Clinical trials from the other side: Lessons learned by a clinician venturing into a clinical trials unit

Introduction

As part of a Cancer Research UK (CRUK) 'Clinical Trials Fellowship', ISB was seconded to The Institute of Cancer Research's Clinical Trials and Statistics Unit (ICR-CTSU), specifically working within the breast cancer radiotherapy trials portfolio on the IMPORT trials (1) (2) and PRIMETIME study (3) [table]. The CRUK 'Clinical Trials Fellowships' embed clinicians in clinical trials units (CTUs) for 1-3 years enabling Fellows to gain day-to-day experience in the conduct and analysis of cancer clinical trials. These Fellowships offer mutual benefits for both CTUs and Fellows. For example, Fellows provide clinical expertise and develop important sub-studies as part of a wider effort to ensure trials deliver maximal outputs. Meanwhile, Fellows gain skills required as future trialists. The CRUK 'Clinical Trials Fellowship' can facilitate effective collaboration between clinicians and CTUs which can improve and streamline clinical trials.

Why do we need clinical trials and what are the practicalities?

Clinical trials are required to identify optimal treatment options for patients. However, as ISB has discovered, clinical trials are multi-faceted. Trial participation can fast-track implementation of new technologies or processes within a stringent quality-assured framework. For example, implementation of intensity-modulated radiotherapy (IMRT) and best-practice guidance regarding surgical tumour-bed clips within IMPORT LOW (1) [table]. Thereby benefiting non-trial patients long before the primary endpoint is reported.

Also, with respect to translational research, several molecular techniques are available. However, results of these are highly dependent on the quality of baseline and follow-up data collected. Therefore, complete and comprehensive data-sets are required to determine the biology of recurrence or predictors of toxicity.

Radiotherapy trials are almost exclusively led by academically funded CTUs, utilising a resource-limited model compared with trials led by the pharmaceutical or technology industry. Similarly, resources are limited within the NHS, and there is an ongoing shortage of research staff and resources in sites. Despite these limitations, optimising clinical trials is paramount.

What is the role of CTUs?

CTUs are specialist multi-disciplinary academic units, usually university-based, with the specific remit to design, conduct, analyse and publish clinical trials. CTUs are academic partners, providing statistical, epidemiological and other methodological, project and data management expertise to undertake clinical trials successfully. Early collaborations between clinicians and CTUs are essential.

What is the role of the clinician?

Firstly, the chief investigator (CI) provides scientific and clinical expertise, identifying important clinical questions (in collaboration with patients and CTU) and has responsibility for the trial from regulatory as well as scientific perspective. Secondly, site (hospital) level principal investigators (PI), provide oversight for trial conduct at their site, and this includes ensuring informed consent is secured for all patients, protocol adherence and that principles of Good Clinical Practice are followed.

The PI's role is especially important in the current NHS climate given constraints in research nurse, radiology and pathology availability. Issues regarding resources and problems with trial set-up and recruitment should be communicated early to the CTU.

Patient advocate and Clinical Fellow involvement in CTUs

Patient advocates should be involved in the trial concept through to development, and throughout the trial lifespan. This is especially important in the current focus of treatment de-escalation. For example, patient advocates were key to the PRIMETIME study (3) [table]. Patient advocates advised the gold standard trial design of a randomised controlled trial (RCT) would not be acceptable, where patients would not want to be randomised to 'endocrine therapy only'. However, a biomarker-directed prospective-cohort study, where IHC4+C directs treatment would be acceptable. Also, it was primarily patient advocates who set the acceptable threshold of a 5-year ipsilateral disease rate of ≤4% for selective de-escalation of radiotherapy (4). Information delivery to patients in de-escalation studies needs careful consideration.

The PRIMETIME Information Giving Study (IGS), led by ISB as part of her Fellowship, is investigating if addition of a patient decision aid video to standard information reduces patient uncertainty regarding PRIMETIME entry. IGS decision aid video and study development involved close collaboration with PRIMETIME patient advocates, trial management group, Production Company and Research Ethics Committee. After Ethics

approval, ISB led implementation of the IGS in all PRIMETIME centres, thereby developing skills required to lead a study through from concept to development to set-up.

Also, patient-reported outcome measures (PROMs) are frequently incorporated into trials, providing valuable information of the patient's experience of treatment. The importance of collecting complete and timely data was apparent when ISB investigated PROMs in IMPORT LOW over 5-years (5). Clinicians should encourage patients to complete questionnaires enabling high quality PROMs data to be collected, benefitting future patients.

The Clinical Fellow as an intermediary – Case Report Form Design and Analysis

The case report form (CRF) is the documentation to be completed for each patient on the respective hospital visit in relation to the time-point of a specific trial. CRFs are the single-most important data document sent from the site to the CTU. Data is uploaded onto a database and cleaned (by data managers) and analysed by trial statisticians. CRFs inform the ability to analyse trial endpoints, for example, recurrence, survival and toxicity. It is therefore important that this form is accurately completed in a timely manner.

Previously, CRF completion may have been assigned to junior staff, who may not have fully appreciated the far-reaching benefit of clinical trials, and the importance of completing CRFs 'real-time'. CRF completion with patients in clinic allow questions to be framed appropriately to identify possible adverse events (AEs) and explore if related to the intervention. For example, is a rib fracture within the radiotherapy field? When coding suspected AEs in IMPORT HIGH (2) (table), ISB noted data were missing. In particular, rib fracture laterality was missing, thereby making it impossible to determine if this was radiotherapy-related. Despite contacting sites for missing information, it usually could not be retrieved as not always documented. This has implications for the patient in question, and future patients.

Also, correct CRFs must be completed. During the fellowship, ISB coded events in IMPORT LOW, including second cancers (1). An important learning point was, the distinction needs to be made as to whether a 'second cancer' or 'disease recurrence' form is required in the case the patient has secondary disease to avoid misreporting. Guidance from the site PI may reduce data queries from inaccurate CRFs, diverting resources to be used elsewhere.

There is also a risk of informative censoring of data if only a sub-set of patients have CRFs completed promptly, as there is a risk that those patients may be characteristically different versus patients without CRFs, resulting in a biased population. Furthermore, if outcomes are reported at time-points different to that specified in the trial protocol, there is a risk of inaccurate reporting and inflation or underestimation of the frequency of a given event.

Finally, in unblinded RCTs (common in radiotherapy), there is a risk of biased reporting, where for example toxicity may be over-reported in experimental versus control groups.

The Clinical Fellow as an intermediary Radiotherapy data

In UK radiotherapy trials, Radiotherapy Trials Quality Assurance (RTTQA) collect radiotherapy data (6). For data analysis, nomenclature of 'structure names' must be uniform for entry into dosimetry software. Within IMPORT HIGH (2), ISB reviewed CT planning scans to investigate if breast seroma was associated with toxicity. It was found, the whole-breast volume was not named uniformly and required re-naming, which was time-consuming and resource-intensive. Required nomenclature is usually specified in radiotherapy planning packs and guidance should be followed.

The importance of collaboration – Experience of the national research agenda

Collaboration with colleagues from multiple disciplines is key to ensure important clinical questions are answered. This was apparent to ISB as a member of the IMPORT and PRIMETIME trial management groups, where radiotherapists must work closely with other medical disciplines for example, surgeons, pathologists, radiologists as well as trial methodologists to ensure clinical trials are conducted successfully. Established networks such as the National Cancer Research Institute (NCRI) Breast Clinical Studies Group (CSG) (7) can facilitate this collaboration. As a trainee representative on the NCRI Breast CSG, ISB witnessed first-hand that these networks, ensure the research community is working together, and research is not conducted in silos. Furthermore, there has been a push to engage trainees in research through the Breast Trainees Collaborative Group who are conducting UK-wide audit/research projects.

Earlier exposure of clinicians-in-training to CTUs

As the number of clinical trials grows, extra clinician involvement and time is needed (8) to ensure appropriate trial conduct. However, there is a workforce crisis in clinical oncology, with a failure to recruit sufficient trainees, to balance future consultant demands (9). Furthermore, new consultants reported the training programme did not adequately prepare them for the research element of consultant posts (10).

Out-of-programme experience is an opportunity for trainees to gain protected time in research. Traditionally, this has been technical radiotherapy or lab-based. However, fellowships such as that described above, allow trainees to be embedded within CTUs, obtaining day-to-day experience and conduct of clinical trials whilst also studying for a PhD.

For CTUs, the Fellowship enables training of future leaders who begin their consultant careers knowledgeable in the skills required to undertake high-quality clinical research and to understand and appreciate the multi-disciplinary team science involved.

Conclusions

Clinical trials determine optimal treatment options for patients. Clinicians and CTUs share the overarching aim, to improve patient care. Open dialogue and effective communication between clinicians and CTUs will facilitate and streamline this process, to ensure high quality efficient clinical trials conduct.

1553 words

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