1. Project title

Evaluation of Image Guided Radiotherapy (IGRT) for more accurate Partial Breast Intensity-Modulated Radiotherapy: comparison with standard imaging technique.

2. Background

2.1 Existing research

Summary of the problem to be addressed

The problem is how to improve the quality of life and survival of women with early breast cancer treated by high dose breast radiotherapy after surgical removal of a malignant tumour. Breast conserving surgery (BCS) followed by radiotherapy is a proven alternative to mastectomy for a majority of women developing breast cancer. For every 100 women treated, radiotherapy prevents 20 local cancer relapses in the breast and 5 cancer-related deaths at 10 years [1]. Approximately 30,000 women are given radiotherapy for early breast cancer in the UK every year, resulting in the prevention of 6,000 local tumour relapses and 1,500 deaths from cancer. An estimated 1,500 local tumour relapses occur despite radiotherapy, a disproportionate number affecting women <50 years of age, who have a 3-fold higher local relapse risk than women in older age groups [2]. A wealth of data from randomised trials confirms that the majority of relapses appear in the region of the primary tumour, and this region is referred to as the tumour bed [3]. This pattern of relapse is the reason for giving a higher dose of radiotherapy to the tumour bed than to the rest of the breast. The extra dose to the tumour bed is called a boost and typically reduces local relapse risk by 50% at the expense of a 30% increase in moderate or severe hardening of breast tissue due to fibrosis [2,4]. Current protocols require a wide margin of healthy tissue to be added around the tumour bed to compensate for significant (5-10 mm) day-to-day shifts in patient position, which limits the radiation dose that can be safely delivered. The challenge is to safely reduce the volume of healthy tissue included in the boost treatment in order to reduce late complications and/or to allow safe dose escalation and higher cure rates. The hypothesis under test in this proposal is that modern treatment machines equipped with on-line x-ray imaging facilities are able to monitor the exact position of internal organs within the radiotherapy beam on a daily basis, allowing a substantial reduction in the safety margin around tumour bed volume, thereby reducing exposure of healthy tissue, reducing chronic complications and/or allowing safe dose escalation. This approach is novel, and will be tested in the context of the UK IMPORT HIGH trial, led by our group. In this randomised trial of radiotherapy dose escalation in women at higher than average risk of local cancer recurrence after removal of a breast lump, the success of the current proposal will be judged in terms of i) direct measurement of the magnitude of tumour bed margin reduction and therefore tumour bed boost volume reduction achieved by tumour bed imaging and ii) estimation of the reduction in rates of moderate and severe fibrosis (breast hardening).

Principles of breast radiotherapy planning and delivery

Breast irradiation is a 2-stage process (see Figure 1). First, the patient has a computed tomography (CT) scan of her breasts and chest lying in a position that we carefully aim to reproduce throughout treatment. The imaging data set serves as a basis for calculating the optimal distribution of radiotherapy dose across the breast. After this, the patient starts a treatment programme consisting of a series of daily treatments, called fractions, over a period of 3 weeks. The same patient position is reproduced each day using laser-light beams which must intersect pre-defined tattooed points on the skin surface. During standard treatment, images are generated by the high energy x-ray beam used to treat the cancer, but these show only the ribs and lungs, not the soft tissues of the breast where the tumour used to be. The images are compared with the CT images collected before treatment to identify small discrepancies, called set-up errors, in the position of ribs and lung within the beam. If set-up errors exceeding predefined limits persist, the patient is re-positioned, usually by several millimetres, before the next treatment fraction is delivered. One problem is that the position of lungs and ribs does not predict with sufficient accuracy where the tumour bed is. That is why wide margins of healthy tissue need to be added to the tumour bed boost volume.
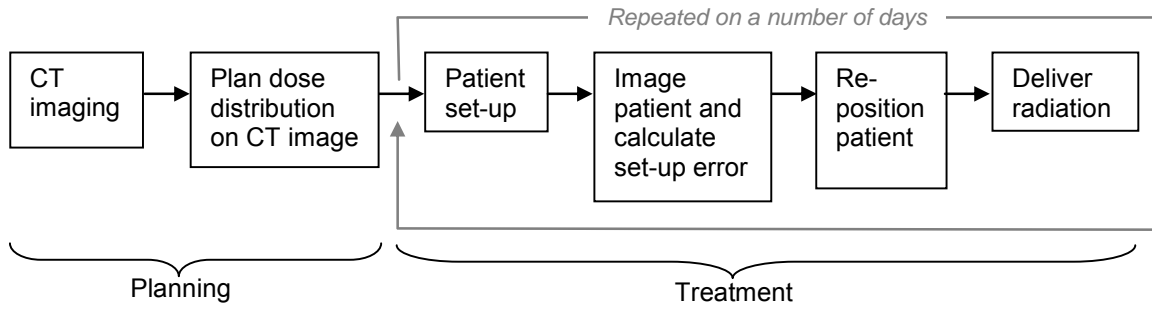
Figure 1: Schematic diagram of the use of imaging for radiotherapy set-up during each treatment fraction.

The inability of standard radiotherapy techniques to image the tumour bed directly means that larger volumes of breast tissue than needed receive high dose
It is standard practice to use the high energy x-ray beam produced by a treatment machine to identify the position of the ribs and lungs interface within the beam. The x-rays are too penetrating to show the soft tissues of the breast, and the tumour bed can move more than a centimetre relative to the bony anatomy and lungs. The inability to directly visualise the tumour bed means that the position of the tumour bed cannot be measured, forcing the cancer specialist to expose larger volumes of breast tissue to higher doses than needed. This concept is illustrated in Figure 2, which shows how a safety margin of normal tissue around the tumour bed is added to ensure that the radiotherapy boost dose adequately treats the tumour bed on each day of treatment. The volume of tissue including the safety margin is called the tumour bed boost volume.
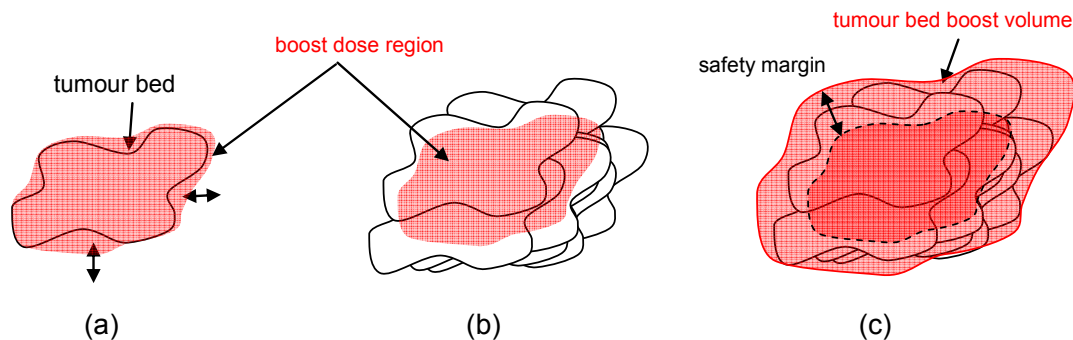

Figure 2: (a) Tumour bed requiring radiotherapy boost dose. (b) Position of tumour bed within the beam varies day-to-day during treatment. On any given day, part of the tumour bed can be outside the boost dose region (shown in red) resulting in under-dosage of the tumour bed. (c) A safety margin is added around the tumour bed to take account of this uncertainty. The adjusted volume is called the tumour bed boost volume.

The larger volume of healthy tissue around the tumour bed also places limits on the total dose that can be safely delivered. The hypothesis under test is that if the tumour bed is imaged directly during treatment, the margin of healthy tissue (tumour bed boost volume) could be reduced, leading to a smaller volume of healthy tissue irradiated and therefore to fewer treatment complications. Alternatively, in women at highest risk of local recurrence, it would allow safe dose escalation to the tumour bed, with better local cancer cure rates. Before justifying these expectations, a simple surgical technique will be described that enables the tumour bed to be imaged directly on a day-to-day basis during radiotherapy.

2

Titanium clips fastened to the excision cavity wall during surgery allow the tumour bed to be imaged during radiotherapy delivery

We have asked UK breast surgeons to attach standard titanium surgical clips to the walls of the tumour excision cavity that accurately record the position of the tumour bed. Pilot work was undertaken in preparation for the IMPORT HIGH trial, and clips are now recommended for all patients undergoing breast conservation surgery by the British Association of Surgical Oncology [5]. The key point is that titanium clips can be visualised directly using the treatment machines' low energy x-ray facility as can be seen in Figure 3, and it has been confirmed that boost treatments verified using the position of clips are more accurate than those relying purely on rib and lung imaging [6].
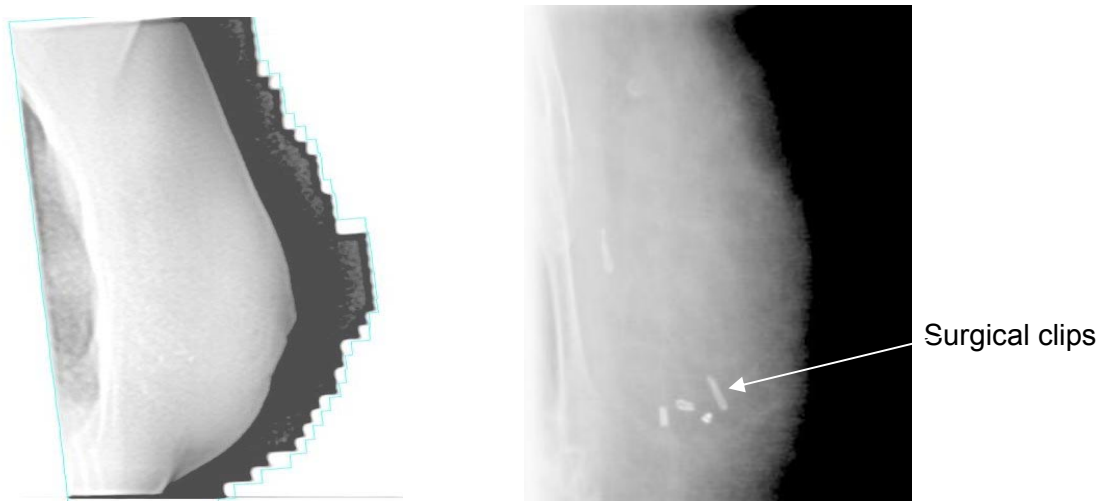

Figure 3. Standard image (left) and low energy x-ray CT image (right) of an IMPORT patient with implanted surgical clips. On the right, the titanium clips clearly indicate the position of the tumour bed, which otherwise can only be estimated in relation to overlying skin tattoos and underlying lung.

Differences between the planned positions of the titanium clips, based on the x-ray CT scan performed before treatment, and the actual positions of clips imaged during radiotherapy are corrected using small (a few millimetres) movements of the patient. The application of x-ray imaging of titanium clips to verify radiotherapy accuracy in real-time, i.e. *before* each treatment is given, is referred to as image guided radiotherapy (IGRT). The pilot study for the IMPORT HIGH trial suggests that IGRT is likely to allow narrower safety margins of healthy breast tissue around the tumour bed [7].The narrower margins typically achieved are shown in Figure 4, in this example delineating a volume of $70cm^3$ compared to $130cm^2$ needed when standard imaging is used.

If standard imaging is used to verify patient treatment no information about the tumour bed is obtained. In a comparison of IGRT and bony anatomy set-up (standard imaging), *additional* radial safety margins of 4.5 - 5.5mm were needed when standard imaging was used [8]. Another study found the average set-up error to be on average 4mm ($\pm$ 3mm) greater when using standard set-up compared to IGRT [9]. In a recent review of the growing amount of literature in which significant changes in the size and position of the tumour bed are reported, Kim et al [10] highlight the fact that clinical factors such as the time between surgery and planning CT influence the amount of change in the tumour bed that occurs during treatment. If large changes occur standard imaging is unable to detect this and as a consequence errors in patient positioning will increase. For any subset of patients, for whom clinical factors that result in large changes in the size and position of the tumour bed are present we would expect that the inaccuracy of standard imaging compared to IGRT would be greater and subsequently greater margins would need to be applied. An example of a sub-set of patients who have a longer time interval between surgery and the start of radiortherapy are those that receive chemotherapy. These patients may have a

more stable tumour bed and therefore the advantages of IGRT may be less than for those patients who have not received chemotherapy. A 5mm safety margin is added around the tumour bed in the IMPORT HIGH trial, compared to approximately 10mm when standard set-up is used. In summary, reduced margins around the tumour bed translate into smaller volumes exposed to high doses and fewer late side effects, including less hardness and tenderness. Clinical evidence justifying this expectation is now reviewed.
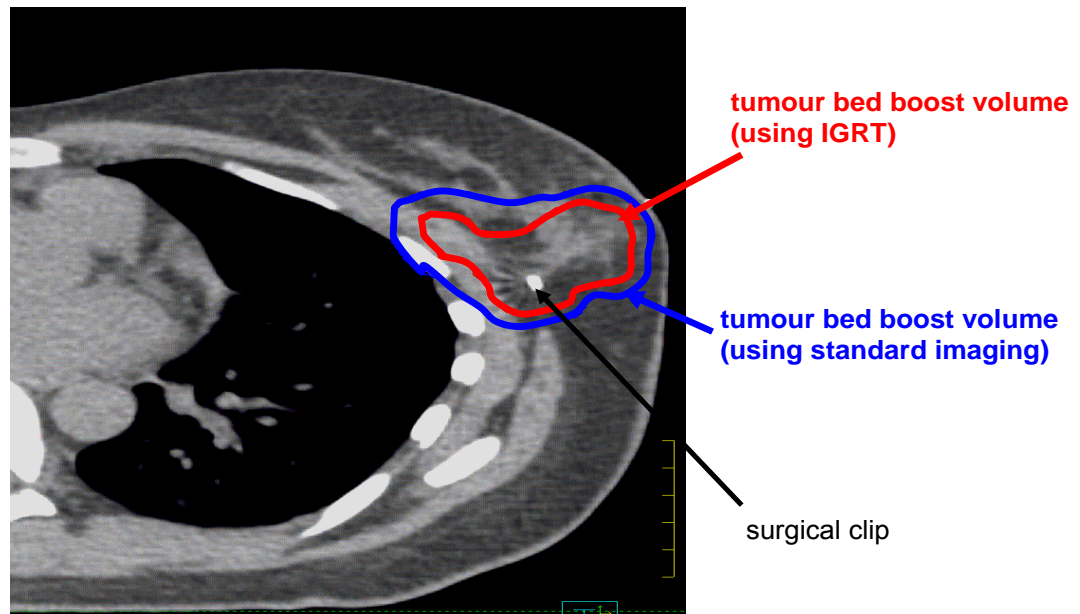

Figure 4. CT image of a patient showing the smaller tumour bed boost dose region for a patient having image guided radiotherapy (IGRT), outlined in red. One of the surgical clips is seen as a white dot within the tumour bed boost volume on this anatomical section. The blue line shows the larger volume if standard imaging of bony anatomy is used. The tumour bed boost volume is 70cm^3 using IGRT and 130cm^2 using standard imaging.

2.2 Risks and benefits

Dose-limiting adverse effects of breast radiotherapy

Radiotherapy dose responses for tumour control and normal tissue damage are long established and well quantified. In the UK Standardisation of Breast Radiotherapy (START) trials conducted by members of our group, physical morbidity was defined in terms of breast shrinkage, distortion and fibrosis scored by i) independent observers from serial clinical photographs, ii) clinical examination by physicians in the clinic and iii) by patients themselves at regular time-points over 5 years of follow up [4,11]. We reported one-third of women with minor or marked change in photographic breast appearance (shrinkage and distortion). These chronic effects increase in incidence and severity even after 5 years following radiotherapy. The photographic changes were in accordance with prospective patient self-assessments of adverse effects, including moderate or marked change in skin appearance (reported by around 30% of women), breast hardness (over 40%), and breast shrinkage (over 20%). A study in 254 patients undergoing breast conserving surgery and radiotherapy reported that physical changes in breast tissue had a marked bearing on subsequent psychological outcome [12]. Patients completed questionnaires assessing satisfaction with treatment outcome and scored psychosocial morbidity using the Hospital Anxiety and Depression (HAD) scale, the Body Image questionnaire and the Rosenberg Self-esteem scale. There was a strong association between breast appearance and levels of anxiety ($r = -0.81$, $P <0.001$), depression ($r = -0.7$, $P <0.001$), body image ($r = -0.4$, $P <0.001$), sexuality ($chi^2 = 22$, $P = 0.001$) and self-esteem ($r = -0.64$, $P <0.001$). Similar findings were recorded in the START trials, which detected a significant association between body image and anxiety and depression [13].

In the START trials, we confirmed a steep dose response for radiotherapy complications, such that a 10% increase in whole breast radiotherapy dose doubled the rate of late adverse effects. There is also a clear volume response, by which we mean that the probability of an adverse

effect of radiotherapy varies according to the volume of breast tissue irradiated. The magnitude of the volume response can be generated in different ways, most directly by comparing outcome of the same dose schedule delivered to different partial volumes of breast tissue. In a retrospective study of a radiotherapy boost dose delivered using radioactive implants in 404 patients, a 4-fold increase in risk of breast fibrosis (hardness) was reported for each 100cm^3 increment in boost volume, suggesting a very steep volume response [14]. This finding is consistent with univariate analysis of 364 patients randomised to a radiotherapy tumour bed boost dose after whole breast radiotherapy, which reported a hazard ratio for poor cosmesis of 0.45 (95% CI, 0.29 – 0.76) for boost volumes ≤200cm^3 compared to >200cm^3 [15]). The volume response can also be quantified by comparing the increased risk of late side-effects after a boost dose to the tumour bed compared with the same dose delivered to the whole breast. This analysis has been performed in 723 patients entered into the START pilot trial randomised to tumour bed boost dose versus no tumour bed boost [14]. Patients randomised to tumour bed boost radiotherapy (15.5 Gy in 7 fractions (radiotherapy doses are measured in units of Gray (abbreviated to Gy)) had a 17% higher risk of moderate or marked breast hardness at 10 years. The same randomised trial compared two dose levels of whole breast radiotherapy. The dose of whole breast radiotherapy causing a 17% increased risk of breast hardening was estimated to be 4.5 Gy. This is much lower than the 15.5 Gy causing the same degree of breast hardening when given to a boost volume of about 200cm^3, representing 20-30% of whole breast volume.

In section 2.1, we described the findings of other small studies that have compared the accuracy of IGRT and standard imaging. From this work and our pilot study [7], we estimate that the margins of a conventional tumour bed boost volume can be safely reduced by approximately 5mm in all spatial dimensions using our IGRT protocol. From our pilot study the average tumour bed boost volume required is approximately 70cm^3 and 110cm^3, this will reduce the total volume of the average breast boost dose by approximately 40cm^3, and is expected (after Borger et al [14]) to reduce the risk of moderate to severe fibrosis by up to a factor of 1.7.

2.3 Rationale for current study

We consider a randomised trial to be a cumbersome and expensive technology to apply to the problem addressed in this application. On the other hand, the lack of empirical research data justifying the widespread use of IGRT means that necessary resources to implement IGRT in routine clinical practice are not available, and that expensive and potentially valuable equipment is left idle. Whatever research methodology is used, the preferred primary endpoint measures treatment accuracy. Gains in accuracy can be derived directly (without assumptions) from data collected in an ongoing clinical trial that uses IGRT to verify treatment accuracy as part of its technical quality assurance protocol. The IMPORT HIGH trial provides a very reliable context in which to test the hypothesis that more accurate treatment verification allows a substantial reduction in breast volume exposed to high boost doses of radiotherapy. By generating direct estimates of the mean volume of breast spared by daily IGRT, it will be possible to estimate the expected reductions in late adverse effects. The estimates will be largely based on the published results of randomised trials conducted by members of our collaboration [4,11,16,17]. It will also be possible to estimate the degree to which dose could be safely escalated in the group of patients at highest risk of local recurrence, and the predicted benefits in terms of improved local tumour control.

The proposed study will quantify the benefit of IGRT using titanium clips in breast cancer patients using a study design that does not jeopardise patient care. Accurate localisation of the tumour bed has been shown to be important to ensure the accuracy of whole breast radiotherapy [7,18]. The results of this study will be applicable for all patients with breast cancer, including those prescribed partial breast radiotherapy. If the study confirms that IGRT for women at higher risk of recurrence is beneficial, then this will justify the routine adoption of IGRT in all UK centres. This will ensure equity of access and optimal treatment for all breast cancer patients.

3. Research objectives
Primary objective
To compare the spatial accuracy of breast radiotherapy based on imaging i) titanium markers implanted in the tumour bed (referred to as IGRT) and ii) bony anatomy and lung position (referred to as standard imaging) during curative radiotherapy for early breast cancer.

Secondary objectives
1. To determine the reduction in volume of normal tissue irradiated to a high dose using IGRT compared to standard imaging.
2. To estimate the reduced risk of late adverse effects resulting from the smaller tissue volume irradiated, using data generated and published from earlier randomised trials conducted by members of our collaboration.
3. To record the time required for each imaging method.

4. Research Design
Multi-centre observational study embedded within a national phase III randomised controlled trial: IMPORT (Intensity Modulated Partial Organ Radiotherapy) HIGH. Six radiotherapy centres will take part in this study. These are: Cambridge University Hospitals NHS Foundation Trust (Addenbrookes), Royal Marsden NHS Foundation Trust (Sutton), Ipswich Hospital NHS Trust, South Devon NHS Foundation Trust (Torbay), Royal Preston Hospital and Clatterbridge Centre for Oncology NHS Foundation Trust.

5. Study population
The study population is patients receiving breast radiotherapy as part of a UK trial: IMPORT (Intensity Modulated partial Organ Radiotherapy) HIGH. These are patients who have had breast conservation surgery and are considered to have higher than average risk of breast cancer recurrence. Eligibility criteria for IMPORT HIGH includes any patient where a boost dose to the tumour bed is deemed beneficial (see attached IMPORT HIGH trial protocol).

6. Planned interventions
As an observational study, there is no direct intervention in the patients' treatment. The intervention involves the imaging data used to plan and verify the treatment. The experimental intervention is image guided radiotherapy (IGRT) and the control intervention is standard imaging. Both are image verification techniques used to determine the position of the patient prior to treatment by measuring positional shifts between treatment time images and the images used to plan the treatment.

Standard imaging
Standard imaging is the use of x-ray imaging to determine the position of bony anatomy prior to radiation delivery. These images are used to determine the distance we have to move the patient so that the bony anatomy and lung position is in the same position as it was for treatment planning. Several x-ray imaging methods are available (CT scanning or a set of planar images). All can achieve the same result, of measuring the position of the bony anatomy relative to the radiotherapy treatment beam in 3D. Imaging using the high-energy treatment beam is the most common form of radiotherapy treatment imaging, but (as discussed in the background) this does not allow implanted surgical clips to be seen.

IGRT
IGRT is the use of x-ray images to determine the position of implanted surgical clips, which mark the tumour bed prior to radiation delivery. X-ray images will be acquired on a minimum of 15 treatment days. These images are used to find the distance we have to shift the patient so that the markers defining the tumour bed are in the same position as for treatment planning. IGRT images contain all the information in standard images plus the implanted marker information (figure 3).

As part of the IMPORT HIGH trial, patients will receive radiotherapy using IGRT as routine. This will contain the information needed for standard imaging evaluation, i.e. the position of bony anatomy.

7. Proposed outcome measures
The primary outcome measure
Positional accuracy of IGRT versus standard imaging. This measure allows us to calculate the safety margin (tumour bed boost volume) required to ensure the tumour bed is treated to a high dose if standard imaging is used for patient set-up.

Secondary outcome measures
1. Volume of normal tissue spared using IGRT compared to standard imaging.
2. Differences in modelled normal tissue complication probabilities (NTCP) for IGRT and standard imaging. We will model the resultant risk of adverse effects, expressed in terms of normal tissue complication probability. The main source of evidence for this part of the project will be the data of Borger et al, which showed a correlation between both total dose and volume of tissue treated and the probability of fibrosis [14].
3. Time required to perform IGRT and standard imaging.

8. Assessment and follow-up

8.1 Assessment of efficacy
Determination of primary outcome positional accuracy of IGRT compared to standard imaging
As part of the IMPORT HIGH protocol, patients will receive IGRT on every day of treatment (15 days). Thus the IMPORT HIGH treatment protocol will not be altered, and patient care will not be jeopardised. To determine the efficacy of IGRT we have to first measure the positional accuracy of IGRT compared to standard imaging. This will be determined using the following steps:

- The difference between patient position at treatment and at planning is called the set-up error. For each patient, 15 measures of set-up error will be determined for each fraction delivered using the IGRT images acquired as part of IMPORT HIGH.
- The same IMPORT HIGH data will be used to simulate standard images of bony anatomy, by ignoring the information from the clips and using the bony anatomy information. These will be used to obtain 15 measures of set-up error for radiotherapy using standard imaging.
- We will determine the difference between IGRT set-up error and standard imaging set-up error on each treatment day for each patient.
- Because the correlation between set-up errors measured using IGRT and standard imaging is not available we will review the patient sample size once we have data for 100 patients. We will determine the correlation between set-up errors measured for IGRT and standard imaging and adjust the sample size accordingly (see section 9).
- The mean absolute difference between the set-up errors for all patients is the mean accuracy of IGRT compared to standard imaging.
- Patient specific positional accuracy of standard imaging versus IGRT will be tested for association with clinical factors that can be expected to influence the accuracy of standard imaging. These factors include time from surgery to planning CT, time from CT to start of treatment, seroma size at time of planning, breast size, position of tumour bed within the breast and the trial treatment to which the patient was randomised (the control schedule of IMPORT HIGH is delivered in 23 fractions whereas the test schedules deliver 15 fractions).

Determination of volume of normal tissue spared using IGRT compared to standard imaging
To determine the volume of tissue spared using IGRT we first have to assess the tumour bed boost volumes required to achieve tumour bed dose coverage for radiotherapy using standard imaging.
- The safety margin will be calculated using the 3D set-up errors measured for standard imaging. This will be achieved using normal protocols that employ formulae from the

literature [19] and account for the interplay between day-to-day (random) and average (systematic) set-up errors and accuracy of dose coverage of the target.

- The tumour bed boost volume required using standard imaging for each patient will be determined by adding the safety margin to the boost volume of IGRT radiotherapy i.e. those used to treat patients in the IMPORT HIGH trial. Thus, we will have two tumour bed boost volumes, one for IGRT and one for standard imaging.

- From IMPORT HIGH we will know the planned dose pattern for the IGRT tumour bed boost volume. For this study we will re-plan the patient using the standard imaging tumour bed boost volume and calculate a new dose pattern.

- From these dose patterns we can determine the volume of tissue that received 95% of the prescribed dose to the tumour bed on a patient by patient basis.

- The volume of normal tissue spared using IGRT compared to standard imaging is the difference between the 95% dose volume using IGRT and standard imaging.

Determination of differences in modelled normal tissue complication probabilities (NTCP) for IGRT and standard imaging
- Boost volume and incidence of adverse effects will be generated from the Cambridge Breast IMRT study [20].

- Using this data and data from the UK START pilot trial [16-17], the EORTC trial 22881-10882 [20] and Borger et al [14] (see section 2.2, paragraph 2), we will determine the relationship between volume of tissue irradiated and the risk of moderate or severe breast hardness.

- Using these relationships, for each patient, the percentage reduction in rate of moderate or severe breast hardness (fibrosis) will be estimated from the absolute reduction in volume achieved by the use of IGRT in preference to standard imaging.

- We will report on the median (95% C.I.) normal tissue complication probabilities associated with IGRT and standard imaging for our patient population.

- We are also interested in relating quality of life (QoL) data obtained from the IMPORT HIGH trial to the volume of tissue irradiated. In the IMPORT HIGH trial quality of life questionnaires will be completed at 6, 12, 36 and 60 months of follow-up; we will be able to link these data with the treated volumes for each patient obtained from the IGRT study. We will be able to test for associations between factors such as anxiety, depression, body image, sexuality and self-esteem and the volume of tissue irradiated. This is not an outcome of this study as it relies upon the follow-up data from IMPORT HIGH, and will be reported when this long-term follow up data is available.

Time required to perform IGRT and standard imaging
We will ask radiographers who will verify patient treatment position using low-energy x-ray imaging of titanium clips (IGRT) to record the time required to obtain images and determine the set-up error. We will determine the time required for standard imaging from normal practice. The time required to determine set-up error from the standard imaging data will also be recorded. If the time taken to perform IGRT is significantly higher than the time taken to perform standard imaging the data collected by the proposed study will be available for a full health economics analysis.

8.2 Assessment of safety
The study involves retrospective analysis of imaging data and thus has no adverse safety implication for the study subjects. Adverse events for patients recruited to the IMPORT HIGH trial are dealt with by the standard trial protocol (attached).

9. Proposed sample size

The sample size calculation has been carried out by the ICR-CTSU. The study statistician (JH) is responsible for overseeing all statistical analyses. In this study the primary outcome measure is the accuracy of standard imaging compared to IGRT. We will use accuracy to determine the probability of adverse effects (fibrosis) using the following steps:

- Accuracy is defined as the overall set-up error for each patient. The overall set-up error for each patient is the mean of the 15 set-up errors measured at each fraction. The accuracy of standard imaging compared to IGRT will determine the additional safety margin.
- The technique-specific safety margin is calculated from the distribution of the patients' overall set-up errors. The size of the margin is approximately twice the standard deviation of the overall set-up errors for all patients [19].
- The volume of normal tissue irradiated when standard imaging is used is then calculated by simply adding this margin to the treatment volume used for IMPORT high (which uses IGRT).
- The probability of adverse effects (fibrosis) for IGRT and standard imaging will be determined from the volumes of tissue irradiated when using IGRT and standard imaging using the relationship between incidence of fibrosis and volume determined using radiobiological modelling (see section 10).

We will have two sets of data: the overall set-up error from n patients acquired using IGRT and the overall set-up error from n patients acquired using standard imaging.

A difference in the standard deviation (or variance) of these data sets will result in a difference in safety margin and the volumes of normal tissue irradiated. Thus, we base our sample size calculation on finding a significant difference in the variance of these two data sets. To perform the sample size calculation we have estimated the standard deviation of set-up errors for IGRT and standard imaging the correlation between the data-sets using evidence from the literature:

- *Standard deviation:* From a small study of 20 patients, Topolnjak et al. [8] found that, if standard imaging were used daily, the standard deviation of the set-up errors was between 2.7mm and 3.8mm. In a similar study of 10 patients by Kim et al. [22], the standard deviation of set-up errors was measured to be between 0.9 mm and 1.4 mm when daily IGRT is used. Kim et al. estimate that this range of values rises from 2.2mm to 2.6mm when other factors such as deformation of the breast are taken into account. To calculate our sample size, based on these studies we will aim to detect differences in standard deviations corresponding to a decrease from 3mm for standard imaging to 2mm for IGRT.
- *Correlation:* Because no similar studies have previously been performed directly comparing IGRT and standard imaging the correlation between the two data sets is unknown. Work by Penninkhof et al [23] shows that set-up errors measured in the same patient using two imaging techniques to image bony anatomy are highly correlated (~0.85). We expect the correlation between set-up errors for IGRT and standard imaging to be high (> 0.5) as they will be measured in the same patient but not as high as for two techniques measuring bony anatomy (i.e. < 0.85).

We have determined the sample size required for high correlation, 0.7 and very low correlation, 0.1. Using computer simulations [24] based on Fisher's test, with 128 patients, it will be possible to detect a 1mm difference in the standard deviations from 2mm to 3mm assuming correlation=0.7, power=80%, alpha=0.05; using the same analysis but assuming very low correlation (correlation = 0.1), with 250 patients it will be possible to detect the same difference (2mm v.s. 3mm) in standard deviations (power=80% and alpha=0.05). As this sample size calculation has been based upon estimates from studies using small numbers of patients and a definitive value for the correlation between set-up errors measured using the two techniques is not available, we have based our study on the requirement for a larger cohort of patients, 250 which allows for smaller correlations. An Independent Data Monitoring Committee will confidentially review the data after the first 100 patients, and advise on the final sample size.
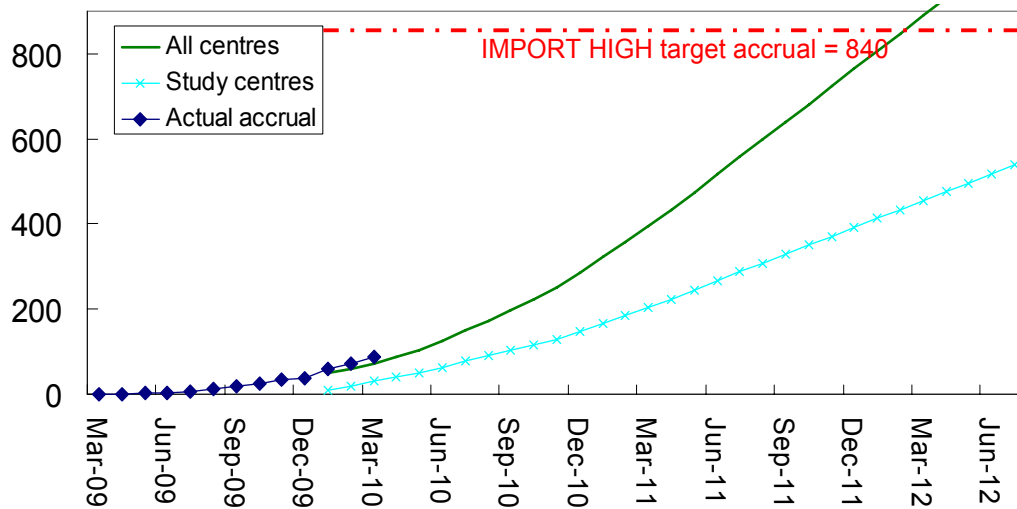
Figure 5 Predicted and actual accrual rates for all IMPORT HIGH centres and those taking part in this study.

Figure 5 shows a plot of predicted accrual rate for all IMPORT HIGH centres and those taking part in this study. Also shown is the actual accrual rate which exceeds the predicted rate. The total number of patients accrued by the end of March 2010 was 84, and patients are so far being treated at four centres, which will all participate in this study. Proposed study start is January 2011, and we hope to have accrued data from a minimum of 250 patients by January 2012; predicted trial accrual for centres participating in this study at January 2012 is ~400.

10. Statistical analysis

As each patient acts as their own control, paired analyses will be done comparing accuracy of IGRT versus standard imaging. Standard deviations will be compared using Fisher's test and means will be compared using the paired t-test. If the distribution of differences is skewed then a suitable transformation will first be sought to try to normalise the data; if no such transformation can be found then non-parametric methods of analysis will be used, such as the Wilcoxon rank-sum test.

Heterogeneities in accuracy may arise due to a number of factors, including clinical factors such as the time elapsed between surgery and planning CT, the time elapsed between planning CT and the end of treatment, breast size, size of seroma, tumour bed position, tumour bed size and allocated treatment (i.e. IMPORT HIGH trial arm). Also there may be differences in accuracy between centres. Distributions of random and systematic set-up errors will be compared between centres and tested for association with clinical factors using analysis of variance (ANOVA) or the non-parametric equivalent (Kruskal-Wallis test), depending on the distribution of the differences in errors. For quantitative clinical factors (e.g. time between surgery and planning CT), either the data could be categorised and then analysed using an ANOVA or kept as continuous data and analysed using an analysis of covariance. If there are apparent centre differences, this information would lead to further exploration of work-process details, so that good practice at those centres achieving smaller positional errors can be widely adopted. If clinical factors are associated with differences in accuracy these can be used to determine sub-sets of patients for whom IGRT or standard imaging is more or less appropriate.

To calculate the difference in normal tissue complication probability (NTCP) of standard imaging compared to IGRT we will start with the standard approach to NTCP modelling which describes the probability of normal tissue injury, such as fibrosis, in terms of two main effects. First is the relationship with dose. The probability of normal tissue injury has a sigmoid variation with dose, see Figure 6. Two factors characterise this behaviour, the dose value for 50% injury probability (NTD_{50}) and the steepness of the slope of the curve at this dose value (k). The second effect to be described is the volume effect. This accounts for the saving in the severity of normal tissue damage that can be achieved by reducing the volume of the tissue subject to high dose, i.e. if $50cm^3$ of tissue is irradiated to high dose, this will have a less severe effect on the patient than if $100cm^3$ is irradiated to that dose (dashed lines in Figure 6). We expect the accuracy of IGRT to be greater than standard imaging and therefore, the safety margin we would use for standard imaging will be greater and the average volume of tissue irradiated will be greater leading to an increase in tissue toxicity. The strength of this volume dependence is characterised by a parameter (n). We shall use the data from the Cambridge Breast IMRT study [20], the UK START pilot trial [16-17], the EORTC trial 22881-10882 [20] and Borger et al [14] to determine best estimates of the above parameters that characterise the relationship between dose and fibrosis and use the results to model the difference in fibrosis between standard and IGRT based treatment margins. Once follow-up data from the IMPORT HIGH trial are available, the developed model will be validated by relating the volumes of tissue irradiated measured during this study to the incidence of fibrosis during follow-up, which is the primary endpoint in the trial.
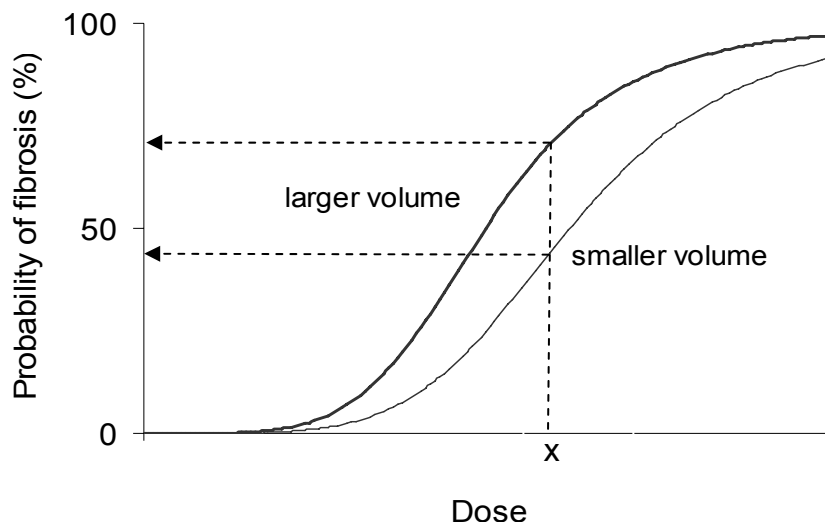

Figure 6: Graphical illustration of the volume effect. For a given dose (x), the probability of fibrosis is less for smaller volumes.

The mean time required for each imaging method will be compared between IGRT and standard imaging using the paired t-test.

11. Ethical arrangements

This study will involve retrospective analysis of imaging data acquired in the IMPORT HIGH national trial. All patients recruited to the IMPORT HIGH trial have given informed consent to their imaging data being used for related studies. The IMPORT HIGH protocol and the patient consent form for IMPORT HIGH is attached. In addition, we have confirmed approval of this study from the Research Ethics Committee that approved IMPORT HIGH. Patient confidentiality will be maintained at all times.

12. Research Governance

The sponsor of the study will be the Institute of Cancer Research. This organisation is the sponsor of the IMPORT HIGH trial and the employer of the Chief Investigator of both IMPORT HIGH and this study. The Trial Steering Committee of IMPORT HIGH provides the proposed governance framework for this study.

The main funding body of IMPORT HIGH (Cancer Research UK) has provided a letter expressing support for this study.

13. Project timetable and milestones

The project will last for 30 months. Eligible patients are currently being recruited into IMPORT HIGH and we expect to have exceeded accrual of 250 patients by the end of the first year of this study. There will be three monthly project meetings to coincide with IMPORT HIGH trial management group meetings. The project is split into the following tasks:

I. Establish study methodology (months 1-3): The physics post will be filled at the start of the project. The first 6 months activity will be to establish and develop the research tools and other infrastructure, such as a common software platform for image and dosimetric analysis and efficient data exchange methods.

II. Data collection (months 3 – 12): (The CRF start at month 6) Patient CT, daily images, patients shifts and plans will be extracted from all centres and collected centrally. Clinical data (as detailed in section 8.1) will be extracted from CT and daily images (both CRF and physicist will share this work).

III. Analysis of positional accuracy and margins (Physics lead) (months 6 – 12): The analysis of images to extract set-up errors for IGRT and standard radiotherapy will be conducted. Accuracy of differing matching techniques and imaging technologies and the association between clinical factors will be investigated (see section 10). The time to perform IGRT and standard imaging positional analysis will be recorded, The study statistician (JH) takes responsibility for overseeing the statistical analysis.

> **Milestone 1** (Month 9): Once data has been analysed for 100 patients we will determine the correlation between set-up errors measured using IGRT and standard imaging and the sample size will be reviewed by an Independent Data Monitoring Committee.
>
> **Milestone 2** (Month 12): Accuracy of standard imaging compared to IGRT (Primary Outcome) and safety margins (secondary outcome).

IV. Background Review (CRF lead) (month 6 – 9): A comprehensive and critical review of the relationship between irradiated breast volume and late normal tissue side effects will be carried out. The manuscript will be prepared for submission to a peer reviewed journal.

V. Development of a radiobiological modelling tool (CRF lead) (months –6-12): The CRF will use new data from the NIHR Cambridge Breast IMRT trial to develop the radiobiological modelling tools. The dataset consists of 1145 patients with comprehensive late normal toxicity data with clinical, photographic and quality of life endpoints using validated assessment tools. The CRF will be required to calculate the tumour bed boost volume for all patients. The data will then be divided to produce a training and validation dataset. The training dataset of ~500 patients with linked toxicity endpoints will be used to develop the radiobiological modelling tool. These data will be analysed with all other existing trials data to determine relationships between volume of tissue irradiated, dose, fraction size and incidence of adverse effects.

VI. Validation of a radiobiological modelling tool (CRF lead) (months 12 - 18): Radiobiological modelling will be used to determine the probability of normal tissue toxicity as a function of volume of tissue irradiated for a given dose. This will be validated in the in the ~ 500 patients in the validation dataset. JH will oversee the validation of the model and the generation of estimations of model accuracy.

> **Milestone 3** (Month 16): Interim report/publications (radiobiological review and accuracy).

VII. Re-planning of patient dose distributions (Physicist/CRF) (months 12 - 24): Planned volumes will be re-contoured based on new margins (CRF) and clinically acceptable dose distributions recalculated (physicist).

     Milestone 4 (Month 24): Patient treated volumes (secondary outcome).

VIII. Calculation of probability of tissue toxicity and the cost of reduction in toxicity (CRF) (months 21-27): Re-planned dose data and the developed radiobiological models will be used to calculate the normal tissue complication probabilities. The CRF will analyse the timings for IGRT versus standard imaging. Additional time taken will be converted into additional cost. A simple estimate of cost of possible reduction in toxicity and improvement in quality of life using IGRT will be produced.

     Milestone 5 (Month 27): Estimation of increase risk of adverse effects (secondary outcome) and cost (secondary outcome).

IX. Preparation of publications and final report (CRF/Physicist/Statistician) (months 27 – 30)
     Milestone 6 (Month 30): Estimation of increase risk of adverse effects.

A detailed work plan for the Clinical Research Fellow is given in appendix A.

14. Gantt chart
Yellow denotes the timing of employed posts, dark blue indicates physics time, light blue indicates CRF time and hatched mid blue indicates where both will contribute time to the task. Red diamonds represent the milestones listed above. The vertical lines show the three monthly meetings of the project group.

TASK	Year 1 Q1	Q2	Q3	Q4	Year 2 Q5	Q6	Q7	Q8	Year 3 Q9	Q10
	PHYSICS POST									
1. Development of methodology		■								
			CRF POST							
2. Data collection			■	▨						
3. Positional accuracy and margins			■	■						
Sample size review ◆										
Accuracy of techniques ◆										
4. Background review			■	■						
5. Development of radiobiological modelling tool				■	■					
6. Validation of radiobiological modelling tools						■	■	▨		
Interim report ◆										
7. Re-planning					▨	■	■	■		
Patients' treated volumes ◆										
8. Calculation of tissue toxicity / cost								■	▨	
Risk of adverse effects ◆										
9. Publication / final report preparation									▨	▨
Final report ◆										

15. Expertise

Oncology: Prof Yarnold has a long record of instigating and leading large national trials and local trials in all aspects of the clinical, biological and technical aspects of radiotherapy. Dr Coles is Chief Clinical Coordinator of the NRCI IMPORT trials and a breast cancer specialist and as co-principal investigator will oversee the project. Dr Jena is a clinical oncologist with significant experience in breast radiotherapy and expertise in the development of models to describe patient treatment accuracy. Dr Kirby is also a clinical oncologist with experience of breast radiotherapy and significant research experience in image guidance for breast radiotherapy.

Statistics: Mrs Haviland Senior Statistician at the Institute of Cancer Research Clinical Trials and Statistics Unit (ICR-CTSU) will oversee all statistics and analysis, with input from Mr Sumo (ICR-CTSU), the IMPORT trial statistician. ICR-CTSU, Sutton is an NCRI-accredited trials unit with a recognised portfolio of radiotherapy trials. ICR-CTSU is currently running an IGRT trial in prostate cancer. Ms Titley is the IMPORT HIGH Trial Co-ordinator in ICR-CTSU, she has considerable experience of supporting trials and liaising with patient representatives in those trials. She manages much of the data in the IMPORT HIGH study and will do so in this study.

Radiotherapy Physics: Dr Evans and Dr Harris have expertise in radiation physics research, including development of imaging systems, and the scientific basis of breast radiotherapy. Dr Fenwick has expertise in radiotherapy physics and radiobiological modelling. Mr Poynter, Mrs Mayles, Mr Shentall and Mrs Cross are leads for Radiotherapy Physics.

Radiography: Ms Rawlings and Ms Perry are senior research radiographers with expertise in the delivery of complex radiotherapy.

Co-ordinators and post holders: Dr Evans is Principal Investigator and will have overall responsibility for running the study. Dr Coles is Clinical Co-Principal Investigator and will manage the Clinical Research Fellow included in this grant. Dr Harris is Physics Co-Principal Investigator and will manage the Physics post with Dr Evans. The Physics post holder will liaise between the centres, collect and anonymise data, and carry out the primary data analysis of patient positional shifts and corresponding treatment volumes. The Clinical Research Fellow will liaise with the Physics post holder to investigate the effects of the differences between standard imaging and IGRT on planned dose distributions and their effect in terms of probability of side effects, calculated using the NTCP models.
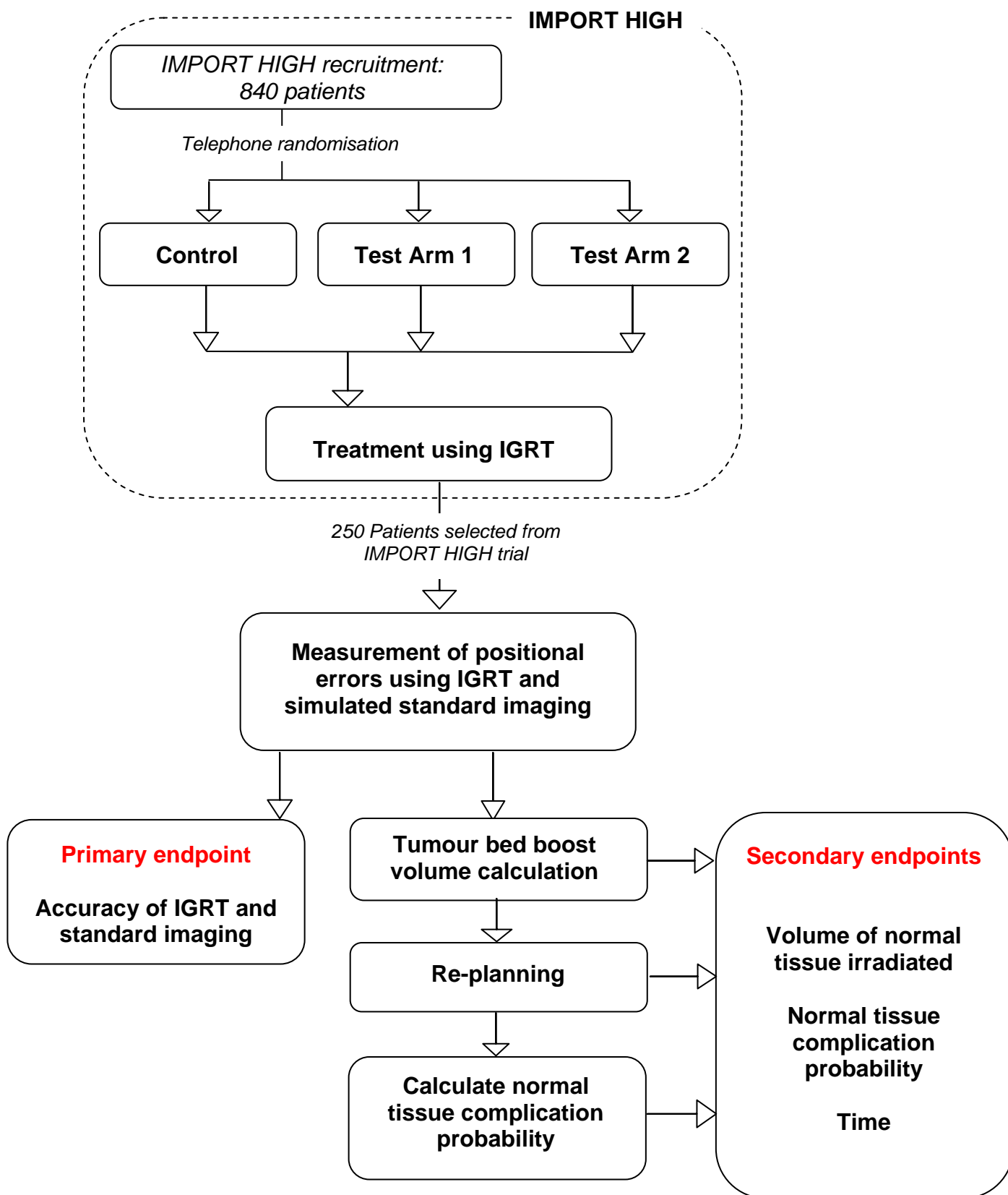

16. Service users

A service user is a member of the IMPORT HIGH trial management group. They have been involved in the formulation of this study, particularly in terms of commenting on the description of the study design. We anticipate they will provide further input when the preliminary and final results are reported to the Trial Management Group of IMPORT HIGH.

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18. Flow Diagram

IMPORT HIGH

IMPORT HIGH recruitment:
840 patients

Telephone randomisation

Control | Test Arm 1 | Test Arm 2

Treatment using IGRT

250 Patients selected from
IMPORT HIGH trial

Measurement of positional errors using IGRT and simulated standard imaging

Primary endpoint

Accuracy of IGRT and standard imaging

Tumour bed boost volume calculation

Re-planning

Calculate normal tissue complication probability

Secondary endpoints

Volume of normal tissue irradiated

Normal tissue complication probability

Time

Project 09/150/16: Evaluation of Image Guided Radiotherapy (IGRT) for more accurate Partial Breast Intensity-Modulated Radiotherapy:

Appendix A: Role of Clinical Research Fellow

RESEARCH OBJECTIVES
Primary objective
To compare the spatial accuracy of breast radiotherapy based on imaging i) titanium markers implanted in the tumour bed (referred to as IGRT) and ii) bony anatomy and lung position (referred to as standard imaging) during curative radiotherapy for early breast cancer.
Secondary objectives
1. To determine the reduction in volume of normal tissue irradiated to a high dose using IGRT compared to standard imaging.
2. To estimate the reduced risk of late adverse effects resulting from the smaller tissue volume irradiated, using data generated and published from earlier randomised trials conducted by members of our collaboration.
3. To record the time required for each imaging method.

ROLE OF THE CLINICAL RESEARCH FELLOW (CRF)
The entire project is split into nine project tasks, the CRF will contribute to tasks I to IX. Eight CRF-specific deliverables that will directly contribute to project outcome (linked to project milestones) have been identified; these are labelled D1 to D9. The project tasks, project milestones and CRF-specific deliverables are displayed in the Gantt diagram.

CRF-specific deliverables:

D1: Establish a clinical study database for up to 250 IMPORT HIGH patients, detailing surgical, histological and imaging details

D2: Assessment of serial imaging and 3D contouring of seroma for all patients in database

D3: Report on literature review of the relationship between volume of breast tissue irradiated and the development of late normal tissue toxicity

D4: Develop a dose response model of normal tissue response with increasing breast boost volume irradiated

D5: Develop a novel dose response model of normal tissue response with increasing breast boost volume irradiated,using Quality of Life metric as the clinical endpoint

D6: Produce new contours for 250 MPORT HIGH IGRT study patients

D7: Validate the radiobiological dose response model of normal tissue response and quality of life with increasing breast boost volume irradiated

D8: Calculate the additional cost of IGRT to treatment workflow

The Gantt Chart illustrates that all of these deliverables must be completed between month 6 and month 30 of the project timeline, with no training time available to acquire the prerequisite clinical skills. It is therefore essential that the CRF will be a senior Clinical Oncology Specialist Registrar (year 4 or 5 of specialist training or equivalent) so that he/she can complete the necessary deliverables in a timely fashion.

Essential clinical skills required for CRF:
  (i)   Interpretation of clinical data, e.g. surgical operation notes and histology reports

(ii)   Interpretation of computed tomography (CT) imaging data, e.g. differentiation of normal breast anatomy from post-operative seroma

(iii)   Critical review of literature to identify clinically meaningful normal tissue endpoints and their relationship with increasing breast boost volume irradiate, which will be incorporated into the dose response radiobiological model

(iv)   Knowledge of radiotherapy planning to produce new contours and radiotherapy plans (dose distributions) for the study patients, e.g. when 2 plans meet the specified dose constraints for IMPORT HIGH, the CRF must distinguish which plan is superior based on clinical knowledge of effects of dose to the target and normal tissues

Primary objective
The CRF will provide the necessary clinical skills to achieve the primary objective in conjunction with the physicist as outlined below.

Data collection (task II)
(a) Study database (D1): The CRF will establish a study database for up to 250 IMPORT HIGH IGRT study patients. Figure 1 shows a plot of predicted accrual rate for all IMPORT HIGH centres (using conservative estimates). These figures are based on accrual rates up until August 2010. The total number of patients accrued by the end of August 2010 was 148 (all within IGRT study centres). Proposed CRF start is July 2011, and it is now anticipated that data will be accrued from a minimum of 325 by July 2011; the majority (>80%) of these will be IGRT study centre patients. The study database will include surgical, histological, anatomical and imaging parameters. Surgical, clinical and histological data will be interpreted from patient case notes by the CRF (see table 1). To extract imaging and anatomical parameters, all patients will require transfer of DICOM images of the radiotherapy CT planning images for assessment by the CRF (see Table 2). This will include the contouring of seroma in daily imaging data **(D2).**
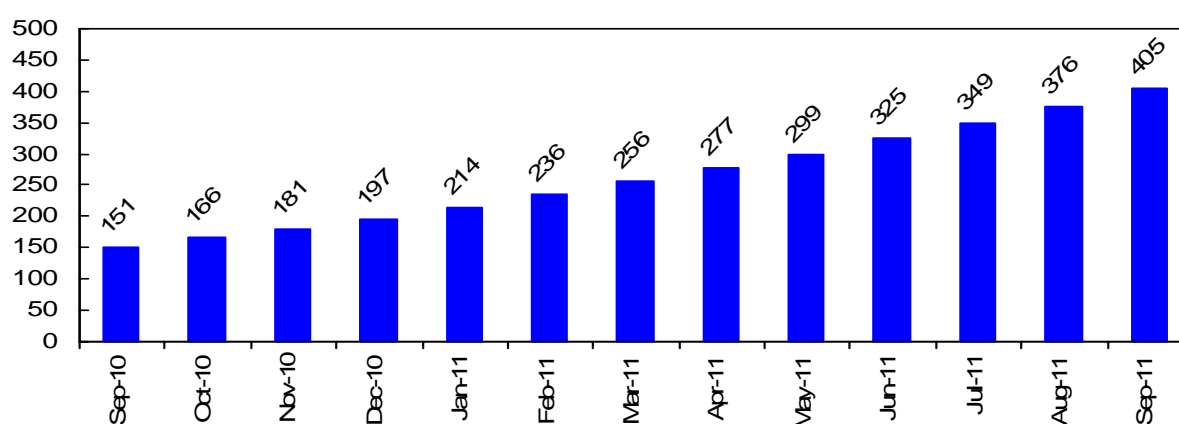

Figure1. Predicted (conservative) accrual rates for all IMPORT HIGH centres revised September 2010 based on current recruitment

Table 1: Surgical and histological parameters required for study database

		Data Source	**Patient Numbers**
Surgery	Index breast quadrant containing tumour	Patient case notes / IMPORT HIGH Case Report Form	250 IMPORT HIGH IGRT study patients
	Presence/absence of breast re-modeling		
	Type of surgery: open vs closed		
Histology	Weight of breast excision specimen (g)		
	Size of minimum radial excision margin (mm)		

	Size of invasive tumour (mm)		

Table 2: Imaging and anatomical parameters required for study database

		Data Source	Patient Numbers
Imaging and anatomy	Time interval from surgery to radiotherapy CT planning scan (days)	Patient case notes / IMPORT HIGH Case Report Form	250 IMPORT HIGH IGRT study patients
	Number of tumour bed clips (or pairs of clips)		
	Posterior clip(s) attached to deep fascia: yes/no		
	Visibility of tumour bed seroma: score 1-4 using validated scoring system	IMPORT HIGH QA data	
	Volume of tumour bed seroma (cm^3)		
	Volume of tumour bed clinical target volume – CTV (cm^3)		

Analysis of positional accuracy and margins (task III) Using the database compiled by the CRF and the set-up error data acquired by the physicist, association between positional accuracy of IGRT and the clinical data collected will be investigated. Both the CRF and physicist will report the results of the primary objective as a joint manuscript for publication (project milestone 2).

Secondary Objective 1. To determine the reduction in volume of normal tissue irradiated to a high dose using IGRT compared to standard imaging.

Re-planning of patient dose distributions (task VII)
(a) Re-contouring of boost volumes: The physicist will calculate the safety new for standard imaging using the 3D set-up errors measured in the primary objective. The CRF will apply these new safety margins to each of the 250 sets of radiotherapy CT scans to create a new tumour bed volume boost volume, which will be recorded for all patients. The physicist will use these new 3D volumes to create a revised radiotherapy plan with a new dose pattern for each patient **(D6).**

(b) Clinical assessment and validation of plans: The CRF will assess the plans and any clinical implications for the new margins (for example any increases in heart or lung doses) will be recorded. Plans will need to be approved as if for clinical use.

Secondary Objective 2: To estimate the reduced risk of late adverse effects resulting from the smaller tissue volume irradiated, using data generated and published from earlier randomised trials conducted by members of our collaboration.

Background review (task IV)
The CRF will review the literature and prepare a comprehensive and critical review manuscript of the relationship between volume of breast tissue irradiated and the development of late normal tissue toxicity. This will include land mark randomised controlled studies such as the EORTC boost versus no boost trial and the START trials. In addition, the dose-volume boost data form the Borger series will be reviewed. This review will provide the basis to develop and refine the radiobiological modelling tool to predict the effect of increasing breast volume irradiation with late toxicity. It will also be submitted for publication in a peer reviewed journal **(D3).**

Development of a radiobiological modelling tool (taskVI)

(a) Effect of irradiated volume on late normal tissue toxicity (D4): The radiobiological modelling tool is already at a preliminary stage of development by using parameters from the Borger review paper (see Figure 2 below). The CRF will re-implement this model for study usage and extend the model by incorporating 5-year late normal tissue toxicity data from the EORTC and START trials, along with the associated breast boost volume data.
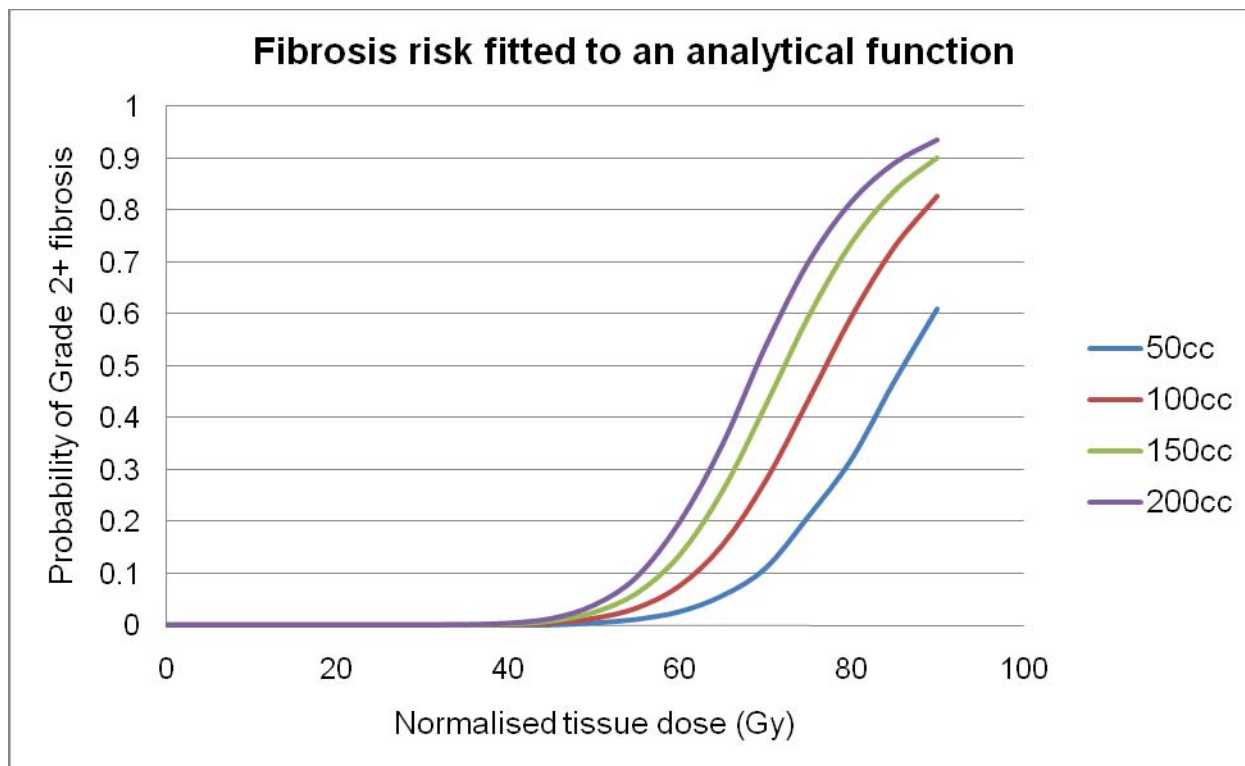

Figure 2: Graph demonstrating how clinical data collated by Borger et al (1994) can be fitted to an analytical function, modelling the risk of breast fibrosis according to radiotherapy dose and the volume of irradiated breast tissue. The CRF will revise and extend this fitting using newer datasets available from the EORTC and START Trials.

(b) Effect of irradiated volume on quality of life (D5): The CRF will have access to the 5 year follow up data of a 225 patient dataset from the NCRN Cambridge Breast IMRT trial, which has both comprehensive late toxicity data and quality of life data recorded using validated scoring systems. In addition, radiotherapy details regarding the breast boost area and depth of irradiation are available for the 60% of trial patients who received a boost dose. Therefore, the CRF will be able to calculate the irradiated breast boost volume for each patient.

The same radiobiological modelling techniques will be used to provide a predictive outcome model using Quality of Life metrics rather than breast fibrosis as the clinical endpoint. This novel approach will provide the opportunity to develop a patient focussed model, predicting the patient's quality of life at 5 years following breast radiotherapy (see Table 3). This is not achievable with either the EORTC or START data there is no available information regarding quality of life or boost volumes in each trial respectively.

Table 3: Cambridge Breast IMRT trial patients for quality of life model

IMRT TRIAL PATIENTS	QUALITY OF LIFE SCORING SYSTEM		
	EORTC QLQ-C30	EORTC BR23	HADS
No boost	n = 75		
Boost < 200 cm^3	n = 75		
Boost ≥ 200 cm^3	n = 75		

Validation of the radiobiological modelling tool (task VI)
The CRF will use Monte Carlo simulation techniques to optimise fitting of radiobiological parameters to the EORTC and START data sets. Parameter set validation will be performed using a separate data set of 250 patients from the Cambridge Breast IMRT trial. These patients would not have been included in the development of any of the previous models. All these patients will have reached 5 years follow up from completion of radiation treatment and will have both late normal tissue toxicity and quality of life 5-year follow up data available. Currently, there are 350 IMRT trial patients with 5 years of follow up (September 2010) and there will be an additional 150 patients by June 2011. This will give a total of 500 patient's data to be used within both the development and validation of the radiobiological model **(D7).**

Secondary Objective 3. To record the time required for each imaging method.

Data collection (task II)
(b) Collation of timing data: The CRF will collate the additional time taken for delivery and analysis of IGRT compared with standard imaging.

Calculation of probability of tissue toxicity and the cost of reduction in toxicity (task VIII)
(a) Calculation of risk of adverse effects: Following validation of the model, it will be used to estimate the additional burden of late normal tissue toxicity and impact on quality of life with increasing breast volume irradiated using standard imaging. Re-planned dose data and the developed radiobiological models will be used to calculate the normal tissue complication probabilities.

(b) Cost-effectiveness analysis for addition of IGRT to treatment workflow (D8): The CRF will convert the additional time will be converted into the cost of employing a middle-band radiographer by the CRF. This will give a simple measure of possible benefit with IGRT, with reduced normal tissue toxicity and/or improved quality of life for a given cost of radiographer time. The CRF and the physicist will submit the results of the secondary objectives as a peer-reviewed publication.

Preparation of publications and final report/MD thesis (task IX)

Project Gantt Chart

Project TASK	Year 1				Year 2				Year 3	
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
I. Development of methodology										
II. Data collection										
(a) Study database				D1	D2					
(b) Collation of timing data										
III. Positional accuracy and margins										
Sample size review ◆										
Accuracy of techniques (publication) ◆										
IV. Background review			D3							
V. Development of radiobiological modelling tool										
(a) Effect of irradiated volume on normal tissue toxicity				D4						
(b) Effect of irradiated volume on quality of life					D5					
VI. Validation of radiobiological modelling tools							D7			
Interim report (publication of background review) ◆										
VII. Re-planning of patient dose distributions										
(a) Re-contouring of boost volumes						D6				
(b) Clinical assessment and validation of plans										
Patients' treated volumes ◆										
VII. Calculation of tissue toxicity / cost										
(a) Calculation of risk of adverse effects:										
(b) Cost-effectiveness analysis										D8
Risk of adverse effects ◆										
IX. Publication / final report preparation										
Final report and MD thesis ◆										

◆ Project milestones