, unless they specify otherwise.

8. STATISTICAL CONSIDERATIONS

8.1. STATISTICAL DESIGN AND SAMPLE SIZE JUSTIFICATION

This is a partially randomised patient preference study, allowing participants to choose a preferred modality for questionnaire completion if they are unwilling or unable to be randomised between electronic or paper questionnaires. The randomised and patient preference groups will be analysed separately.

Sample size estimates are based on numbers required for the randomised part of the study. Based on compliance reports from existing ICR-CTSU trials, return rates for paper questionnaires are expected to be in the region of 90% at the first post intervention time point. 244 patients would therefore be required to be randomised (1:1) to exclude $\leq$80% compliance rates with ePRO (i.e. 10% non-inferiority margin), with 80% power and 1-sided alpha=0.05).

We have assumed that approximately two-thirds of patients entering the SWAT will agree to be randomised thus anticipate needing to recruit 366 patients overall (244 randomised and 122 preference).

The proportion of participants opting for allocation via randomisation versus preference will be monitored throughout SPRUCE; if the numbers in the randomisation cohort are lower than anticipated then the study design may be changed to offer all patients the choice of electronic or paper questionnaires (see Section 8.4).

8.2. QUESTIONNAIRE FORMAT ALLOCATION

Participants providing written informed consent will first be asked if they agree to being randomised between the two groups. If they agree they will be randomised 1:1 based on minimisation factors of age and sex and host trial to receive either electronic or paper questionnaires. A minimum of two and a maximum of six host trials will be included. The minimisation algorithm used in ICR-CTSU has a random element.

If participants do not agree to be randomised they can take part in the study in the group of their choice i.e. paper or electronic questionnaires and the reason for refusing randomisation/preferring one format will be recorded.

8.3. STATISTICAL ANALYSIS PLAN

The randomised and patient preference cohorts will be analysed separately for all endpoints as confounders including patient baseline characteristics (e.g. age, sex) will need to be taken into account for the comparisons between electronic and paper questionnaires in the non-randomised patients. Regression analyses will adjust for potential confounders such as patient demographics and clinical characteristics for the comparison of outcomes between the patient preference groups. Additionally, descriptive analyses will summarise demographic and clinical characteristics of patients opting for randomisation versus expressing a preference.

The primary outcome of compliance at the first post intervention time point within the host trial will be calculated as percentage of returned questionnaires out of those expected (i.e. not withdrawn or died) for the electronic and paper questionnaire groups, and the difference calculated along with a 2-sided 90% confidence interval. Non-inferiority for electronic questionnaires will be concluded if the lower confidence limit for the difference in compliance for electronic versus paper questionnaires is greater than -10%.

For the secondary outcomes of questionnaire compliance at further time-points and data completeness, percentages between groups at each time-point will be tabulated. Questionnaire domain scores will be calculated as per guidance for each specific measure (e.g. the global health/overall quality of life score from the EORTC QLQ-C30), and compared between electronic questionnaires and paper questionnaires at each time-point using descriptive statistics appropriate for the distributions (e.g. means or medians for numeric scales and percentages for categorical outcomes). Completeness of data and change in domain scores from baseline will be calculated for each follow-up time point, and described between the electronic and paper questionnaire groups. Patient satisfaction with each questionnaire modality and patient demographics across groups (randomised, chose electronic and chose paper) will be captured via patient completed questionnaire and summarised descriptively. Time taken to distribute questionnaires and proportion of reminders sent will also be described. Where appropriate further statistical tests will be used to compare electronic and paper groups for the secondary endpoints including t-tests or Mann-Whitney tests for continuous data. For ordinal data, the chi-squared test for trend will be used. Chi-squared tests will be used for categorical data; Fisher's exact will be used if assumptions of chi-squared are not met.

Further details of analysis methods will be specified in a Statistical Analysis Plan in accordance with ICR-CTSU Standard Operating Procedures.

8.4. INTERIM ANALYSES AND STOPPING RULES

The number of patients opting for a preference rather than allocation via minimisation will be monitored monthly and assessed after 50 patients have been recruited. If greater than 50% of participants have declined allocation via minimisation, or subsequently declined allocated modality, consideration will be given to ceasing randomisation and adopting an alternative recruitment and analysis strategy.

The overall feasibility of recruitment for the study will be monitored and re-evaluated if a third of the required patients have not been recruited within 6 months of the study commencing. If recruitment was an issue at that point, the decision to increase the number of sites that the SWAT is run at or to embed the SWAT into further ICR-CTSU trials could be taken to improve recruitment.

Impact of SPRUCE on PRO uptake and drop out in host trials will be monitored to ensure that PRO data collection within the host trial is not adversely affected by the SWAT. Under format A this will consider the number/proportion of patients consenting to provide PRO data pre and post implementation of SPRUCE.

An interim analysis to review emerging data is planned between 12-18 months after the trial opens and will include the facility to include data in a confidential PhD thesis. Analyses will follow the main statistical analysis plan, although may be largely descriptive if the number of patients are insufficient for formal statistical analysis. Results will be confidential and only for the purposes of the PhD.

9. STUDY MANAGEMENT

9.1. STUDY MANAGEMENT GROUP (SMG)

A Study Management Group (SMG) will be set up and will include the Chief Investigator, ICR-CTSU Scientific Lead, Co-investigators and identified collaborators, the Study Statistician and Study Manager. Principal Investigators and key study personnel will be invited to join the SMG as appropriate to ensure representation from a range of sites and professional groups. Membership will include a lay/consumer representative. The SMG will meet at regular intervals, and at least annually. Notwithstanding the legal obligations of the Sponsor and Chief Investigator, the SMG have operational responsibility for the conduct of the study. The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSU.

9.2. PATIENT AND PUBLIC OVERSIGHT COMMITTEE

A patient and public oversight committee will be constituted from members of the focus groups which advised on SPRUCE study design. This committee will meet at regular intervals to oversee the study from a PPI perspective and advise on any issues as they arise. They will also help with dissemination of results through their links with national PPI groups and other routes as appropriate.

10. RESEARCH GOVERNANCE

10.1. SPONSOR RESPONSIBILITIES

The Sponsor of this study is the Institute of Cancer Research (ICR).

10.2. PARTICIPATING SITE RESPONSIBILITIES

Responsibilities delegated to participating sites are defined in an agreement between the Sponsor and the individual site. The Principal Investigator is responsible for the trial team and trial conduct at the participating site.

11. TRIAL ADMINISTRATION & LOGISTICS

11.1. SITE ACTIVATION

Before activating the trial, participating sites are required to sign the organisational information document (OID) accepting responsibility for all trial activity which takes place within their site.

Sites may commence recruitment once the OID has been signed by all required signatories, the required study documentation is in place (as specified by ICR-CTSU) and a site initiation has taken place.

11.2. DATA ACQUISITION

Participants will complete an initial questionnaire booklet on paper, then further questionnaires will be completed in accordance with their randomly allocated or preferred format. All participants will be sent a demographics questionnaire following study entry.

Participants completing questionnaires electronically will receive invitations at the required time points, with a personalised email link sent to the patient for electronic questionnaire completion. ICR-CTSU will provide guidance to participants to aid the completion of questionnaires. If the questionnaires are not returned within a reasonable time frame, a reminder email will be sent to participants. If two consecutive questionnaires are not completed within a reasonable time frame, a change in participation email will be sent, prompting the participant to inform the ICR-CTSU team if they no longer wish to participate in the study.

Participants completing questionnaires on paper will receive booklets by post by the ICR-CTSU following confirmation from the participating site that the patient is alive and able to fill in the questionnaire. Completed booklets will be posted to ICR-CTSU for data entry. If the questionnaires are not returned within a reasonable time frame, a reminder letter will be sent to participants. If two consecutive questionnaires are not completed within a reasonable time frame, a change in participation letter and form will be sent, prompting the participant to inform the ICR-CTSU team if they no longer wish to participate in the study.
If necessary, ICR-CTSU may ask sites to administer the questionnaire for the first post-intervention time point.

A participant satisfaction survey will be sent by ICR-CTSU to all participants for completion on paper 14 months after joining the study.

11.3. PATIENT TRANSFER

If a participant is transferred within their host trial for clinical follow up at a site not participating in SPRUCE, it remains the responsibility of the original SPRUCE site to respond to health checks or other potential queries from ICR-CTSU. If the participant is transferred to a site participating in SPRUCE, the ICR-CTSU should be notified to transfer SPRUCE site.

11.4. CENTRAL DATA MONITORING

Questionnaires with missing data will not be returned to participants for completion as responses should relate to the timeframe specified on the individual questionnaires (e.g. EORTC QLQ-C30 concerns symptoms within the past week). Additionally, data completeness is a secondary endpoint within SPRUCE. Nevertheless, missing data will be monitored regularly to check that there are no issues with the electronic data capture system for example.

11.5. COMPLETION OF THE STUDY AND DEFINITION OF STUDY END DATE

The study end date is deemed to be the date of last data capture.

11.6. ARCHIVING

Essential study documents should be retained according to local policy and for a sufficient period for possible inspection by the regulatory authorities (at least 5 years after the date of last data capture). Documents should be securely stored and access restricted to authorised personnel.

12. PATIENT PROTECTION AND ETHICAL CONSIDERATIONS

12.1. RISK ASSESSMENT AND APPROVAL

This study has been formally assessed for risk and approved by the Sponsor's Committee for Clinical Research.

12.2. PUBLIC AND PATIENT INVOLVEMENT

The need for robust PPI has been recognised from the outset of the ICR-CTSU's ePRO implementation project. The patient and public involvement plan for this work commenced prior to implementation of the SWAT and will continue throughout the project

An initial survey was undertaken to assess attitudes to the use of electronic patient reported outcomes in clinical trials. Participants in the survey were asked whether they would be interested in being involved in a focus group relating to the design of the SWAT. These groups provided feedback on the user friendliness of the ePRO system, potential amendments to the system for greater acceptability amongst patients and provided insights into the potential level of guidance required to be provided to participants in the SWAT to help them to use the system. Members of the initial focus group were invited to join the patient and public oversight committee to oversee the remainder of the project and advise on study progress and results dissemination.

Patient advocates were involved in protocol design including methodology, design of the electronic system, patient information sheet and consent form, participant electronic questionnaire guidance, demographics questionnaire and participant feedback survey, and are represented on the SMG and patient and public oversight committee.

12.3. ETHICS APPROVALS

The study will not commence at any participating site until the required approvals are in place. ICR-CTSU, on behalf of the Sponsor, will ensure that the study has received ethics approval from a research ethics committee (REC) for multi-centre studies, HRA approval and relevant NHS Permissions. Before recruiting patients, the Principal Investigator at each site is responsible for obtaining local approvals.

12.4. STUDY CONDUCT

This study will be conducted according to the approved protocol and its amendments, supplementary guidance and manuals supplied by the Sponsor and in accordance with the UK Policy Framework for Health and Social Care and the principles of GCP.

12.5. INFORMED CONSENT

The Principal Investigator retains overall responsibility for the conduct of research at their site; this includes obtaining informed consent from participants. They must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to do so in accordance with the ethically approved protocol, principles of Good Clinical Practice and Declaration of Helsinki. The Principal Investigator can be any suitably qualified healthcare professional.

Patients should be asked to sign the current ethics approved SPRUCE consent form at study entry after receiving both verbal and written information about the trial, having been given sufficient time to consider this information. All consent forms must be countersigned by the Principal Investigator or a designated individual. If consent is taken remotely, the date of remote consent should be recorded in the participant's medical notes and on the consent form once received.

A signature log of delegated responsibilities, listing the designated individuals and the circumstances under which they may countersign consent forms, must be maintained at the participating site. This log, together with original copies of all signed patient consent forms, should be retained in the Site Investigator File and must be available for inspection. The current ethics approved SPRUCE patient

information sheets should be provided in addition to any standard patient information sheets that are provided by the site and used in routine practice.

12.6. PATIENT CONFIDENTIALITY

Patients will be asked to consent to their full name being collected at study entry in addition to their date of birth, address, and email address (if applicable).

Each investigator should keep a separate log of all participants' study IDs, names, postal and email addresses and hospital numbers. The investigator must retain study documents (e.g. participants' written consent forms) in strict confidence. The investigator must ensure the participants' confidentiality is maintained at all times.

Representatives of ICR-CTSU will require access to participants' hospital notes for quality assurance purposes. ICR-CTSU will maintain the confidentiality of participants at all times and will not reproduce or disclose any information by which participants could be identified.

12.7. DATA PROTECTION

All investigators and trials staff must comply with applicable data protection laws at all times.

12.8. LIABILITY

Indemnity to meet the potential legal liability of investigators participating in this study is provided by the usual NHS indemnity arrangements. The ICR has in force clinical trials liability insurance for harm arising from the design or management of the study.

13. FINANCIAL MATTERS

The study is investigator designed and led. The study is supported via the ICR-CTSU's core programme grant from Cancer Research UK. The CI is supported by a Cancer Research UK CTU clinical fellow award. The study meets the criteria for R&D support as outlined in the Statement of Partnership on Non-Commercial R&D in the NHS in England. The trial is part of the National Institute for Health Research Clinical Research Network (NIHR CRN) portfolio. NIHR CRN resources should therefore be made available for the study to cover UK specific research costs.

14. PUBLICATION POLICY

The main study results will be published in a peer-reviewed journal, on behalf of all collaborators. The manuscript will be prepared by a writing group, consisting of members of the SMG. Participating PIs may be selected to join the writing group on the basis of intellectual and time input. All participating PIs will be acknowledged in the publication.

A lay summary of findings will be written in collaboration with the patient and public oversight committee members, and distributed to study participants, with the potential for wider dissemination, for instance via social media.

Any presentations and publications relating to the study must be authorised by the SMG. Authorship of any secondary publications will reflect intellectual and time input. Authorship of all publications will usually be in accordance with ICMJE guidance.

No investigator may present or attempt to publish data relating to SPRUCE without prior permission from the SMG.

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A1. FORMAT A HOST STUDIES

Format A host studies have an existing quality of life sub study within their protocols. In this circumstance the main quality of life questionnaire already used within the trial will be the questionnaire of interest and the time points of administration will be those used within the existing trial protocol.

Format A host trial details are summarised below.

A1.1 HOST TRIAL - PACE-C

A1.1.1. PATIENT POPULATION

Men with intermediate or high risk localised prostate adenocarcinomas defined by:

Intermediate risk (**includes the presence of any of the following, assuming no high risk features apply):**

- Gleason 7 (3+4 OR 4+3)
- T2
- PSA 10-20 ng/ml

High risk includes the presence of any one of the following (max 2 are allowed to be PACE eligible)

- Gleason 4+4*
- T3a (M0N0)
- PSA >20-30 ng/ml

Patients who are not suitable for surgery or who do not wish to consider an operation, and who are planned to receive 6 months of ADT (or, for those diagnosed or due to start radiotherapy during the COVID-19 pandemic, planned to receive extended ADT to allow delayed radiation), will be invited to enter PACE-C.

A1.1.2. TRIAL DESIGN

The PACE trial (ISRCTN: 17627211) is a multi-centre, international phase 3 randomised controlled study comprising three parallel randomisations with a common control experimental arm. The PACE-C cohort compares the use of conventional radiotherapy (60Gy in 20 fractions) to stereotactic body radiotherapy (SBRT) (36.25Gy).

The primary objective is to determine whether prostate SBRT is non-inferior to conventional radiotherapy for freedom from biochemical or clinical failure in patients with intermediate or high-risk prostate cancer.

Secondary objectives are to determine the relative benefits of surgery, conventional radiotherapy and prostate SBRT in terms of local failure, distant failure, disease-free survival, disease-specific survival, overall survival, toxicity, quality of life in generic and organ specific domains.

Non-surgical candidates or patients who decline surgery are randomised to receive either conventional radiotherapy or SBRT. Randomisation is stratified by randomising centre and by PACE-C stratification risk group.

A1.1.3. QUESTIONNAIRE INSTRUMENTS

Patient reported outcomes and quality of life assessments will be completed by all PACE-C trial participants. The following questionnaires will be used:

- International Index of Erectile Function-5 (IIEF-5),
- International Prostate Symptom Score (IPSS),
- Vaizey Incontinence Questionnaire,
- Expanded Prostate Index Composite-26 (EPIC-26)

Bladder, bowel and sexual function will be assessed using EPIC-26. Erectile dysfunction will be assessed using IIEF-5. Urinary and bowel incontinence will also be assessed using the IPSS and Vaizey questionnaires respectively.

A1.1.4. FOLLOW UP TIMEPOINTS

Questionnaire timepoints will be as described in the approved PACE-C trial protocol.

A1.1.5. STATISTICAL CONSIDERATIONS

The time-point of interest for the purposes of SPRUCE primary endpoint will be the first post radiotherapy assessment. Secondary endpoints in SPRUCE will be assessed at follow up timepoints corresponding to PACE-C data collection time-points listed in the approved PACE-C trial protocol.

For the purposes of SPRUCE, the EPIC-26 tool will be considered the primary QoL questionnaire for the SPRUCE primary endpoint. Summary scores will be calculated according to scoring manual guidelines for the questionnaire measures.

A1.1.6. DATA LINKAGE

PRO data completed by PACE-C participants who enter SPRUCE will be collected within the SPRUCE study and collated by the SPRUCE study management team. PRO data from SPRUCE will be integrated with data collected within PACE-C for the purposes of analysis of the PACE-C trial endpoints. Data will be linked via the host trial ID number and SPRUCE study ID.

A1.2 HOST TRIAL - PIVOTALBOOST

A1.2.1. PATIENT POPULATION

Patients receiving radical radiotherapy for localised, node negative prostate cancer.

A1.2.2. TRIAL DESIGN

PIVOTALboost (ISRCTN 80146950) is a multicentre randomised controlled phase III trial in patients with localised prostate cancer, with an adaptive parallel arm design. Patients approached about SPRUCE will be allocated to one of the following treatment groups:

- Prostate alone intensity modulated radiotherapy (IMRT)
- Prostate IMRT and prostate boost.
- Prostate and pelvic IMRT and prostate boost.

The primary objective is to assess whether pelvic lymph node radiotherapy with or without dose escalation to the prostate with high dose-rate brachytherapy (HDR), HDR incorporating a focal boost or focal boost IMRT when delivered at multiple centres can lead to improved failure free survival with similar levels of bladder (genitourinary) and bowel (gastrointestinal) side effects experienced by patients.

Secondary objectives are to assess acute bladder and bowel toxicity of hypofractionated prostate radiotherapy at 18 weeks, late toxicity, quality of life, time to loco-regional recurrence, time to biochemical or clinical failure, metastatic relapse free survival, overall survival and prostate cancer specific survival, time to recommencement of androgen deprivation therapy, and health economic endpoints.

Balancing factors at randomisation are centre, NCCN risk group, boost volume on MRI and type of boost.

A1.2.3. QUESTIONNAIRE INSTRUMENTS

Completion of patient reported outcomes and quality of life assessments is optional for PIVOTALboost trial participants. The following questionnaires will be used:

- Assessment of Late Effects of Radiotherapy - Bowel screening tool (ALERT-B)
- Gastrointestinal Symptom Rating Scale (GSRS),
- International Index of Erectile Function-5 (IIEF-5),
- International Prostate Symptom Score (IPSS),
- Expanded Prostate Index Composite-26 (EPIC-26)
- EQ-5D

Bladder, bowel and sexual function will be assessed using EPIC-26. Erectile dysfunction will be assessed using IIEF-5. Urinary incontinence will also be assessed using the IPSS questionnaire. Gastrointestinal symptoms will be assessed using ALERT-B and GSRS. EQ-5D will be used to measure general health-related quality of life.

A1.2.4. FOLLOW UP TIMEPOINTS

Questionnaire timepoints will be as described in the approved PIVOTALboost trial protocol.

A1.2.5. STATISTICAL CONSIDERATIONS

The time-point of interest for the purposes of SPRUCE primary endpoint will be the first post radiotherapy assessment. Secondary endpoints in SPRUCE will be assessed at follow up timepoints corresponding to PIVOTALboost data collection time-points listed in the approved PIVOTALboost trial protocol.

For the purposes of SPRUCE, the IPSS tool will be considered the primary QoL questionnaire for the SPRUCE primary endpoint. Summary scores will be calculated according to scoring manual guidelines for the questionnaire measures.

A1.2.1. DATA LINKAGE

PRO data completed by PIVOTALboost participants who enter SPRUCE will be collected within the SPRUCE study and collated by the SPRUCE study management team. PRO data from SPRUCE will be integrated with data collected within PIVOTALboost for the purposes of analysis of the PIVOTALboost trial endpoints. Data will be linked via the host trial ID number and SPRUCE study ID.

A1.3 HOST TRIAL – PACE-NODES

A1.3.1. PATIENT POPULATION

Patients with high risk localised prostate cancer, deemed suitable for SBRT radiotherapy and planned for 12 - 36 months androgen deprivation therapy

A1.3.2. TRIAL DESIGN

PACE-NODES (ISRCTN 80146950) is a multicentre randomised controlled phase III trial in patients with high risk localised prostate cancer. Patients approached for SPRUCE will be allocated to one of the following treatment groups:

- Prostate alone SBRT (P-SBRT) to receive 36.25Gy in 5 fractions to the prostate and seminal vesicles.
- Prostate and pelvic node SBRT (PPN-SBRT) to receive 36.25Gy in 5 fractions to the prostate and seminal vesicles and 25Gy in 5 fractions to pelvic nodes.

The primary objective is to determine whether PPN-SBRT has superior biochemical/clinical-failure free rate (reduces the risk of biochemical or clinical failure by 50% or more) than P-SBRT, in patients with high risk localised prostate cancer.

Secondary objectives are to assess acute and late GI and GU toxicity with SBRT and PPN-SBRT, to assess patient reported outcome measures of bowel, urinary and late erectile dysfunction with the two treatments, to assess efficacy of the two treatment approaches in terms of subsequent occurrence of metastatic disease and (prostate cancer) deaths, and to demonstrate feasibility of PPN-SBRT with respect to radiotherapy planning and delivery (adherence to pre-specified dose constraints) in a multi-centre setting.

Balancing factors at randomisation are centre, radiological staging method, use of peri-rectal spacers, and use of chemotherapy or androgen receptor target agents.

A1.3.3. QUESTIONNAIRE INSTRUMENTS

Completion of patient reported outcomes and quality of life assessments is optional for PACE-NODES trial participants. The following questionnaires will be used:

- International Prostate Symptom Score (IPSS),
- International Index of Erectile Function-5 (IIEF-5),
- Expanded Prostate Index Composite-26 (EPIC-26)
- EQ-5D-5L

Bladder, bowel and sexual function will be assessed using EPIC-26. Erectile dysfunction will be assessed using IIEF-5. Urinary and bowel incontinence will also be assessed using the IPSS questionnaire. EQ-5D-5L will be used to measure general health-related quality of life.

A1.3.4. FOLLOW UP TIMEPOINTS

Questionnaire timepoints will be as described in the approved PACE-NODES trial protocol.

A1.3.5. STATISTICAL CONSIDERATIONS

The time-point of interest for the purposes of SPRUCE primary endpoint will be the first post SBRT assessment. Secondary endpoints in SPRUCE will be assessed at follow up timepoints corresponding to PACE-NODES data collection time-points listed in the approved PACE-NODES trial protocol.

For the purposes of SPRUCE, the EPIC-26 tool will be considered the primary QoL questionnaire for the SPRUCE primary endpoint. Summary scores will be calculated according to scoring manual guidelines for the questionnaire measures.

A1.3.6. DATA LINKAGE

PRO data completed by PACE-NODES participants who enter SPRUCE will be collected within the SPRUCE study and collated by the SPRUCE study management team. PRO data from SPRUCE will be integrated with data collected within PACE-NODES for the purposes of analysis of the PACE-NODES trial endpoints. Data will be linked via the host trial ID number and SPRUCE study ID.

A2. FORMAT B HOST STUDIES

Format B is relevant where the trial has not yet initiated an embedded quality of life study. In this circumstance we have chosen a well validated questionnaire on general quality of life in cancer patients, which is the EORTC QLQ-C30. The EORTC QLQ-C30 will be administered as the questionnaire of interest and the time points of administration will be selected to fit the patient pathway within the trial but will include baseline and a first time point within 3-6 months of enrolment.

Format B host trials and associated documentation will be added by substantial amendment in due course.