RAPPORT: Reduce Anxiety for Patients with Physicist appOintments in RadioTherapy

Radiotherapy patient anxiety: its correlation with treatment setup and reduction with medical physicist consultations

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Funder	NHS England

i. SIGNATURE PAGE

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

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

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

For and on behalf of the Trial Sponsor:

Signature: Date: ...../...../.....

.....

Name (please print):

.....

Position:

.....

Chief Investigator:

Signature:  Date: 08/04/2025

.....

Name: (please print): Charlie Martin

.....

ii. KEY TRIAL CONTACTS

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iii. LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
CBCT	Cone Beam CT
CI	Chief Investigator
CRF	Case Report Form
CT	Computed Tomography
CTU	Clinical Trials Unit
DIBH	Deep Inspiration Breath Hold
EPR	Electronic Patient Record
GCP	Good Clinical Practice
HCPC	Health and Care Professions Council
HRQoL	Health-Related Quality of Life
HSST	Higher Specialist Scientist Training
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
NSHCS	National School of Healthcare Science
MID	Minimally Important Difference
OIS	Oncology Information System
PI	Principal Investigator
PIS	Participant Information Sheet
PPI	Public & Patient Involvement
QA	Quality Assurance
QC	Quality Control
QoL	Quality of Life
QP	Qualified Person
RCT	Randomised Control Trial
REC	Research Ethics Committee
RT	Radiotherapy
RTDs	Realtime Deltas
RWRC	Robert White Radiotherapy Centre
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SD	Standard Deviation
SGRT	Surface Guided Radiotherapy
SOP	Standard Operating Procedure

STAI	State Trait Anxiety Inventory
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
UHD	University Hospitals Dorset
UoM	University of Manchester

iv. TRIAL SUMMARY

Full Trial Title:	Do additional patient appointments with a medical physicist reduce patient anxiety? A single-centre randomised control trial with additional analysis of imaging and setup data versus reported anxiety levels.
Short Trial Title/Acronym:	RAPPORT (**R**educe **A**nxiety for **P**atients with **P**hysicist app**O**intments in **R**adio**T**herapy)
Trial Design:	Phase II interventional randomised control trial
Trial Participants:	***Inclusion Criteria*** • Referred for radical radiotherapy at the Robert White Radiotherapy Centre (RWRC) • Histological or radiological diagnosis of cancer, or appropriate referral for benign condition • Provision of informed consent to participate ***Exclusion Criteria*** • Under 18 years old • Patients who are unable to understand the study information or unable to complete questionnaires or the consultation, for example unable to speak English fluently • The documentation of an ongoing psychiatric condition in the patients' medical notes to which the researchers have access • Is participating in another patient-reported outcome investigation that may interfere with this study • Referred for palliative or emergency radiotherapy treatment • Prisoners in the custody of HM Prison Service

Planned Size of Sample:	60 patients (30 in each arm)	
Follow-up duration:	No patient follow-up is required once they have completed their radiotherapy treatment. Patient-reported data will be collected on the day of their first radiotherapy treatment, approximately two weeks after baseline, and at the end of their radiotherapy treatment (5 days – 6 weeks after).	
Planned Trial Period:	18 months (12-month recruitment period).	
Study aim:	To evaluate the effectiveness of additional technical information (through a medical physicist patient consultation) of reducing patient-reported anxiety.	
	Objectives	Outcome Measures
Primary:	Determine whether an additional consultation with a medical physicist reduces patient anxiety	State-trait anxiety inventory (STAI)
Secondary:	To determine if any correlation exists between patient-reported anxiety and magnitude of set-up shifts	Magnitude of 2D and 3D imaging shifts will be correlated with anxiety scores, as well as variability of real-time deltas (RTDs) from surface-guided radiotherapy (SGRT).
Intervention:	Patients will be randomised 1:1 to receive either standard care or a single consultation (20-30 minutes) with a medical physicist before their first radiotherapy treatment.	

v. FUNDING AND SUPPORT IN KIND

Funder(s)	Financial and Non-Financial Support Given
NHS England	£13,260 per annum Funding for the HSST program, to cover staffing backfill, travel expenses occurred by academic commitments, and research project costs.

vi. ROLE OF TRIAL SPONSOR AND FUNDER

University Hospitals Dorset NHS Foundation Trust will act as the sponsor for this trial and retain all roles and responsibilities this entails. This includes trial design, conduct, data analysis, interpretation, manuscript writing and dissemination of results.

The project is funded by Health Education England, as part of the doctoral component of the Higher Specialist Scientist Training (HSST), conducted through the National School of Healthcare Science (NSHCS) and the University of Manchester (UoM) as the academic awarding body.

vii. ROLES & RESPONISBILITIES OF TRIAL MANAGEMENT COMMITTEES / GROUPS

The Trial Management Group (TMG) chaired by the Chief Investigator, will include the research academic and workplace supervisors, a representative of the sponsor, and any other relevant local staff involved with the study. The TMG will take responsibility for monitoring progress, ensuring development of documentation and forms, monitoring participant recruitment, discussing analysis, results, draft reports and dissemination. The TMG will meet every 3 months.

viii. PROTOCOL CONTRIBUTORS

The sponsor (University Hospitals Dorset NHS Foundation Trust) and Chief Investigator are responsible for the trial design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results. The funder (NHS England) does not have any control over aspects of the trial. Input from the research academic and workplace supervisors is also recognised (Dr Marianne Aznar & Jonny Lee respectively). Statistical advice on the trial sample size was sought from Christopher Long (Bournemouth University).

Patient and public involvement (PPI) has been sought via patients undergoing radiotherapy at the Dorset Cancer Centre. A short questionnaire was distributed to patient waiting rooms at both the Poole and Dorchester radiotherapy departments. Most patients indicated they would say yes to an additional appointment with a medical physicist to address technical aspects of their treatment, and this response was independent of whether the patient had initial anxiety or worries about technical aspects of their treatment. An advert for patient advocates for the trial was made through this questionnaire. 1 patient responded and provided feedback on general aspects of their treatment, but no comments on the research proposed. Ad-hoc patient-physicist consultations done prior to this research proposal have been extremely well received, in particular allowing one patient to tolerate their treatment successfully when they were struggling. Another patient commented that they sincerely hoped these consultations would be something offered to patients regularly.

Further PPI will be undertaken as part of the study: participant feedback on the intervention, their experiences, and thoughts on a future role or clinical service will be sought when they leave the trial as part of the final data collection timepoint.

ix. KEY WORDS

Physicist direct patient care, physicist consultations, patient anxiety in radiotherapy, reducing anxiety.

x. Amendment History

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

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

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1	1.1	08-Apr-2025	Charlie Martin	Changes made at request of REC: detailing phone consent; definition of end of study; details of key code document.

1. BACKGROUND

A cancer diagnosis, along with the associated treatment, often leads to considerable psychological distress. Studies indicate that approximately half of diagnosed cancer patients should receive radiotherapy[1] and, of these, it's commonly estimated that up to half experience heightened anxiety and distress[2,3]. Lewis et al.[4] showed that up to 16% of individuals exhibit clinically relevant anxiety, mirroring the prevalence of anxiety disorders in the general population.

The impact of anxiety on radiotherapy patients extends beyond emotional well-being, affecting aspects from lower quality of life (QoL)[5] to lower survival[6]. This presents a need for a renewed focus on patient-centred care. Addressing patients' fears, concerns, and anxieties, along with providing the right level of information, is recognised as a central tenet of patient-centred care[7]. As a cornerstone of the care that the NHS should be providing[8] it is therefore incumbent on all staff groups to identify opportunities to improve patient-centred care, especially given the prevalence of anxiety in radiotherapy patients, although there are barriers to this[9]. The Health and Care Professions Council (HCPC) explicitly incorporates this in their revised standards of proficiency for clinical scientist[10]:

> *"Identify anxiety and stress in service user, carers and colleagues, adapting their practice and providing support where appropriate."* (p.7)

Anxiety in radiotherapy patients can have many sources, from fear of the disease, of their treatments and associated pain, through to social factors such as reliance on others and economic factors such as income[11,12], although the factors affecting the mechanism and predisposition to anxiety are not well understood[13]. It is therefore acknowledged that no single intervention will alleviate anxiety in a particular cohort. It can be managed pharmacologically[14], for example with benzodiazepines, but their use is not problem-free with long-term use difficult due to addiction, advice not to drive, as well as their contraindications, e.g. opioid users and elderly patients[15]. Therefore, non-pharmacological interventions must be considered. Interventions to reduce anxiety in patients that have been investigated include: music therapy; psychological intervention such as cognitive behavioural therapy, breathing techniques and hypnosis; massage and reflexology; aromatherapy, and education and information interventions[16–23]. The effect of additional information provision or information-based interventions has been extensively investigated in radiotherapy patients, showing benefits in quality of life and reduced anxiety[24–36].

Radiotherapy patients, during their course of treatment, are quickly introduced to complicated treatment machines, daunting environments (including torture-like and claustrophobia-inducing immobilisation), an array of imaging modalities, and challenging decisions around their treatment. Radiation is often perceived by patients, families, and other parts of the medical community, as a black box. Gillian et al.[37] found wide-spread negative connotations of radiotherapy with patients using words such as 'burn' and 'poison', and other patients having negative associations with disasters such as Fukushima and Chernobyl[38]. This can consequently lead to patients who are anxious and misinformed, with the associated distress having a negative outcome on their treatment.

This may be a significant source of anxiety for certain patients and one that Atwood et al.[36] propose medical physicists, with their unique skill set, are well-placed to ease or dispel. The overwhelming majority of information or educational interventions are radiographer or nurse led, with Elsner et al.[39] presenting a systematic review of radiotherapy therapist interventions to reduce anxiety.

The Atwood et al. team, based in San Diego in the United States, have carried out a phase II trial[40] and subsequently a phase III randomised trial[36]. The intervention consisted of two patient-physicist consultations, focussing on technical aspects of the patients' treatment, with a review of the patient questions during the phase II trial showing over half were focussed on treatment planning and delivery[41]. The phase III trial demonstrated a significant reduction in patient anxiety and improvements in technical and overall satisfaction compared to the standard care control arm. A similar study by Burmeister et al.[42], set up as a phase II screening randomised trial, obtained results that corroborated Atwood et al.[36]. However, Burmeister et al.'s control arm consisted of printed materials describing the technical aspects of treatment, significant improvements in anxiety were still identified in the intervention arm compared to the control arm[42].

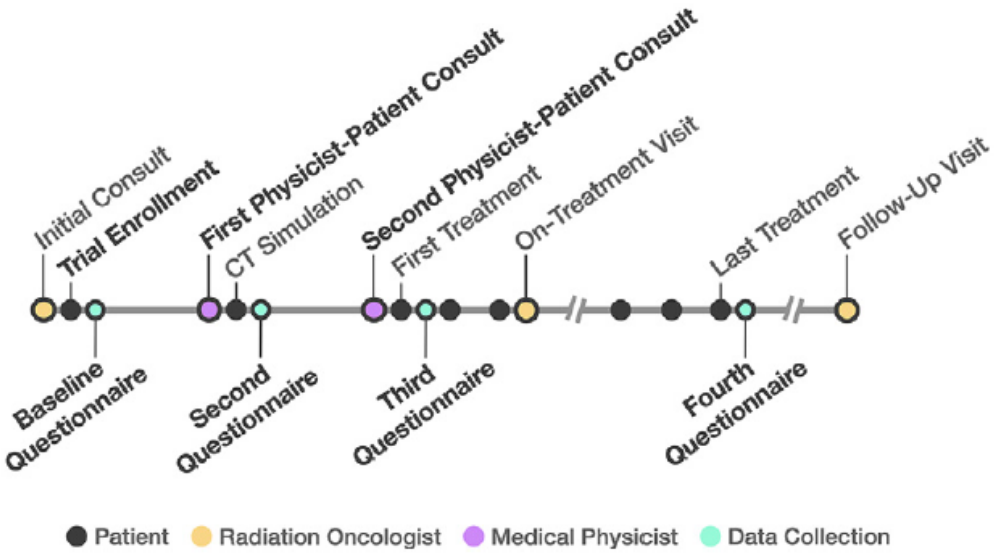


Figure 1: Reproduced from Atwood et al.[36], timeline of physics direct patient care trial arm showing consultations and data collection points.

Whilst Atwood's work showed promise it has initiated much debate across the American community[43–46] with plenty of criticism. One problem frequently cited is the limited physicist time, although Burmeister et al.[42] succinctly state that this is an issue for individual institutions whether they can manage the overhead of staff time at the beginning of patient treatments. The control arm of Atwood et al.'s work[36] received standard care and it has been argued that if the same technical information was supplied by a different member of the radiotherapy team then the merit of utilising a physicist could be determined[44]. The benefit of the physicist is somewhat demonstrated compared to written information in Burmeister's work[42]. There are other statistical critiques such as the use of average anxiety scores at each time point (instead of comparing each patient to their baseline), although these appear to be minor concerns.

It cannot be assumed the same or similar intervention will have comparable results in the UK. The healthcare landscape between the two countries is significantly different, with different healthcare models, patient expectations[47] and staff roles; for example, consultant clinical oncologists in the UK are additionally responsible for medical oncology compared to their US colleagues meaning far more responsibility and expertise, this may be viewed as a disadvantage from the patient perspective. Conversely, UK therapy radiographers have a

wider-reaching scope of practice than technicians in the US, and this allows their patient care to stretch across more domains.

There is a clear gap in the literature on a medical physicist-based information intervention for radiotherapy patients in the NHS to better understand the translation from US to UK-healthcare.

There are further gaps in the literature around the effect of patient anxiety on setup accuracy in radiotherapy. Conventional radiotherapy relies on random variation averaging out over the course of many fractions. However, with the increase in hypofractionation[48], patient variations day-to-day are becoming more relevant, and accurate and consistent patient set-up is key to modern radiotherapy. Tremor in patients with anxiety has been well described for at least 80 years, showing increased amplitude and rate of tremor with increasing anxiety[49,50]. There is some evidence from hand tremor in neurosurgeons that beta blockers can reduce this[51]. Other physiological reactions or symptoms of anxiety are also known, such as increased breathing rate, blood pressure and heart rate[52]. In the context of radiotherapy, there is evidence suggesting that targeted interventions to alleviate anxiety can reduce the associated somatic symptoms. Chen et al.[53] demonstrated that a fifteen-minute music therapy intervention to reduce state anxiety also saw decreases in heart and respiration rate, as well as a statistically significant reduction in systolic blood pressure.

It is hypothesised that an increase in patient movement through tremor or other anxiety-induced restlessness, and an increased or inconsistent breathing rate and amplitude, has implications for radiotherapy treatment (particularly areas affected by lung, diaphragm and abdominal movement, including those utilising deep-inspiration breath hold (DIBH)). He et al.[54] showed a correlation between anxiety and magnitude of setup errors. However, not all anxiety measures they utilised evidenced this correlation, and there was no control cohort. Nonetheless, it is an intriguing finding and one that, as far as can be determined, is not corroborated or refuted in any published studies. There is some evidence that breathing rate variability could be a surrogate for anxiety[55].

Surface-guided radiotherapy (SGRT) is a relatively new technology but one that is increasingly accepted and recognised[56], and it allows continuous monitoring of the patient surface. This is a relatively untapped source of data, although studies correlating SGRT to other imaging setup shifts such as cone-beam CT (CBCT) have become common[57]. A search of the literature (shown in Table 4) related to SGRT and anxiety returned no results. Therefore, the use of SGRT in potentially identifying signs of anxiety is, as far as can be determined, novel and warrants investigation. Existing work in the literature on imaging shifts and their correlation to anxiety is also noted as an area of potential development, including extending it to include CBCT, correlation with SGRT shifts, and the use of a randomised, control cohort appearing to be novel.

2. AIMS AND OBJECTIVES

2.1. Aim

To evaluate the effectiveness of additional technical information (through a medical physicist patient consultation) of reducing patient-reported anxiety.

2.2. Objectives

2.2.1. Primary objective

- To determine if an additional patient consultation with a medical physicist influences patient-reported anxiety compared to standard of care (no consultation with a medical physicist).

2.2.2. Secondary objectives

- To determine whether the magnitude of patient set-up errors correlate with patient-reported anxiety.
- To determine whether data reported by SGRT (such as surface variability) correlate with patient-reported anxiety.
- To determine whether there is a difference in technical satisfaction between the intervention and control arms.
- To determine if treatment adherence (attendance, treatment preparation such as bladder filling) is influenced by having more technical information.
- To collate patient questions and report common themes
- To explore patient experiences, including their interest in physicist consultations as a clinical service, and their information requirements.
- To determine the staff time requirement for physicist consultations

3. STUDY DESIGN

3.1. Study design overview

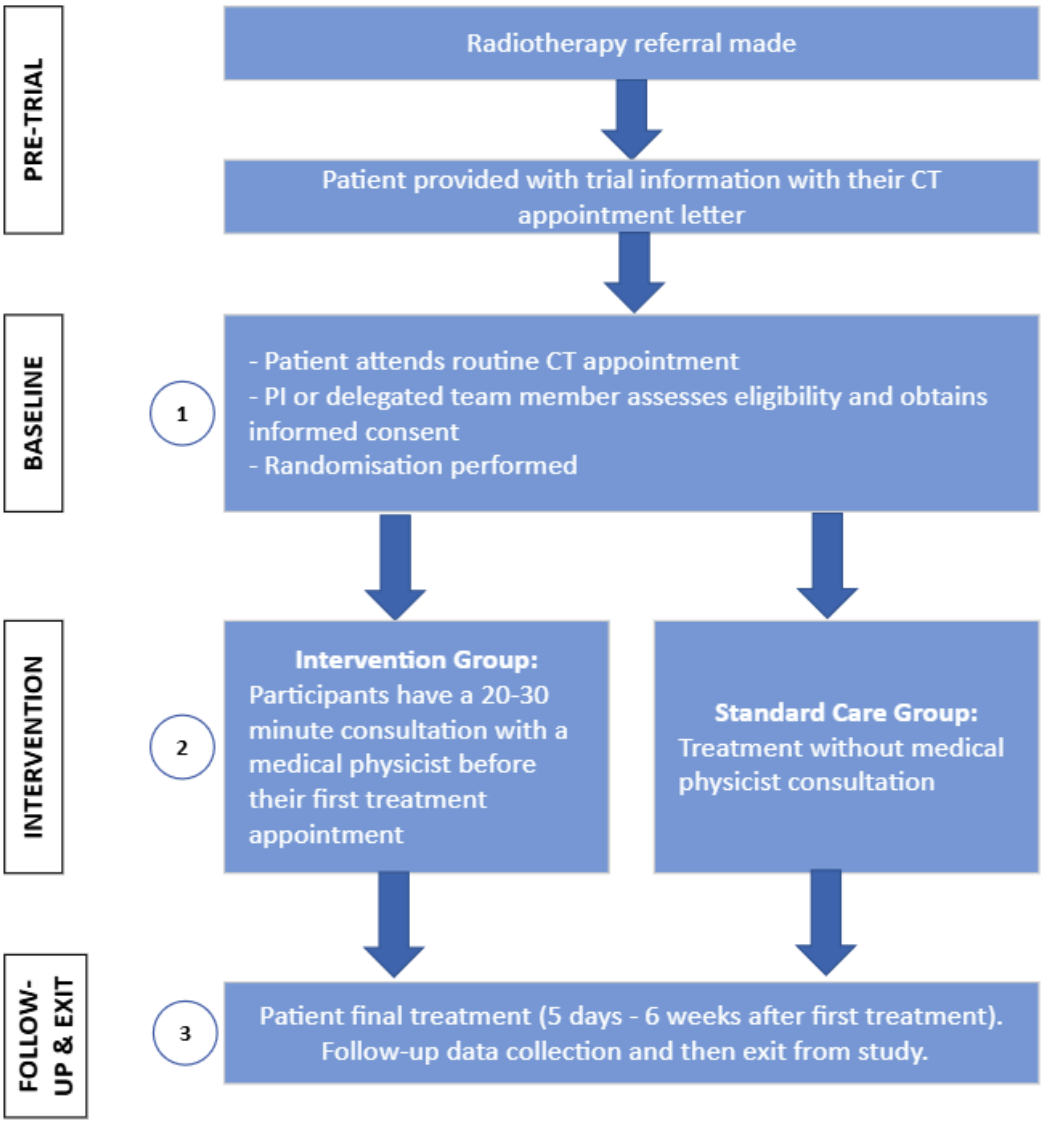
This study is designed as a phase II interventional randomised control trial to evaluate the effectiveness (through patient-reported anxiety) of patient-physicist consultations, providing evidence for their use in clinical practice.

3.2. Design and bias considerations

The nature of the intervention makes it impossible to blind the patient or staff. However, data analysis will be undertaken on a pseudonymised basis. Participant selection bias will be present, with those patients wanting to know more self-selecting. It is not possible to account for this, however statistical analysis will be stratified by education and health literacy level (as well other sociodemographic data).

Figure 2: Study design flowchart

Illustrating flow of patients through the trial and the time points for data collection (3 time points numbered)



3.3. Duration of patient participation

The duration of patient participation will vary depending on their individual treatment regime. It is expected that there will be a two-week interval between consent and baseline, and the patients' first treatment (and intervention for those randomised to receive it). Subsequently, follow-up will be between 5 days and 6 weeks from the first treatment to the last treatment. End of patient participation will be defined as the completion of data collection for the last patient followed-up in the study.

3.4. Study setting

The study will be conducted at a single site – University Hospitals Dorset NHS Foundation Trust. The intervention will be delivered at the Robert White Radiotherapy Centre (RWRC) at Dorchester County Hospital, a satellite centre of the radiotherapy department at University Hospitals Dorset NHS Foundation Trust. RWRC has been chosen as it meets the requirements to run the study: suitable space for an additional patient consultation.

4. OUTCOME MEASURES

This section is intended to list, describe, and justify the choice of outcomes rather than to describe how the data are collected for research purposes. Data collection is addressed in Section 6.

4.1. Primary outcome measure

The primary outcome measure for this study is patient-reported anxiety utilising a short form of the state scale of the Spielberger State-Trait Anxiety Index (STAI)[58]. The STAI is one of the most used and cited measures of anxiety, with over 10,000 citations for Spielberger's two studies on the STAI[58,59]. It has been used widely in radiotherapy settings. Short forms of the STAI have been investigated to create more clinically usable tools. These have been shown to perform well versus the full STAI[60–62]. The STAI6 will be utilised here, as used by Marteau et al[60].

Anxiety will be measured at three timepoints:

a. Baseline (after patient consent and enrolment on the trial)
b. First treatment appointment, before treatment.
    a. For patients on the intervention arm, this will be after the physicist consultation but before treatment
c. End of treatment, before the last radiotherapy treatment

Scores range from 20 to 80, and a score of 40 is commonly used to differentiate between high and low anxiety[63]. Scores at timepoints 1 & 2 will be corrected for baseline scoring for each participant, and the average (mean) score across both trial arms compared.

4.2. Secondary outcomes measures

4.2.1. Imaging Data

Imaging data, to include the treatment setup shifts determined by either two-dimensional (kV planar) or three-dimensional cone-beam CT (CBCT) imaging.

Surface-guided radiotherapy (SGRT) data analysis from the AlignRT system will include the variability of patient movement via the real-time deltas (RTDs). Additional metrics available for analysis are not currently known and will be explored.

4.3. Exploratory outcome measures

4.3.1. Technical satisfaction and patient information needs

Technical satisfaction will be rated using a 5-point Likert scale to determine whether patients understood their treatment from a technical perspective. Additional questions will be used to examine the information requirements of patients who did and did not receive the intervention to inform the ongoing design of patient information provision and potential for a physicist consultation clinical service.

4.3.2. Sub-group analysis

Analysis of the primary outcome measure will be sub-divided by demographic information collected, to include gender, health literacy level and education level.

4.3.3. Comparison at each visit

Longitudinal analysis of patient-reported state anxiety at each timepoint, and comparison of the number of “high” and “low” anxiety patients in each arm at each timepoint (determined using a threshold value of 40 for the STAI).

4.3.4. Treatment adherence

Dependent on patient recruitment, is adherence to treatment influenced by the amount of technical information provided. Attendance and patient preparation (e.g. bladder filling conformance and treatment delays).

4.3.5. Quality of life and cost-effectiveness

The EuroQol EQ-5D-5L questionnaire will be used to measure health-related quality of life (HRQoL). There is an increasing emphasis on reporting HRQoL by regulatory agencies to determine treatment value.

4.4. Table of endpoints/outcomes

Table 1: Study objectives and outcome measures

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Primary Objective To determine whether an additional patient consultation with a medical physicist lowers patient-reported anxiety.	Short form of state scale of Spielberger State-Trait Anxiety Inventory (STAI), administered at patient recruitment (baseline), after patient first treatment, and after patient final treatment.	Three timepoints: recruitment, before first and last treatment
Secondary Objective To determine whether patient set-up errors or SGRT data correlate with patient-reported anxiety.	Magnitude of setup errors (determines by 2D or 3D imaging), variability of SGRT real time deltas (RTDs) and correlation with patient-reported anxiety	Two timepoints: first and last treatment
Tertiary / Exploratory Objectives Technical satisfaction	Two technical satisfaction questions on a 5-point Likert scale. Comparison between groups and additional questions examining patient information needs.	One timepoint: before first treatment
Sub-group analysis	Variation/correlation of patient-reported anxiety and demographic information	Three timepoints: recruitment, before first and last treatment
Comparisons at each timepoint	Patient anxiety – longitudinal analysis of anxiety and comparison of proportion of high and low anxiety patients, including analysis by treatment length/duration.	Three timepoints: recruitment, before first and last treatment
Treatment adherence	Treatment attendance adherence, defined as 1 – [(number of	Every treatment fraction (varying on an individual patient basis)

	treatment days missed) / (total prescribed treatment fractions)] Bladder filling adherence, defined as the difference in bladder volume daily compared to planned volume.	
Health-related Quality of Life (HRQoL)	Correlation of EQ-5D-5L scores with STAI and demographics. Change in HRQoL with intervention vs control	Three time points: recruitment, before first and last treatment

5. PARTICIPANT ELIGIBILITY CRITERIA

5.1. Inclusion Criteria

- Referred for radical radiotherapy at the Robert White Radiotherapy Centre (RWRC)
- Histological or radiological diagnosis of cancer, or appropriate referral for benign condition
- Provision of informed consent to participate.

5.2. Exclusion Criteria

- Under 18 years old
- Patients who are unable to understand the study information or unable to complete questionnaires or the consultation, for example unable to speak English fluently.
- The documentation of an ongoing psychiatric condition in the patients' medical notes to which the researchers have access.
- Is participating in another patient-reported outcome investigation that may interfere with this study.
- Referred for palliative or emergency radiotherapy treatment.

5.3. Withdrawal Criteria

The patient at any point can ask to be withdrawn from the trial without an explanation or reason. Any patient results and questionnaires will be retained in line with Trust policy, and the quality of care they receive will not be affected.

6. TRIAL PROCEDURES

This section describes conduct of the study in chronological order, detailing the procedures for data collection at each of the time points.

Table 2: Tabulated Study Schedule
A tabulated study schedule to illustrate all data collection at each time point of the study.

TIMEPOINT	Baseline	Week 2 (before RT)	End of Study (before RT)
ENROLMENT:			
Eligibility screen	X		
Informed consent	X		
Baseline characteristics	X		
Baseline socio-demographics	X		
Randomisation	X		
INTERVENTION:			
Physicist consultation		X	
ASSESSMENTS:			
Health literacy	X		
STAIS6 Questionnaire	X	X	X
EQ-5D-5L	X	X	X
Information & communication needs	X		X
Technical Satisfaction Questionnaire	X	X	X
Questions about Medical Physicist consultation			X

6.1. Recruitment

Table 3: Summary of recruitment tasks

Recruitment Process	Detail	Responsible staff
Participant identification	Referral for radiotherapy will indicate patients who are having radical treatment at Dorchester.	Radiotherapy Bookings
Patient invitation	Invite letter and patient information sheet (PIS) with CT appointment letter, printed and posted.	Radiotherapy Bookings

6.1.1. Participant identification & invitation

Participants will be identified by radiotherapy staff already involved in their routine care (and therefore have authorised access to their identifiable information). Identification will occur when the referral for radiotherapy treatment is received from the Consultant Oncologist (or other entitled member of staff) by radiotherapy bookings staff in the Mosaiq Oncology Information System (OIS). The referral contains the required information to identify patients having radical radiotherapy at Dorchester. These patients will receive an invitation to the study (comprising the patient information sheet) with their CT appointment letter which is printed and posted to them. A record will be kept of patients who receive the invitation, and patients who decline to participate will be recorded (along with any reason if given) to identify recruitment problems as early as possible. The primary mechanism for recording recruitment will be the clinical trials label/alert available in Mosaiq.

Providing the patient information sheet (PIS) with the patient CT appointment letter ensures appropriate time to consider the information. The minimum period of time required (if the above process is not followed) is 24 hours. It will be documented in the OIS that the patient has had been provided with the PIS and had time to consider participation.

6.1.2. Screening

Confirmation of eligibility against the inclusion and exclusion criteria will be performed by the PI or delegated member of the research team when a patient notifies the trial team they would like to participate (before the routine CT appointment), or otherwise before patient consent. If the patient has consented and found to be ineligible the PI will contact the patient to inform them they won't be able to participate in the trial. Eligibility will be determined by examining the patients' medical record (EPR & Mosaiq).

6.1.3. Payment

It is not expected that any reimbursement for additional visits will be required as the trial intervention and data collection will occur during routine outpatient visits to the radiotherapy department.

6.2. Baseline visit

6.2.1. Consent

At the routine CT appointment of patients who received the study invitation and participant information sheet, the patient will be approached by the CI or delegated member of the research team to review the study information and discuss their participation in the trial, unless they have already contacted the study team to confirm/decline involvement. The right of a participant to refuse participation without giving reasons will be respected.

Participants will have been provided with contact details to obtain further information about the trial via the participant information sheet. This will be the dedicated study email address. This will be provided again at consent as required.

Potentially eligible patients who express willingness to participate will be asked to provide consent in accordance with Good Clinical Practice. The consent process will involve a full explanation of the trial given by the person taking consent. The person responsible for taking consent will be trained in GCP and Informed Consent. Patients will be advised that they are under no obligation to take part and that their ongoing care will be unaffected if they choose not to take part. Patients who choose not to take part will be asked to provide a reason for declining but will be told that they do not have to give a reason if they wish not to. Patients will also be advised that they are free to withdraw from the trial at any time and that doing so will not affect their ongoing care. Following this discussion, patients who are willing to participate will be asked to complete, sign and date the trial consent form, which will also be signed and dated by the person obtaining consent.

The CI is responsible for obtaining consent but may delegate these duties appropriately to other members of the research team. Such delegation will be captured on a site-specific site delegation log. Any person obtaining written informed consent must have current GCP training and have received trial-specific training from the trial team. No trial information will be gathered, or intervention carried out, prior to taking consent from the patient.

A copy of the signed Informed Consent form will be given to the participant. The original signed form will be retained in the Investigator Site File and a copy placed in the patient's hospital notes. Note that any new information that arises during the trial that may affect participants' willingness to take part will be reviewed by the TMG. If necessary, this information will be communicated to all participants, and they will be asked to re-confirm consent in light of the new information.

Patients who are found to be ineligible or who are unwilling to participate will be managed as per usual care. Reasons for non-participation (where given) will be recorded by the research team.

Participant ongoing consent will be confirmed on the first and last days of treatment (through asking "are you willing to continue in this study?"), including assessment of capacity to continue, and documented in their medical record.

Following any amendments to this protocol, the appropriate patients will be reconsented.

6.2.1.1. Remote / telephone consent

Due to the cross-site nature of this study, it is feasible that an appropriately delegated member of the research team is not available to obtain participant consent. Alternatively, the participant might require further time to consider the study information. In these circumstances, if the participant wishes to join the study:

- The participant will go home with a copy of the PIS and the baseline questionnaire
- A member of the research team will contact the participant via telephone to discuss the study and obtain consent.
- Once consent has been obtained, the participant will complete the baseline questionnaire and bring with them to their first radiotherapy appointment (to maintain required timelines for data collection outlined below).

Telephone consent will be undertaken in line with the following:

- A telephone consent form will be used.
- The participant will be asked to complete a written Consent form at their next visit.
- The participant will receive copies of all consent forms, to include the telephone consent form.

6.2.2. Baseline data

After eligibility has been confirmed and written consent obtained, and prior to randomisation, patients will be provided with a baseline questionnaire packet to be completed, and a member of the research team will complete the baseline case report form (CRF).

- Sociodemographic information – collected from either medical records or self-reported by the participant.
    - Contact details, and preferred method of contact (to facilitate sending of appointments and questionnaire reminders).
    - Year of birth
    - Gender
    - Education level
    - Marital status
    - Employment status
    - Whether the participant deems English to be their ‘first’ or ‘second’ language
- Clinical information – collected from medical records
    - Area/site of treatment
    - Number of radiotherapy treatments (fractions) referred.
    - Has the participant had previous radiotherapy?
    - Has the participant been scanned with particular motion management, e.g. deep inspiration breath hold (DIBH)?
- Patient-reported anxiety - STAIS6 questionnaire
- Health literacy assessment
- EQ-5D-5L questionnaire
- Information and communication questions
- Technical satisfaction questions

Ideally the participant-reported data will be collected on the day of consent, however it is acknowledged this may not be possible in all cases. This must be completed within 1 week of the CT appointment, either by post or electronically.

6.3. Randomisation

Following completion of baseline information collection, a member of the research team will randomise the participant to one of the two treatment arms: physicist consultation or standard of care.

Patients will be randomised in order to minimise systematic bias, using a secure web-based system Sealed Envelope (https://www.sealedenvelope.com/simple-randomiser/v1/trials/rapport), certified as meeting ISO/IEC 27001 standards and the NHS England Data Security and Protection Toolkit.

Participants will be allocated to intervention group or to the control group in a 1:1 ratio. Randomisation will be stratified by gender. This is a surrogate for treatment site: the most common radiotherapy treatment sites (particularly at RWRC) are breast and prostate cancer. However, to ensure approximately equal distribution of treatment sites in each arm and avoid problems of low numbers of less common treatment sites, gender has been chosen has the stratification criteria. It is acknowledged that with the low sample size required in this study, distribution is likely still to be unequal but there is little evidence that the primary outcome varies by gender.

Upon randomisation, each participant will be assigned a unique Trial Number which will be used as the principal identifier on trial data collection forms and questionnaires. The research team member will disclose the allocation to the participant and will ensure the allocation is followed as described below.

6.4. Provision of Treatment

Following allocation, the participant will be informed of which trial arm they have been randomised to. Where required, the consultation will be booked by the PI or delegate and the patient informed what time this will be (as it will not be on their routine appointment list given at the CT appointment). If possible, a reminder will be sent via the DoctorDoctor service.

6.5. Start of treatment

When patients start treatment, they will be asked to complete a questionnaire on the day of their first treatment. Ideally this will be completed before the treatment appointment, otherwise it must be completed after the treatment appointment and on the day of first treatment. This is due to some patients having very short treatment regimens. Patients will be provided with a questionnaire packet to be completed, and a member of the research team will complete a case report form (CRF). The start of treatment data collected (either participant-reported or medical records) will be:

- Patient-reported anxiety – STAIS6 questionnaire
- EQ-5D-5L questionnaire

- Technical satisfaction questions
- Clinical information – collected from medical records
    - Scheduled number of treatment fractions (this can change between referral and prescribing by Oncologist)
    - Does the patient have bladder filling/preparation. If so, baseline volume and details from planning CT
- Intervention information (where applicable):
    - Physicist conducting consultation.
    - Consultation duration.
    - Discussion points and patient questions – analysis of themes and topics will be conducted.

6.6. End of treatment

The time between the start and end of treatment clinic visit will be patient-specific, according to their radiotherapy treatment prescription. It is anticipated that it will be between 5 days and 6 weeks after the first treatment. The patient will be given a questionnaire to complete and a member of the research team will complete a CRF. Ideally the participant will be complete the questionnaire before their last treatment appointment, but it must be completed on that day. The end of treatment data collected (either participant-reported or medical records) will be:

- Patient-reported anxiety – STAIS6 questionnaire
- EQ-5D-5L questionnaire
- Technical satisfaction questions
- Information and communication needs
- Questionnaire regarding physicist intervention (where applicable)
- Clinical information – collected from medical records:
    - Where applicable: bladder prep information (to include volume at CT, volume each fraction, delays or incorrect prep)
    - Imaging data (to include 2D shifts, CBCT shifts where applicable)
    - SGRT data
- PPI free-text comments on the participants experience, the intervention, thoughts on a future clinical service etc.

6.7. End of Study

The end of the study is defined as the last day of radiotherapy of the last participant. The end of study declaration form will be completed after this date (and within 90 days) once all required data is present and the database is locked.

7. INTERVENTION DETAILS

7.1. Rationale, risks & benefits

Anxiety in radiotherapy patients is a known and common occurrence, with evidence around the negative consequences on health and outcomes it can have for cancer patients. Interventions to reduce this and improve quality of life (QoL) are a continued focus of research in the literature and novel approaches such as utilising medical physicists have

shown some benefit for reduced anxiety in the US. To date, there is no research demonstrating benefit from similar interventions in the UK (noting the substantially different healthcare systems and demographics). This research aims to establish whether a reduction in anxiety is observed in radiotherapy patients for a physicist-based education intervention. Additionally, the research will examine correlations between radiotherapy treatment shifts and patient-reported anxiety. Accurate setup is essential for effective treatment, and this may provide evidence to further embed anxiety interventions in standard practice for radiotherapy, ensuring patient-centred care is a leading priority in research and practice.

7.2. Assessment and management of risk

There are no known risks regarding the provision of information, with no adverse events reported in literature or regulating bodies. It is possible that additional information about the technical aspects of their treatment will have the unintended consequence of increasing anxiety. This will not impact the safety or efficacy of their radiotherapy treatment, and further support regarding anxiety via the routine radiotherapy patient review pathways will be available. Patients on the trial will be able to access complimentary therapies in the same way as standard of care patients.

The STAI, as discussed, is a widely validated tool that has lots of published evidence regarding its utility. However, it is still not widely adopted as a clinical screening tool, particularly in this cohort of patients. In normal populations a cut-off score of 40 (STAI manual) is used to indicate clinically significant symptoms of anxiety. However, it is expected that anxiety in cancer patients undergoing a procedure or treatment will be higher than that encountered in a normal population. There is little published population data on state (or situational) anxiety scores, but a recent paper examining anxiety in radiotherapy patients during the Covid-19 pandemic demonstrated the majority of patients had STAI scores ≥40[64]. Additionally, patient-reported anxiety is the primary outcome measure of the study (and correlation with it the secondary outcome measure). Directing patients to additional help during their treatment and highlighting high anxiety scores may bias the outcome. To counter these difficulties and ensure patients are as well-supported as possible, an information leaflet will be provided to all participants at the start of treatment detailing the support available developed in conjunction with the RWRC review radiographer/Macmillan lead.

It is acknowledged that radiotherapy physicists undertaking a more patient-facing role could be considered a risk. Any physicist undertaking the intervention is required to complete additional communication training (a uniquely tailored course developed by Atwood et al. who were one of the first to explore this expanded role for physicists[65].

7.3. Patient-Physicist Consultation

Medical physicists in radiotherapy do not undertake patient consultations as part of standard care, although they are done on an-hoc basis at a patients request. Any physicist undertaking the intervention must be documented on the delegation log and must have completed suitable training (as determined by the PI) in patient communication, and the intervention itself. The intervention will be conducted in line with a standard of practice (SOP), available to physicists undertaking the intervention to ensure consistency. The scope of the technical consultation is outlined below but will be driven by individual patient requirements and questions.

Typical discussion sequence during a medical physics consultation:

i	To give an overview of the role of the medical physicist (and other technical staff) in patient care
ii	Explain the CT simulation and treatment planning process
iii	Explain the treatment delivery process
iv	Overview of what to expect in the treatment room
v	Patient questions

It will be made clear to participants that non-technical and clinical questions, for example about side effects or medication, cannot be answered by the medical physicist and, where appropriate, questions will be passed onto relevant staff.

The intervention will take place on the patients' first day of treatment, ideally face-to-face. In circumstances where this is not possible, then a virtual consultation is permissible. This will be conducted via UHD Microsoft Teams, with staff at RWRC assisting the participant to ensure they have access to an appropriate device.

8. STATISTICS AND DATA ANALYSIS

8.1. Sample size calculation

Advice on the sample size calculation has been sought from Christopher Long, Principal academic in healthcare statistics at Bournemouth University.

The study is powered to detect a 10-point difference in patient-reported anxiety on the STAI. There is evidence that this is the minimally important difference (MID)[18,42,66]. An estimate of standard deviation was made from work by Burmeister[42] and Atwood[36] in similar radiotherapy populations, both studies used the STAI to measure patient anxiety. Atwood found standard deviations ranging from 10.2-15.6, whilst Burmeister found a lower standard deviation of 8.1. A standard deviation of 13 has been chosen to represent an average within the range of observed values from Atwood.

Based on an unpaired t-test with two groups of equal size, assuming 80% power, a two-sided 0.05 significance level, a standard deviation of 13 and a mean difference of 10 points in patient-reported anxiety, a total sample size of 54 (27 in each group) is required. The study will over-recruit by 10% to allow for non-responders, missing data, or attrition (drop-out). Therefore, the study will aim to recruit 60 patients in total (30 in each group) over a 1-year recruitment period. This gives a similar sample size to the work of Atwood, and a sample size 1.5 times larger than Burmeister.

This sample size is also in the region of that calculated by an independent method (using the varying-slope varying-intercept model). Whilst this doesn't consider the repeated timepoints as independent, it represents a worst-case scenario. The details of this calculation are in Appendix 1, but the calculated sample size is 76 (although this doesn't account for attrition), slightly larger than the sample size calculated but of the same magnitude.

8.2. Description of statistical methods

A detailed statistical analysis plan will be developed and signed off by the Trial Management Committee before any analyses commence. The pseudonymised data will be analysed by intervention group (i.e. patients who did or did not receive the additional consultation).

8.2.1. Baseline Descriptives

Baseline descriptive data on demographics (gender, age, marital status, employment status, education level), health literacy) will be presented overall and for both groups separately. This will help to see whether the 2 groups were comparable at baseline.

8.2.2. Primary outcome

The primary outcome is the Spielberg state-trait anxiety index (STAI). Questionnaires that were not completed in the required timeframes will be treated as missing data:

- Baseline – within 1 week of CT appointment
- Start of treatment – on day of treatment
- End of treatment – on day of treatment

Anxiety scores will be compared at each time point between the two groups for a statistically significant difference. The 2nd and 3rd timepoints will use baseline-corrected anxiety scores. Some additional analyses (including sensitivity analyses) on the primary outcome will also be conducted:

a. The effectiveness of the intervention may vary across different subgroups of patients (e.g. age, education level). Therefore, supplementary statistical analyses are proposed in which it is tested if there is a statistical interaction between socio-demographic data and the primary outcome. This will include health literacy level measured at baseline.

b. Any baseline variables that appear, by chance, to differ between the groups will be added in as covariates.

c. Whether or not the patient has had previous radiotherapy will be added as a covariate.

d. Longitudinal analysis of anxiety scores at all three time points to assess variation across treatment

e. Proportions of high and low anxiety scores in each group at each time point.

8.2.3. Secondary outcomes

The primary outcome (STAI score) will be tested for correlation against imaging and surface-guided data collected for participants.

8.2.4. Exploratory outcomes

The exploratory outcomes will not be tested for statistical significance. Correlation with group anxiety scores will be tested against:

a. Technical satisfaction
b. Patient information needs
c. Treatment adherence (appointment attendance and bladder filling)

8.3. Qualitative Component

Patient questions during the physicist consultation will be thematically analysed. Free text questions will also be available for patients to provide comments on their experiences and other feedback they may have. These will be analysed as appropriate.

8.4. Economic evaluation

A criticism of utilising physicist-time for direct patient care is the cost and time involved for, often, highly paid and specialised technical staff. This study will collect data on the time spent preparing and conducting patient consultations to inform future cost-effectiveness studies.

8.5. Planned recruitment rate

Patients referred for radical radiotherapy at the RWRC will be invited to participate in the trial. Approximately 400 patients meet these criteria annually. Results from a patient engagement questionnaire given to radiotherapy patients in August 2024 indicate that over half of patients would be interested in having an additional consultation with a medical physicist. The planned recruitment period of 12 months (based on academic timescales for thesis submission) should be sufficient, with recruitment having to fall below 20% of eligible patients to not meet this deadline.

9. DATA MANAGEMENT, HANDLING AND RECORD KEEPING

9.1. Participant numbering

Upon randomisation, each participant will be allocated a unique trial number and will be identified in study documentation by their trial number and initials. A key code document (locally called the “Participant Identification and Contact Log”) will link the pseudonymised

data with identifiable data. This will be stored securely in the site file separate from the study database and won't be shared with the Sponsor or collaborators.

9.2. Source Data

See Section 6 for details of all data collected at every timepoint.

The first record of any study related visit or assessment should be recorded in the patient's medical record or patient questionnaire, which becomes the source data. Data from the source documents will be transcribed into study specific CRFs by authorised personnel on the delegation log.

9.3. Data Entry

Data will be recorded on study-specific case report forms (CRFs). Completed CRFs will be entered onto a password-protected Excel spreadsheet on a study-specific SharePoint site. The trial master file (TMF) will also be stored here in electronic form.

9.4. Access to data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits, and inspections- in line with participant consent. Members of the research team who have access to data will be clearly documented on the delegation log.

9.5. Data confidentiality and security

Investigators will ensure that the patients' anonymity is maintained on all documents. Data will be collected and stored in accordance with the Data Protection Act 2018. Records will be stored securely in line with the Trust's research policies and procedures. Electronic records will be stored in a study-specific repository, with access given only to delegated members of the research team.

9.6. Archiving

All documents and data generated by this study are the responsibility of the Chief Investigator and will be kept in lockable filing cabinets within a restricted access office. The Sponsor and the Chief Investigator shall ensure that the documents contained, or which have been contained, in the trial master file are retained in accordance with the Sponsor's standard operating procedure (SOPs). Participant's medical files will be retained in accordance with applicable legislation for a minimum of 10 years as per University Hospitals Dorset NHS Foundation Trust archiving policy. The documents can be retained for a longer period, however, if required by the applicable regulatory requirements or by agreement with the Sponsor. No trial-related records should be destroyed unless or until the Sponsor gives authorisation to do so.

10. ETHICAL, REGULATORY, ADMINISTRATIVE AND QUALITY CONSIDERATIONS

10.1. Ethical considerations

The trial was designed around the patient pathway and the usual management of oncology patients within University Hospitals Dorset NHS Foundation Trust. Patient information is a key part of the oncology patient pathway, and therefore the trial raises no special ethical issues. Staff will be trained in Good Clinical Practice which will be followed at all times.

An application for ethics approval will be made to a National Research Ethics Service Committee (REC). The trial will not proceed until Ethics approval and Trust approval from each participating site is obtained. Any amendments to the protocol will be submitted for REC approval and local NHS approval as appropriate.

An end-of-trial declaration will be provided to the REC within 90 days of trial conclusion or within 15 days of trial termination in the event the trial is prematurely terminated. This is the responsibility of the chief investigator (CI). If the trial is terminated prematurely the CI will notify the REC, including the reasons for the premature termination. Within one year after the end of the trial, the CI will submit a final report with the results, including any publications/abstracts, to the REC.

Since the trial involves no Investigational Medicinal Product or non-CE marked medical devices, authorisation from the Medicines and Healthcare products Regulatory Agency will not be sought.

10.1.1. Declaration of Helsinki

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP.

10.1.2. Research Governance

This trial will adhere to the principles outlined in the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines. It will be conducted in compliance with the protocol, NHS Research Governance Framework for Health and Social Care (2005 2nd edition) and other regulatory requirements as appropriate.

10.2. Study Management

The Chief Investigator will co-ordinate the study. The Research & Innovation department at University Hospitals Dorset NHS Foundation Trust will conduct randomisation, manage the data, and provide trial management support, following their Standard Operating Procedures.

Bournemouth University and University of Manchester will support both the quantitative and qualitative analysis.

10.3. Monitoring

Continuous data monitoring will be undertaken by the study team. The study is single site, and therefore no monitoring visits to other sites are required.

10.4. Audit and Inspection

The investigator(s) / institution(s) will permit trial-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data and essential documents. Trial participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes.

In the event of the site being notified directly of a regulatory inspection, the sponsor requests the investigator to notify the sponsor.

10.5. Peer review

Peer review has been conducted by the academic supervisor from the University of Manchester during the development of the study. Independent peer review has been conducted by a medical physicist with expertise in running similar trials.

10.6. Protocol compliance

No prospective, planned deviations or waivers to the protocol are not allowed. Any accidental breaches from the protocol must be documented and reported to the Chief Investigator and Sponsor immediately.

10.7. Notification of Serious Breaches to GCP and/or the protocol

A “serious breach” is a breach which is likely to effect to a significant degree:

- the safety or physical or mental integrity of the participants of the trial; or
- the scientific value of the trial

The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase. The sponsor will notify the licensing authority in writing of any serious breach of:

- the conditions and principles of GCP in connection with that trial; or
- the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach

10.8. Indemnity

University Hospitals Dorset NHS Foundation Trust holds standard NHS Hospital Indemnity and insurance cover with NHS Litigation Authority for NHS Trusts in England. Standard NHS cover for negligent harm is in place. There are no specific arrangements to cover for non-negligent harm.

10.9. Amendments

The Chief Investigator will be responsible for the decision to amend the protocol and, in conjunction with the sponsor, deciding whether an amendment is substantial or non-substantial.

10.10. Access to the final trial dataset

The Chief Investigator and any authorized staff on the delegation log will have access to the full dataset. A pseudonymised final dataset will be made available upon request.

10.11. Dissemination Policy

At the end of the trial, a Final Trial Report will be prepared by the Chief Investigator.

The results of the study will be disseminated via presentations at appropriate scientific meetings and conferences and publication in appropriate peer-reviewed journals.

If the participants would like to be informed of the results of the study they can be sent a plain English summary of the study results after the end of the study.

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12. APPENDICIES

12.1. Appendix 1: Independent Sample Size Calculation

The following is provided by Christopher Long.

Similar to the currently proposed study, [42] also describes itself as a two-group repeated measures design with patients modelled as random effects and patient visits as the repeats. While the model is not explicitly stated we can postulate a similar model here that captures the current scenario and explicate in more detail its different components and the assumptions we will make. With a repeated measures-type design we can choose to fit the data using a varying-slope varying-intercept model i.e. $y_{j,t} \sim N(\alpha_j + \beta_j t, \sigma_y^2)$ where j is patient and t indexes time while the variance term reflects a combination of error terms deriving from measurement error, variation in the STAI and departures for each patients' repeated data from the assumed linear model. We can further assume that the anxiety treatment will affect the slope but not the intercept (since at the baselinfiguree time zero there is no treatment). From [36], we can compute that the slope for controls is -.2 and the slope for the intervention group is -4.85. We can also derive the mean of the control group (at baseline) as 36.3 from the same paper. To complete the model we need three further standard deviations, (i) the residual standard deviation (taken as the larger of the two deviations computed from the Altman paper – 2.57) (ii) the intercept standard deviation (computed from Fig4 in Altman) as 11.31. For (iii) the time-by-treatment effect slope standard deviation, neither paper reports these values and so the main assumption for these power calculations are that this standard deviation will be at best equal to the residual standard deviation and at worst equal to the baseline mean standard deviation.

Study design: We assume that N-patients will be randomly assigned into two treatment groups (intervention/control), with N/2 receiving the anxiety intervention and N/2 receiving no such intervention. We further assume that the patients will have repeated equi-spaced visits=3 where the first visit is taken as baseline. We need to determine the N required for 80% power, if the true treatment effect is -4.65, as assumed above.

Simulation: Given these values we can simulate data deriving from our hypothetical parametrized model with the above assumptions by repeatedly sampling data from the specified distribution and then fitting the above model to each such simulated dataset. We next fit each such dataset (using the lmer package in R) to progressively larger and larger sets of patients (x-axis in Figure 3), each measured three times in our case. For each choices of N(ranging from 20 to 150), we generate data from each N-sized sample (half-treated half control) each measured three times within the study window. Next we embed this data simulation into a loop to generate 1000 sets of data for that size of N. For each fit we obtain all parameters as described above and confidence intervals for the treatment parameter of interest (treatment effect over time).

The figure shows on the y-axis the probability of the estimated anxiety intervention effect being statistically significantly) as a function of the size of patient group, N, computed using the proposed data simulation mechanism with mixed-effects inference performed by lmer(). The simulations are based on all of the assumptions about the treatment effect outlined earlier including the expected variation among patients and among measurements within patients. We have assumed three measurements for each patient throughout the study. The overall simulation is repeated three times, one for each choice of sigma_b (the patient/time

trend error) with three guesses: (i) sigma_b=residual SD (ii) sigma_b=(residual SD+intercept SD)/2 (iii) intercept SD (worst case).

From the simulation figure, reading off the three curves and as indicated on the rhs of the graph, 80% power is achieved for scenario (i) at approximately N=42, for scenario (ii) at N=48 and for scenario (iii) at N=76. Thus in our worst case scenario, with N=76, we would need 38 subjects in each group. With an assumed attrition rate of 10% this would increase to approximately 42 subjects in each group.

Figure 3: Simulation power-curve