The Institute of Cancer Research

PHD STUDENTSHIP PROJECT PROPOSAL:

PROJECT DETAILS	
Project Title:	Enabling better reporting of outcomes for breast cancer radiotherapy trials
SUPERVISORY TEAM	
Primary Supervisor(s):	Professor Judith Bliss, ICR-CTSU Director & Methodology Lead for Breast Cancer Trials Professor Charlotte Coles (NIHR Research Professor, Cambridge)
Associate Supervisor(s):	Jo Haviland, ICR-CTSU Principal Statistician Dr Indrani Bhattacharya (Consultant Clinical Oncologist, Cambridge)
Backup Supervisor:	To be decided
Lead contact person for the project:	Professor Judith Bliss (for ICR purposes)
DIVISIONAL AFFILIATION	
Primary Division:	Division of Clinical Studies
Primary Team:	ICR-Clinical Trials and Statistics Unit
PROJECT PROPOSAL	

BACKGROUND TO THE PROJECT

Technology-enabled data collection is a rapidly-developing field in routine clinical practice and within clinical trials. This has primarily two strands i) collecting data directly from patients via electronic patient-reported outcomes (ePRO) using technology-based user friendly solutions such as smartphone apps [1], and ii) emerging opportunities for trials to link with routinely-collected NHS data. Whilst the merits of the goal are obvious, achieving that goal is challenging for multiple reasons. These include governance / data access issues and difficulties with collection of recurrence data from routine sources for cancer clinical trials. In addition, the ePRO is not always user-friendly or deemed cost effective or sufficiently inclusive for the trial-specific patient population and/or type of data being requested.

The COVID-19 pandemic has had a huge impact on people's technological capabilities. It is therefore pertinent to appraise what good adaptations for clinical care and trial conduct will endure and how this may help data outcome ascertainment for cancer clinical trials, using breast radiotherapy trials as the context for this specific project. The project is part of a wider programme of work within ICR-CTSU into assessing trial outcomes including ePRO and linkage with routine data [2], and builds on existing knowledge and infrastructure to allow specific focus on the type of data required for breast radiotherapy trials.

Outcomes relevant to breast cancer radiotherapy trials

As for any medical treatment, radiotherapy for breast cancer has to balance clinical benefit in terms of treating the cancer against minimising treatment-related adverse effects. Hence important outcomes in breast cancer radiotherapy trials include disease-related efficacy outcomes, i.e. recurrence and survival, as well as radiotherapy-related adverse effects. These radiotherapy adverse effects are usually termed "normal tissue effects" (NTE) as they relate to the healthy normal tissues that may receive some radiation dose when the area around where the tumour site is treated. These normal tissue effects can occur in the short-term (during and shortly after radiotherapy) and tend to resolve quickly, but long-term effects can occur up to many years following radiotherapy. Although rates of these so-called late normal tissue effects have declined following developments in radiotherapy techniques, they remain prevalent (around 25% may experience a moderate/marked adverse effect in the treated breast by 5 years following radiotherapy), and can be permanent (e.g. breast shrinkage), potentially having a long-term impact on patients. Severe radiotherapy-related adverse effects such as cardiac or lung disease are rare, but clearly clinically important. In the era of very low disease event rates (around 2% of patients experience a recurrence of the cancer in their breast within 5 years) it is even more imperative to minimise treatment-related adverse effects, and hence appropriate measurement of these effects within clinical trials is essential.

Outcome ascertainment

Traditionally, measurement of radiotherapy-related early and late adverse effects has relied on clinical assessments using graded scales, which compare the treated and untreated breast at regular intervals following treatment. Within UK breast radiotherapy trials conducted over the last few decades, other approaches to measuring normal tissue effects have been used, including photographic assessments and patient assessments from self-completed questionnaires, captured longitudinally throughout the trials [3-6]. The various modes of assessment have methodological differences (e.g. whether comparing treated and untreated breasts at a specific time-point or comparing treated breast before and after radiotherapy, whether assessment is blinded to which randomised treatment was received, etc), and so capture slightly different aspects. Retrospective analyses conducted within the START and IMPORT LOW trials [4] showed that whilst concordance between the different modes of assessment on an individual patient-level was low (with patients reporting more effects compared with clinicians), the randomised comparisons nevertheless produced similar results regardless of the NTE assessment method. Given the obvious importance of the patient perspective of treatment-related adverse effects, the question could be asked as to whether patient-reported outcomes (PRO) could form the primary endpoint for NTE, and if so, how can this best be done for future trials?

Although NTEs to the treated breast and arm/shoulder (when radiotherapy is given to the regional lymph nodes) are most common, there are other important outcomes such as rare serious NTE previously mentioned (including cardiovascular disease, rib fracture, pneumonitis), as well as outcomes that are less easily measured (including treatment-related fatigue, pain and cough). Whilst the serious but rare effects are likely to be documented in clinical notes and hence can be potentially extracted from NHS databases, other outcomes are not always systematically captured within clinical trial patients. We would also like to know what is missing from our current evaluations of NTE within radiotherapy trials, simply on the basis of have been deemed too difficult to collect historically.

PROJECT AIMS

Aims

(1) Literature review on use of ePRO for evaluation of NTE in breast radiotherapy trials (and clinical care), with specific reference to radiotherapy-related NTE but including consideration of other effects such as fatigue, pain, cough etc.

(2) Work with patients as equal research partners at all stages using existing funded patient and public involvement (PPI) networks and patient focus groups to develop and conduct a patient survey to ascertain considerations of how to collect such data differently – study within a trial (SWAT) (A) within existing trials i.e. where patients have already completed standard data collection methods
(3) Having identified best methods for collection of data, conduct SWAT (B) in radiotherapy trials or in separate patient series collecting outcome data using traditional and technology-enabled methods. Seek serial data collection and consider both acute and chronic effects.
(4) Compare and contrast user acceptability, completeness, quality and consistency of different data ascertainment methods.
(5) Develop recommendations for implementation of ePRO including use of visual tools to implement the enhanced methodology, working closely with clinicians and trial team.
(6) Pursue record linkage opportunities with routine NHS data to enable more holistic collection of future morbidities within clinical trials.

RESEARCH PROPOSAL

The overarching aim of this proposal is to develop data ascertainment methods for breast cancer radiotherapy trials that are more relevant to modern trials than the traditional routes of paper-based questionnaires, clinical physical examination and hospital-based photographic assessment.

This project will comprise the following main components:

(1) Identification of preferred data ascertainment methods

- Review existing literature of current practice – both traditional and novel
- Identify opportunity / gaps most suited to technology-enabled data ascertainment (e.g. daily reporting during and after radiotherapy for acute side effects, long-term serial data ascertainment for chronic effects). This will build on work done elsewhere comparing pictures vs questions for example.
- The proposed approaches would be motivated by real-world data from existing trials to identify key questions to incorporate, with a focus on breast NTE.
    - Conduct SWAT A – using patients in existing ICR-CTSU trials (potentially to include IMPORT HIGH (selected centres, e.g. Cambridge and RMH); FAST-Forward lymphatic radiotherapy sub-study (Cambridge and RMH)) and test possible data ascertainment methods to evaluate validity, completeness, consistency, use acceptability etc.
    - Design and conduct SWAT B informed by findings of SWAT A to formally compare different data capture methods, assessing patient preference, validity, reliability, consistency of reporting.
    - Ascertain record linkage completeness for other rarer side-effects, for example comparison with a cohort of patients with known outcomes.

(2) Practical Implementation

- Draft guidance for implementing technology-enabled data ascertainment within clinical trials or clinical practice, for example a checklist of considerations when choosing between data capture methods for different scenarios.

Expected Outputs:
Peer reviewed publications are anticipated in both clinical and methodological journals to report results of literature review and of SWAT (A) & SWAT (B). Culmination in guidance / best practice recommendations paper.

LITERATURE REFERENCES

[1] Warrington L, Absolom K, Conner M, Kellar I, Clayton B, Ayres M, et al. Electronic Systems for Patients to Report and Manage Side Effects of Cancer Treatment: Systematic Review. J Med Internet Res 2019;21:e10875. URL: https://doi.org/10.2196/10875

[2] Kilburn LS, Aresu M, Banerji J, Barrett-Lee P, Ellis P, Bliss JM. Can routine data be used to support cancer clinical trials? A historical baseline on which to build: retrospective linkage of data from the TACT (CRUK 01/001) breast cancer trial and the National Cancer Data Repository. Trials. 2017 Nov 23;18(1):561. doi: 10.1186/s13063-017-2308-6.

[3] Haviland JS, Ashton A, Broad B, Gothard, L, Owen JR, Tait D, Sydenham MA, Yarnold JR, Bliss JM. Evaluation of a method for grading late photographic change in breast appearance after radiotherapy for early breast cancer. Clin Oncol (R Coll Radiol) 2008; 20: 497-501.

[4] Bhattacharya IS, Haviland JS, Hopwood P, Coles CE, Yarnold JR, Bliss JM, Kirby AM, on behalf of the IMPORT Trialists. Can patient-reported outcomes be used instead of clinician-reported outcomes and photographs as primary endpoints of late normal tissue effects in breast radiotherapy trials? Results from the IMPORT LOW trial. Radiother Oncol (2019); 134: 220-230. https://authors.elsevier.com/sd/article/S0167814019300660.

[5] Bhattacharya IS, Haviland JS, Kirby AM, Kirwan CC, Hopwood P, Yarnold JR, Bliss JM, Coles CE on behalf of the IMPORT Trialists. Patient-Reported Outcomes Over 5 Years After Whole- or Partial-Breast Radiotherapy: Longitudinal Analysis of the IMPORT LOW (CRUK/06/003) Phase III Randomized Controlled Trial. J Clin Oncol. 2019 Feb 1;37(4):305-317. https://doi.org/10.1200/JCO.18.00982.

[6] Brunt AM, Haviland JS, Wheatley DA, Sydenham MA, Alhasso A, Bloomfield DJ et al, on behalf of the FAST-Forward Trial Management Group. Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. Lancet (2020); 395 (10237): 1613-1626. https://doi.org/10.1016/S0140-6736(20)30932-6

CANDIDATE PROFILE

Note: the ICR's standard minimum entry requirement is a relevant undergraduate Honours degree (First or 2:1)

Pre-requisite qualifications of applicants: e.g. BSc or equivalent in specific subject area(s)	Candidate must already have been awarded a first-class or second upper class honours degree in Mathematics, Statistics or other relevant data or research methodology. A Masters degree or equivalent in Medical Statistics and / or Medical Informatics or a related quantitative discipline, or experience of working in clinical trials would be highly desirable. The project will suit a candidate with strong statistical and research methods skills who has an interest in enabling optimal data ascertainment. The candidate will have a keen interest in applied research methods, systematic reviews, clinical trials, holistic reporting of outcomes and technology-enabled data ascertainment for cancer clinical trials.

Intended learning outcomes: .	- Will work in a high-quality multi-disciplinary clinical trials environment, and learn how to optimise outcome data ascertainment and apply methods in practice. - Ability to test reliability and validity of novel data ascertainment methods. - Gain both theoretical and applied skills critical in the development of an applied trial methodologist, including design and analysis of study design. - Understand the clinical setting of breast cancer radiotherapy and practical challenges that are often encountered in collection of required data. - Will learn to work collaboratively with clinicians and scientists in a highly interdisciplinary environment, and will benefit further from interaction with external leading experts in the field. - Ability to work with patient advocates to enable co-production of optimised methods of data collection.
ADVERTISING DETAILS	
Project suitable for a student with a background in:	☐ Biological Sciences ☐ Physics or Engineering ☐ Chemistry ☒ Maths, Statistics or Epidemiology ☒ Computer Science ☐ Other (provide details)
Keywords:	**1. Trial methodology / Medical statistics**
	2. Outcome ascertainment
	3. Patient Reported Outcomes
	4. Linkage with routine data
	5. Technology enabled trials
	6. Breast cancer radiotherapy trials