IMPORT HIGH

(Intensity Modulated Partial Organ Radiotherapy)

PROTOCOL

Randomised trial testing dose escalated intensity modulated radiotherapy for women treated by breast conservation surgery and appropriate systemic therapy for early breast cancer

On behalf of the IMPORT HIGH Trial Working Party

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A National Cancer Research Network Portfolio Clinical Trial; approved by the Clinical Trials Advisory and Awards Committee (CTAAC)

Endorsed by the National Cancer Research Institute radiotherapy clinical studies group

Main REC Reference Number: 08/H0305/13

ISRCTN: ISRCTN47437448

Protocol Number: ICR-CTSU/2007/10013

Protocol Version 7.0 07/02/2014

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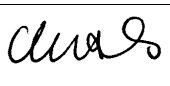
Dr Charlotte Coles (Chief Investigator)	**07/02/2014**	
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This clinical trial protocol is intended to provide guidance and information only for the conduct of the IMPORT HIGH Trial in participating centres. It is not for use as a guide for the management of other patients outside of the trial. If you have an urgent clinical query please contact Dr Charlotte Coles or Dr Anna Kirby.

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1. TRIAL SUMMARY

Title	Randomised trial testing dose escalated intensity modulated radiotherapy for women treated by breast conservation surgery and appropriate systemic therapy for early breast cancer.
Aim	To test dose escalated intensity modulated radiotherapy after conservation surgery for early breast cancer in women with higher than average local recurrence risk.
Eligibility Criteria	**Inclusion criteria** • Operable unilateral breast cancer (T1-3, pN0- pN3a, M0 at presentation). • Breast conserving surgery. • Age ≥ 18 years • Histological confirmation of invasive carcinoma. • Complete microscopic resection. • Patient requires a tumour bed boost plus whole breast radiotherapy for inclusion within the trial. • Written informed consent and available for follow-up. **Exclusion criteria** • Past history of malignancy except i) basal cell skin cancer and CIN cervix uteri or ii) non breast malignancy allowed if treated with curative intent and at least 5 years disease free • Mastectomy. • Concomitant chemotherapy (primary or sequential chemotherapy allowed). • Presence of ipsilateral breast implant
Study Design	Prospective randomised controlled clinical trial.
Trial Treatment	**Control group delivers 23 fractions**: 40 Gy in 15 fractions (Fr) to whole breast plus 16 Gy in 8 Fr sequential photon boost to the tumour bed. **Test groups deliver 15 fractions**: 36 Gy in 15 Fr to whole breast; 40 Gy to partial breast plus 48 Gy (Test Group 1) or 53 Gy (Test Group 2) in 15 Fr concomitant photon boost to tumour bed.
Endpoints	**Primary endpoint** is local tumour control. **Secondary endpoints** include induration in the ipsilateral breast, other late adverse effects in normal tissues, quality of life, location of tumour relapse in breast, contralateral primary tumours, regional and distant metastases and survival.
Sample Size	2568 patients will provide 80% power to exclude no more than a 3% increase in local relapse with each test group compared to the control schedule, assuming a 5% local relapse rate at 5 years in the control group.

2. BACKGROUND

Intensity modulated radiotherapy (IMRT) can reduce local tumour recurrence and breast cancer mortality

The 2005 Early Breast Cancer Trialists Collaborative Group (EBCTCG) systematic overview confirms a 70% proportional reduction in local tumour recurrence risk after radiotherapy in patients treated by breast conservation surgery for early breast cancer (1). The overview confirms that the prevention of 4 local tumour recurrences prevents, on average, one breast cancer death at 10 years, corresponding to 1 – 5 fewer deaths per 100 node negative women and 5 – 10 fewer deaths per 100 node positive patients treated.

In women with early breast cancer, local tumour recurrence remains a significant hazard despite optimal breast conservation surgery, radiotherapy and adjuvant systemic therapies. In the 2005 EBCTCG overview, isolated local recurrence developed by 10 years in 16% of node positive patients randomised to radiotherapy after breast conservation surgery with or without adjuvant systemic therapy. A 16% local recurrence rate is directly responsible for an absolute 4% breast cancer mortality rate that could be reduced by improved local control. It is hypothesised that current biological and technical advances in radiotherapy offer scope to reduce the risks of local tumour recurrence, breast cancer mortality and iatrogenic morbidity in a highly cost-effective manner. The value of a conventional sequential (electron) boost dose in higher risk subgroups has been confirmed in a recent EORTC trial (2). However, the postulated high sensitivity of breast cancer to radiotherapy fraction size leads to a prediction that modulation of dose per fraction will be a more effective approach to dose escalation than increasing the number of fractions (see section 2.4). Intensity modulated radiotherapy offers the technology needed to deliver the biological benefits of an approach that aims to match biological dose intensity more effectively than before to the spatial distribution of tumour recurrence and iatrogenic morbidity. The first step in establishing risk-adapted radiotherapy is to confirm that women with low and high-risk tumours can be reliably identified.

Low and high cancer recurrence risk subgroups can be distinguished

Data from four prospective randomised trials testing radiotherapy after breast conservation surgery have reported on factors associated with local recurrence risk (3). The total number of patients randomised in these trials is 2,578, but the total number of local recurrence events is relatively small. A fifth (Scottish) trial of 585 patients under 70 years of age with clinical tumours < 4 cm did not attempt to identify risk factors for local-regional recurrence (4). Lower level evidence originates from published retrospective analyses of patients treated at single institutions.

Pathological tumour size > 2 cm was associated with a risk ratio for recurrence of 2.3 (95% CI 1.3 - 2.9, p = 0.008) in a Cox multivariate regression analysis of the Canadian trial, which randomised 837 histologically node negative patients with pathological tumour size $<$ 4 cm (5). The Milan II trial reported a local recurrence rate after quadrantectomy alone of 12.6% for tumours $>$ 1.6 cm compared with 6.7% for tumours $\leq$ 1.6 cm in 273 patients with tumours $<$ 2.5 cm pathological diameter randomised to the surgery only arm (3). Note that in this trial, local recurrence was defined as malignancy appearing within 3 – 5 cm of the surgical scar line, more distant tumours being classified as new primaries. In a Cox regression analysis of the NSABP B-06 trial of 1,262 patients treated by tumourectomy +/- radiotherapy, maximum tumour size was associated with a higher risk of recurrence in node negative patients, but not in node positive patients (6). The Swedish trial of 381 women failed to confirm tumour size as a factor

associated with increased risk of recurrence, but there were no tumours > 2 cm mammographic diameter in this study (7).

Lymph node status was not mentioned as a predictor of risk in a Cox regression analysis of the Canadian trial (5). Positive axillary lymph nodes were associated with a local recurrence risk of 12.1% compared to 7.2% for node negative patients in 273 patients randomised to quadrantectomy only in the Milan II trial, but no multivariate analyses was performed (3). In the NSABP B-06 trial, node positive patients had a significantly lower ipsilateral breast recurrence rate than node negative patients (8.8% versus 17% at 20 years), a difference attributed to the increased use of systemic therapies in the former subgroup (8-9). Node status was not a significant negative predictor of local recurrence risk in an earlier multivariate analysis of this trial (6). The Swedish trial does not contribute, since it included only node negative patients (7).

Lymphovascular invasion is not reported in the Canadian, Milan II or NSABP B-06 trials. Lymphovascular invasion was not a risk factor for local recurrence in a multivariate analysis of the Swedish trial (7). In a retrospective analysis of 263 patients treated by breast conservation surgery and radiotherapy in Nottingham, UK, lymphovascular invasion (plus young age, positive node status and large tumour size) were reported as significant risk factors for local recurrence in a multivariate analysis of 56 ipsilateral recurrences (10).

A multivariate Cox regression analysis of the Canadian trial reported a risk ratio for local recurrence of 1.5 (95% CI 1.0-2.3, p = 0.04) for poor nuclear grade (broadly equivalent to histological grade III) (5). Analysis of *tumour grade* is not reported in the Milan II trial. A risk ratio of 1.49 (95% CI 1.20 – 1.85) for high nuclear grade was reported in a multivariate analysis of the NSABP B-06 trial (6). In the Swedish trial, comedo ductal carcinoma (almost exclusively grade III) was associated with a 2.5-fold increase in local recurrence rate in a multivariate analysis (7).

The importance of *resection margins* is impossible to judge in any of the four randomised studies. The clearest demonstration of an effect is gained from the Milan III trial, which randomised 705 women to quadrantectomy (> 2 cm margin) or tumourectomy (≤ 1 cm margin) prior to radiotherapy (11). There were 63 local recurrences in the group randomised to tumourectomy compared to 25 in the group randomised to quadrantectomy, local recurrence being defined as tumours appearing within 3 – 5 cm of the resection scar (12). A retrospective analysis from Boston reported 5–year local recurrence rates (with 95% CI) among 885 patients with negative, close (< 1 mm margin), focally positive, more than focally positive margins as 0% (0 – 4), 4% (0 – 20), 6% (1 – 17) and 21% (10 – 37) respectively (13).

The Canadian trial applied Cox regression analysis to identify *patient age* < 50 years as a risk for local recurrence, with a hazard ratio of 1.8 (95% CI 1.34 - 2.47, p = 0.001) after almost 8 years of follow up (5). The Milan II trial also reported young age as a risk factor for local recurrence, but did not examine this by multivariate analysis (3). The recurrence rates were 17.5%, 8.7% and 3.8% for women aged < 45, 45 - 55 and > 55 years, respectively, at a median follow-up of 39 months (range 28 to 54 months). When the three Milan trials were analysed together (n = 1,973), the effect of young age was still seen (14-15). The NSABP B-06 trial reported age < 50 years as a significant predictor of local recurrence, using Cox multivariate regression, with a risk ratio of 1.29 (95% CI 1.05 – 1.60) (6). Multivariate analysis also identified age < 50 years as a significant risk factor for local recurrence in the Swedish trial, with 3% reduction in recurrence risk per year of increasing age (7). A further demonstration of the age effect is seen among 5,569 women randomised to boost therapy after breast conservation surgery and radiotherapy for early breast cancer, where young age (especially < 40 years) was a highly significant predictor of recurrence risk in a multivariate analysis (2).

Extensive intraductal carcinoma (EIC) was associated with a higher risk of local recurrence in the Milan II trial (3). However, subsequent analysis of 1,973 patients in all three Milan conservation trials reported EIC to be a significant risk factor only if the surgical resection margins were 'narrow' (not defined) or incomplete (14). EIC was not analysed in the Canadian or NSABP B-06 trials. EIC was found not to be a significant risk factor for local recurrence in a multivariate analysis of the Swedish trial that included age, tumour size, lymphovascular invasion and histopathological type (7). Among the most reliable retrospective data reported were those from Boston, where the adverse effect of EIC on local recurrence risk was reportedly neutralised by confirmation of complete microscopic margins (≥ 1 mm) at excision/re-excision (13). The use of EIC as a decision-making tool for breast conservation therapy is no longer recommended for routine practice. This is due to the lack of an internationally accepted definition of EIC, better pre-operative imaging to detect multifocal disease, and improved pathological assessment of surgical margins (personal communication: A Recht, Boston).

The significance of *histological tumour subtype* was not commented upon by the Canadian or Milan II trials. The NSABP B-06 trial reported papillary, tubular and mucinous subtypes to be associated with a significantly lower risk of local recurrence than commoner histological subtypes in multivariate analysis (6). Invasive lobular carcinoma was associated with a 2.5-fold increased risk (95% CI 0.95-6.4, p = 0.06) of local recurrence in a multivariate analysis of the Swedish trial (7).

The EORTC 22881-10882 boost versus no boost trial contributes the highest level of evidence to the analysis of factors prognostic for local tumour relapse after breast conserving surgery and whole breast radiotherapy (16). In this trial, 5318 women were randomised to a tumour bed boost dose of 16 Gy in 8 fractions versus no boost dose after 50 Gy in 25 fractions over 5 weeks to the whole breast. Based on 326 local tumour relapses, corresponding to a 5-year rate of 5.4%, the boost and young patient age were by far the most powerful risk factors in multivariate analysis. Tumour size, tumour grade, excision margins and adjuvant systemic therapy were also independent predictors of local relapse risk, but their contributions were very modest compared to patient age and boost. Women aged < 50 years in this trial had a ≥ 1% annual risk of local relapse after whole breast radiotherapy plus boost. These women represent approximately 30% of all patients with early breast cancer and the most to gain from dose intensification.

Modest dose reduction outside the index quadrant may reduce late morbidity whilst retaining tumour control

A modest dose reduction to non-target tissues and to breast tissue away from the primary tumour site is expected to reduce late morbidity without compromising tumour control. This is based on the observation that local tumour recurrence risk is highest in the index quadrant, whereas iatrogenic morbidity and mortality is strongly influenced by full dose exposure to other parts of the breast, pectoral muscle, ribcage and portions of heart and lung. It is postulated that a modest dose reduction to low risk parts of the breast, underlying muscles and ribcage will cause no detectable increase in local tumour recurrence, but will cause a sharp fall in iatrogenic morbidity with measurable improvement in quality of life. The pattern of local cancer recurrence in the breast will be reviewed first.

Serial sub-gross examination of 264 mastectomy specimens from patient with tumours ≤ 4 cm diameter revealed 40% cases with intraduct and/or invasive disease ≥ 2 cm from the microscopic edge of the index lesion (17). This rate fell to 11% at 4 cm distance from the

tumour edge (7% invasive, 4% intraduct). Tumour foci ≥ 4 cm from the index lesion are likely to be located in different breast duct systems, since the 3D anatomy of the normal breast based on serial sub-gross sectioning shows the duct systems to be arranged in a regular radial array around the nipple (18). Spread of neoplastic cells via anastamoses between duct systems cannot be excluded, but it is reasonable to postulate that a proportion of tumour foci > 4 cm from the primary tumour edge represent independent neoplastic or pre-neoplastic pathological entities. This hypothesis is greatly strengthened by data from the results of autopsy on women not known to have breast cancer at the time of death. In a meta-analysis of seven series identified in a Medline search 1966-96, a total of 852 autopsies were submitted to breast examination ranging sub-gross examination, radiographic examination or sampling (19). With a mean number of breast sections in different series ranging from 9 to 275, the median prevalence of duct carcinoma in situ (DCIS) was 8.9% (0 - 14.7) and of invasive carcinoma was 1.3% (0 – 1.8).

Clinical observation of the spatial and temporal pattern of ipsilateral relapse outside the index quadrant is entirely consistent with a proportion of such lesions being independent tumours. The majority of relapses occur close to the primary site, and are assumed to be true recurrences. For example, in 2,544 patients treated by breast conservation surgery +/- radiotherapy at the National Cancer Institute, Milan between 1970-89, 142/191 (74%) ipsilateral relapses presented ≤ 2 cm from the surgical scar (20). Interestingly, the rate of 'new primaries' outside the index quadrant in the irradiated breast was comparable with the rate of contralateral primary disease. In a separate study of 1,152 women treated by tumour excision and radiotherapy and followed up for a minimum of nine years (mean 14 years), ipsilateral relapses were classified as new primaries if they were of a different histological subtype, had a lower histological grade than the primary lesion or were diploid when the primary tumour had been aneuploid (21). On this basis, 60/136 (44%) were classified as true local recurrences, all of which had appeared by nine years of follow up. These patients had a subsequent 10-year survival of just over 50%. By contrast, 70/136 were classified as new primaries that continued to present over the whole 15-year period of follow-up. This subgroup enjoyed a subsequent 10-year survival rate > 90%. Thus, the distinction between local recurrence (occurring predominantly in the vicinity of the index lesion and within 5 – 10 years of primary treatment) and new primary (occurring anywhere in the breast and at a constant annual rate throughout life) appears valid. The implication is that the absolute risk of a true local recurrence presenting outside the index quadrant is lower than the risk of recurrence within the index quadrant. The conventional emphasis on radiation dose uniformity across the breast is therefore inappropriate, and prompts consideration of a dose reduction outside the index quadrant in terms of the expected impact on local tumour control and late adverse effects.

Traditional radiation dose-response relationships for tumour control are assumed to be sigmoid in shape, with a quasi-threshold dose below which treatment is ineffective. This is the basis on which current schedules are delivered, and it is consistent with the response of clinical disease. However, the dose-response relationships of subclinical disease are expected to be different. After breast conservation surgery, for example, up to 50% patients suffer a local recurrence if no radiotherapy is given. In these patients, the number of residual tumour clonogens ranges from a theoretical minimum of 1 cell up to a maximum of 10^8 cells (the upper boundary of what constitutes subclinical disease in a patient with a microscopic complete excision). Assuming the distribution of residual tumour at the start of radiotherapy in a population of patients is log-linear, the radiotherapy dose-response is also expected to be log-linear, without a threshold (22). Clinical data derived from elective treatment of potential sites of spread from carcinomas of the head and neck, breast, ovary, cervix and lung, and from testis, soft tissue sarcoma and melanoma are consistent with a linear dose response relationship for the eradication of subclinical disease (23). On the basis of these empirical data and the patterns of tumour

relapse data described above, it is predicted that a 10% reduction in dose intensity to tissues outside the index quadrant would increase local cancer recurrence by < 1%. The expected large impact on the risk of late normal tissue injuries will now be considered.

In contrast to the response of subclinical cancer, dose-response relationships for late normal tissue injuries are almost maximally steep as determined by Poisson statistics over the clinical range of curative dose. Whereas a 10% reduction in dose intensity is expected to have no observable impact on eradication of subclinical tumour (see above), the incidence and severity of late normal tissue injuries are expected to fall significantly. In a recent randomised trial comparing 39.0 Gy and 42.9 Gy in 13 fractions over 5 weeks (equivalent to 46.7 Gy and 53.9 Gy in 2.0 Gy fractions assuming an α/β value of 3.0 Gy) to whole breast after complete local resection of primary tumour, there was more than a two-fold difference between regimens in the probability of changes in photographic breast appearance and of palpable breast induration at 5 years (24). These and other clinical data on the dose response of late effects are consistent with an expected halving of the incidence and severity of late adverse effects in response to a 10% reduction in dose intensity (25). If up to two-thirds of the breast volume and a higher proportion of non-target tissues inside the treatment volume are exposed to 10% less dose, the benefits in terms of reduced iatrogenic morbidity are expected to be highly clinically significant and readily detectable in a randomised trial (26). In non-target (ribs and muscle) tissues exposed to an equivalent total dose less than 40 Gy in 20 fractions, very few late radiation sequelae are expected. In conclusion, a reduction in dose intensity outside the index quadrant is expected to have a major beneficial effect on iatrogenic morbidity without measurable detriment in terms of local tumour control. The normal tissue sparing achieved by modifying the dose profile is hypothesised to support safe and effective dose intensification in high-risk subgroups.

Dose escalation by intensity modulation offers a novel and effective alternative to conventional sequential boost techniques

Traditional techniques of dose escalation involve increasing the number of fractions rather than by increasing fraction size above 2.0 Gy. This is the most effective approach for treating squamous carcinomas of the head and neck, lung and cervix uteri, which are relatively insensitive to fraction size compared to dose-limiting late reacting normal tissues (27). Adenocarcinoma of the breast, in contrast, appears much more sensitive to fraction size than squamous carcinomas. This was first reported 20 years ago in an analysis of the response of inoperable and recurrent breast cancer to different radiation regimes published in 1952 (28-29). Subsequently, a randomised controlled clinical trial established to test this hypothesis compared two dose levels of a 13-fraction regimen against 50 Gy in 25 fractions in 1,410 patients treated at The Royal Marsden Hospital and Gloucestershire Oncology Centre. Interim analysis is consistent with previous data suggesting that breast carcinoma is more sensitive to fraction size than previously thought, showing sensitivity comparable to late-reacting normal tissues in the breast (α/β value for tumour control 4.1 Gy, 95% CI 1.0 – 9.7) (30). Similar fractionation sensitivity, including an α/β value as low as 1.5 Gy, has recently been postulated for prostate cancer, suggesting that squamous carcinoma may not be a reliable model of all tumour types (31). If the fractionation sensitivities of breast cancer and of the dose-limiting normal tissues are the same (or similar), the advantage of small fraction sizes vanishes (or diminishes). If this is confirmed by the ongoing UK Standardisation of Radiotherapy (START) Trial, it should transform the approach to dose intensity modulation. Rather than increase dose intensity by increasing the number of 2.0 Gy fractions (as proposed in a trial for high risk breast cancer patients in the Netherlands), it creates opportunities for escalating dose intensity by modulating fraction size (this argument does not hold for the lymphatic pathways). Even if the fractionation sensitivity (as expressed by the α/β value) of breast cancer is not quite as great

as the normal tissues of the breast, shorter overall treatment times needed to deliver concomitant boost using intensity modulated radiotherapy could be advantageous if tumour proliferation is a significant determinant of local control. In conclusion, higher doses per fraction to high-risk areas and lower fraction sizes to low-risk areas of the breast are postulated to offer a clinically superior and cost-effective approach of matching dose intensity to tumour recurrence risk in the breast.

Target volume definition and localisation should be improved in all patients

Improved target volume definition and localisation are long overdue in patients treated by breast conservation surgery and radiotherapy. Accurate localisation of the high-risk volume in the index quadrant is necessary if the expected gains of advanced radiotherapy techniques and fractionation are to be realised. It involves the routine insertion of titanium clips or gold seeds to mark the excision cavity at the time of primary surgery if MRI or 3D diagnostic ultrasound techniques are not available to image the tumour bed. The requirements of target volume definition and localisation are reviewed in Appendices 1 and 2.

Full radiotherapy dose compensation should be used in all patients

Unplanned dose variations in excess of the International Commission on Radiation Units and Measurements (ICRU) guidelines (+7%; -5%) are no longer necessary or acceptable in the breast (32-33). Final analysis of five year follow up data of one prospective randomised trial (n = 306) reports substantially less change in breast appearance five years after full dose compensation compared to standard wedge techniques (24, 34). Full dose (3D) compensation in the breast is now possible in most UK radiotherapy departments, and is recommended in the latest National Institute for Clinical Excellence (NICE) Guidelines (35). It can be planned and delivered using simple methods of intensity modulation, (36-39) .

IMRT to the breast exploits widely available technologies

Significant advances in radiotherapy technology have been made during the last ten years. Linear accelerators have the capability to deliver multiple segment 'step and shoot' fields and dynamic beam deliveries, while treatment planning systems have sophisticated algorithms for both forward and inverse planning (40). Verification technology is similarly developing with amorphous silicon systems allowing high quality imaging at very low dose levels (41-42). These have enabled the clinical application of IMRT in a growing number of UK centres. In the interests of safety, The Royal College of Radiologists (UK) has recently recommended that intensity modulated radiotherapy should only be introduced in the context of well-designed prospective randomised trials (43). The proposed approach in the IMPORT HIGH Trial is to use either forward-planned or inverse-planned IMRT techniques to give different dose levels to the boost, partial breast (quadrant) and whole breast volumes. The IMPORT HIGH Trial will encourage the use of dose modulation and the full use of the technologies recently purchased by UK radiotherapy centres. Once developed and tested, the advanced technologies are likely to be more efficient and cost-effective than those in current use.

2.1 Justification of proposed trial

The IMPORT HIGH Trial aims to measure the extent to which a dose reduction to low risk volumes of the breast allows safe dose escalation to the tumour bed. The biological benefits of hypofractionation demonstrated in the Royal Marsden Hospital/Gloucestershire Oncology Centre (RMH/GOC) Breast Fractionation Trial and tested further in the NCRI Standardisation of Radiotherapy (START) Trial encourage redistribution of dose intensity by modulation of fraction size in preference to fraction number. Since there is virtually no time dependency for

late normal tissue injury in the breast, no allowance needs to be made for shorter overall treatment time. The strong fraction size dependency of late normal tissue responses in the breast is well recognised and accurately quantified, expressed as an α/β value in the range 3 – 4 Gy, so the effects of a concomitant boost on late normal tissue responses compared to a sequential boost regimen of 16 Gy in 8 fractions can be reliably predicted. The question of primary importance is the safety of delivering a concomitant boost and the need to ensure there are not significantly more local recurrences in either test group compared to the control. Addressing this question is essential to be able to safely use a concomitant boost dose routinely in clinical practice. IMPORT HIGH applies dose response data for local tumour control and adverse effects generated by the START pilot trial and more recently by the START and FAST trials to extend the principles of hypofractionated radiotherapy to women at higher than average risk of local relapse after breast conservation surgery and optimal systemic therapy by:

i) Modulating radiotherapy fraction size in preference to fraction number to adjust the dose intensity across the breast

ii) Reducing the current standard dose intensity to breast tissue at low risk of tumour relapse in exchange for dose escalation to the tumour bed, where most relapses occur.

iii) Achieving the proposed dose intensity modulation by reducing fraction size outside the index quadrant and increasing fraction size to the tumour bed.

The results of IMPORT HIGH will be integrated with the results of the current phase III FAST-Forward trial. The latter study (N=4000) tests a curative schedule of adjuvant radiotherapy delivered to the whole breast/chest wall in 5 fractions (1 week). Both of these trials are expected to mature at about the same time thereby informing standards of care and further research in about 2020.

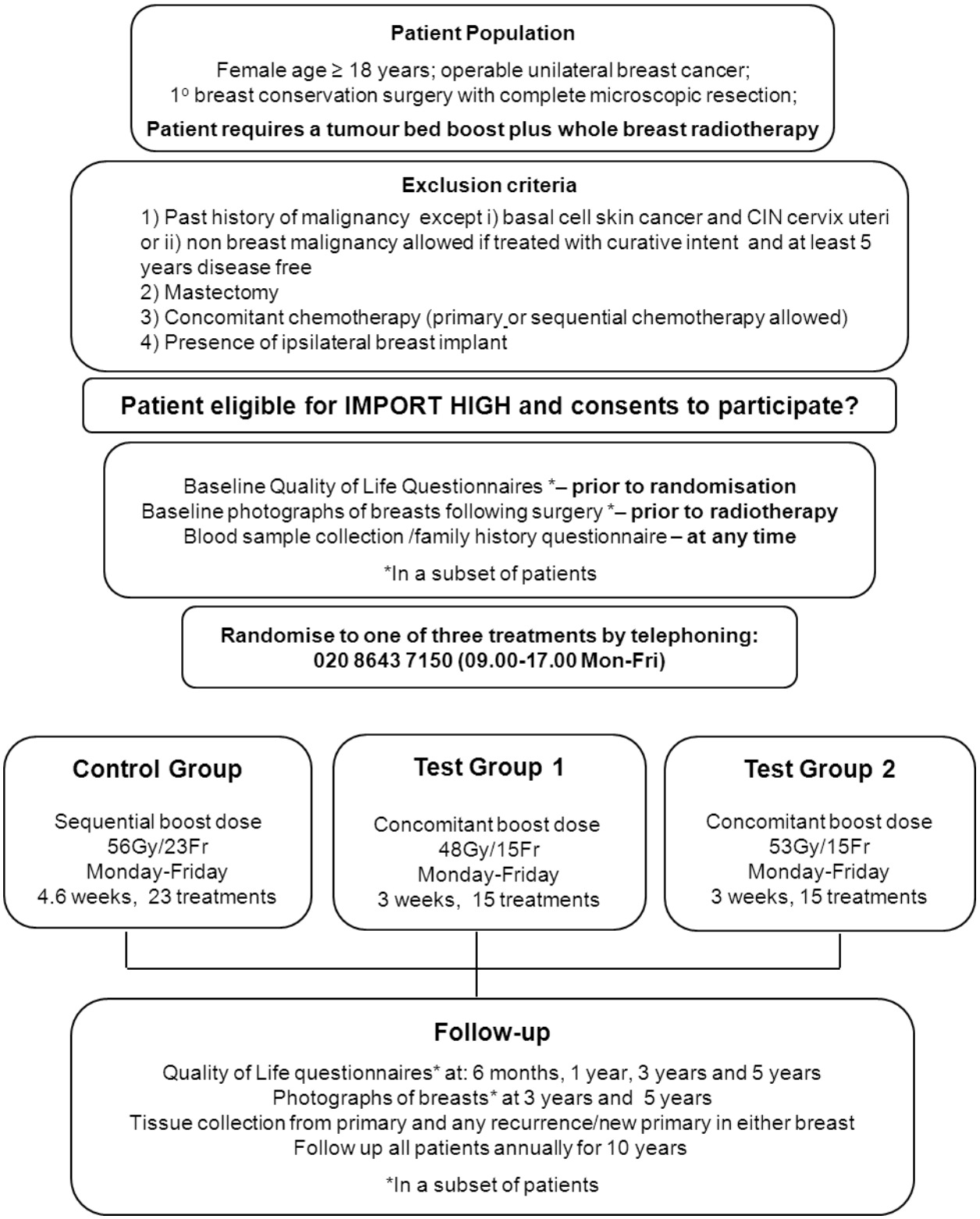
3. AIM

To test dose escalated intensity modulated radiotherapy (IMRT) after conservation surgery for women with higher than average local recurrence risk early breast cancer.

4. TRIAL DESIGN

This is a multicentre phase III randomised controlled trial.

IMPORT HIGH TRIAL SCHEMA



5.0 PATIENT SELECTION AND ELIGIBILITY

5.1 Source of patients

Women who have been treated with breast conservation surgery and appropriate systemic therapy for early breast cancer will be recruited from clinics within the UK.

5.2 Number of patients

A total of 2568 patients will be required.

5.3 Inclusion criteria

- Age ≥ 18 years.
- Operable unilateral breast cancer (T1-3, pN0- pN3a, M0 at presentation).
- Breast conserving surgery.
- Histological confirmation of invasive carcinoma.
- Complete microscopic resection.
- Patient requires a tumour bed boost plus whole breast radiotherapy for inclusion within the trial.
- Written informed consent and available for follow-up.

5.4 Exclusion criteria

- Past history of malignancy except i) basal cell skin cancer and CIN cervix uteri or ii) non breast malignancy if treated with curative intent and at least 5 years disease free.
- Mastectomy.
- Concomitant chemotherapy (primary or sequential chemotherapy allowed).
- Presence of ipsilateral breast implant

6. RANDOMISATION

6.1 Randomisation procedure

An eligibility checklist and randomisation checklist must be completed prior to randomisation. To randomise a patient, telephone ICR-CTSU (see below). The person randomising the patient will then be asked to confirm that an eligibility checklist has been completed and to verify that the patient has signed the IMPORT HIGH consent form.

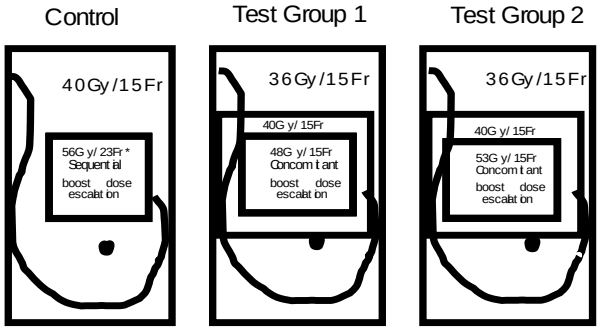
Treatment allocation will be 1:1:1, and will use computer-generated random permuted blocks. Randomisation will be stratified by centre only.

Randomisation telephone: +44 (0)20 8643 7150
Office Hours: 09:00 – 17:00 Monday-Friday

6.2 Following randomisation

A trial number and treatment allocation will be given over the telephone and confirmed by fax

7. RADIOTHERAPY TREATMENT



*56 Gy/23Fr represents 40Gy/15Fr to whole breast plus 16 Gy/8Fr sequential photon boost.

7.1 Dose prescriptions

(See Appendix 5, for isoeffect relationships)

Trial Group	Target volume	Fractions	Dose per fraction (Gy)
Control	Whole breast	15	2.67
	Tumour bed	15 + 8	2.67 → 2.0
Test Group 1	Low dose (whole breast) volume	15	2.40
	Standard dose (partial breast) volume	15	2.67
	Tumour bed	15	3.2
Test Group 2	Low dose (whole breast) volume	15	2.40
	Standard dose (partial breast) volume	15	2.67
	Tumour bed	15	3.5

Table 1: The dose to the breast delivered by tangential fields is prescribed to a reference point near the centre of the whole breast volume. The dose to the axilla and/or supraclavicular fossa delivered by a single anterior field is prescribed to the 100% isodose (build up depth).

8. RADIOTHERAPY TARGET VOLUMES, LOCALISATION AND OUTLINING

8.1 Target volume definition

(See Appendix 1)

Tumour Cavity (Boost) Clinical Target Volume (CTV)

If implanted surgical markers (clips or gold seeds) are used, the tumour bed CTV includes the volume enclosed by the markers plus changes in surrounding tissue architecture on x-ray Computerised Tomography (CT) images. Using ultrasound or Magnetic Resonance Imaging (MRI), the CTV consists of the tumour cavity. The CTV margin may be increased depending on the surgical procedure and localisation technique e.g. if surgical margins are less than 5 mm or ultrasound localisation is used (see Appendices 1 and 2). The boost CTV must be less than or equal to 5% of the whole breast PTV before treatment. Patients with very large tumour bed seromas can have drainage to enable trial recruitment.

Partial breast (quadrant) CTV

The partial breast CTV is not a precise anatomical entity, but approximates to a quadrant of the breast. It is based on the pattern of residual disease reported in whole organ sections of mastectomy specimens. In practice, the tumour bed is firstly delineated as described above, and a *minimum* CTV margin of 15 mm should be added. The partial breast CTV is modified according to the individual breast anatomy. The posterior margin should not extend beyond the deep fascia (unless clearly breached by the tumour). If the anatomy of this region cannot be easily visualised, the posterior margin should not extend beyond 5 mm anterior to the lung/chest wall interface. The CTV should not extend medially or laterally beyond the edges of the visible/palpable breast, i.e. beyond the extent of breast tissue as defined by the whole breast CTV.

Whole Breast CTV

This is based on the recommendations in the START trial (44). The CTV includes the soft tissues of the whole breast down to the deep fascia, excluding muscle and underlying rib cage.
Whole breast voluming on CT requires outlining a CTV volume on each axial slice, adding an appropriate PTV margin, and then a margin for field penumbra. This is the principle IMPORT is working towards, however it can be very difficult to accurately delineate breast tissue, and this can result in an overestimate of the whole breast volume. Therefore an alternative strategy is described in the radiotherapy planning pack which still takes into account all of the CT information.

Planning Target Volumes (PTV)

A margin should be added to whole breast and partial breast CTV, taking into account set-up error, breast swelling and breathing; a typical PTV margin is 10 mm. A smaller 5 mm PTV margin should be added to the boost CTV, as volume definition and planning studies have shown that 95% isodoses for the boost and partial breast volume begin to approximate as the boost volume PTV increases. A modified PTV: PTV_{DVH}, will be used for reporting purposes, and will stop 5 mm beneath the skin surface in order to preserve skin sparing.

Table 2 summarises the planning volumes and the appropriate margins to be used to create the relevant PTV.

	CTV	**PTV**
Whole Breast (WB)	Soft tissues of whole breast	$PTV_{WB} = CTV_{WB}$ + 10 mm margin
Partial breast (PB)	$CTV_{PB} = CTV_{TB}$ + 15 mm margin	$PTV_{PB} = CTV_{PB}$ + 10 mm margin
Boost (TB)	CTV_{TB} = tumour bed	$PTV_{TB} = CTV_{TB}$ + 5 mm margin

Table 2: Summary of radiotherapy planning volumes and margins.

Organs At Risk (OARs)

It is recommended that both lungs, the heart and contralateral breast are contoured for dose volume histogram assessment. The heart should be outlined from the inferior aspect above the diaphragm, to the superior aspect below the pulmonary arch. These volumes should be recorded for the purposes of the trial.

8.2 Tumour bed localisation

(See Appendix 2)

General points

The patient must be scanned in the radiotherapy treatment position, whatever imaging modality is used. Each centre must develop its own localisation protocol, and have it approved by the QA team.

Implanted surgical markers

The use of implanted surgical markers is recommended unless 2D/3D ultrasound or MRI is used for localisation. Six gold markers may be sutured into the tumour bed, marking the anterior, posterior, medial, lateral, superior and inferior margins. The seeds can be seen clearly on megavoltage portal imaging, which will assist on-treatment image-guided radiotherapy (IGRT). Alternatively, 6 pairs of titanium clips can be used. These are less easily seen on megavoltage portal imaging, but can be visualised with kilovoltage planar imaging. The clips protocol provided in the Site Investigator File should be used.

Ultrasound

A combination of 2D ultrasound and CT scanning is a reliable alternative to visualise the tumour cavity without the use of surgical clips. Three-dimensional ultrasound may also be used, either in combination with CT or optical breast contouring system. However, the ability to clearly define the cavity decreases with increasing time from surgery (see Appendix 2). Therefore, it is advised to restrict the use of ultrasound to patients planned within 3 months of surgery.

Magnetic Resonance Imaging

MR imaging can be used to obtain anatomical information of the tumour cavity and surrounding tissues without the use of surgical clips, x-ray CT imaging or ultrasound. Ideally, co-registered images should be imported into the radiotherapy planning system.

8.3 Patient position

The patient must lie supine in a stable and reproducible position. The same position must remain for simulation, CT scanning and treatment. An immobilisation device, such as a breast board with arm and wrist supports, an arm pole and/or vac-fix bag should be used. Ideally, the immobilisation should allow daily reproducibility of +/- 5 mm. The patient must not be moved between tangential and nodal field treatments.

8.4 Acquisition of Outlines.

A facility for taking multiple outlines is OBLIGATORY. A full 3D set of outlines covering the whole breast and the axilla should be collected with a slice separation of ideally 5 mm or less. The imaging technology to be used should be x-ray CT, although it is possible that optical systems (45-46), simulators with CT attachment or MRI may be used following discussions with the IMPORT QA team. If a combination of optical or “SIMCT” outlining with simulation is used, outlines should be acquired at 10mm spacing.

8.5 Lymph nodes

Simulator planning

Simulator planning is only recommended for treating the supraclavicular fossa nodes NOT the axillary nodes, as posterior fields may only be used if the nodal region is CT planned. The CTV consists of the supraclavicular fossa (SCF) nodes, with 1 cm margin added for PTV. The field-based boundaries (50% isodose) are as follows (see figure 1): inferior border, covering medial head of clavicle or matched to the superior border of the breast tangential fields if “high” superior tangential border; medial border, at the sternoclavicular joint; superior border, extending at least 3 cm above the medial end of the clavicle; and the lateral border, the apical surgical clip defining the medial extent of axillary surgery or 1 cm lateral to the outer border of the first rib if no clips are used and a level II/III dissection has been performed (47). Lung blocks are not routinely recommended.

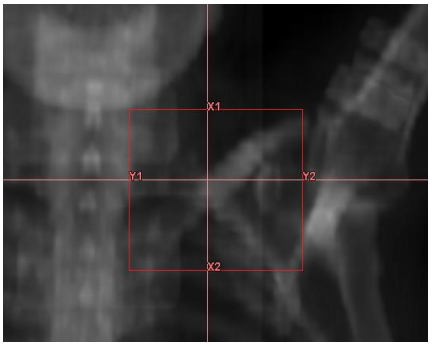


Figure 1
Simulator planned boundaries for the anterior supraclavicular field. If it requires matching to the tangents, the inferior border will be non-divergent.

CT planning

The CT planning scan should be performed from the patient’s mid-neck to below the diaphragm, for breast and nodal CT planning. A slice spacing of 5 mm or less is required. Intravenous contrast may facilitate the outlining process, but is not obligatory. The SCF nodes are outlined on each CT section using reproducible anatomical boundaries (48). The SCF boundaries are as follows: medial, lateral edge of trachea (excluding thyroid gland and cartilage); anterior, sternocleidomastoid muscle; posterolateral, anterior scalene muscle; posteromedial, carotid artery and internal jugular vein; posteroinferior, the subclavian artery.
The infraclavicular fossa (ICF) nodes may also be included if a level 3 axillary dissection has not been preformed. The borders of the ICF nodes are as follows: superior, the superior aspect of pectoralis minor; inferior, insertion of clavicle into the manubrium; lateral, medial border of pectoralis minor, medial, lateral edge of clavicle, anterior, pectoralis major, and posterior, subclavian-axillary artery.

It is preferable that a patient with positive axillary lymph nodes has definitive axillary dissection. If this is not possible, or sampling has only been carried out, then the axilla can be CT planned and treated using local protocol, after discussion with the QA team.

The PTV is generated according to local protocol (suggested margins are 5 -10 mm). A PTV is not added inferiorly if the border is matched to the tangents.

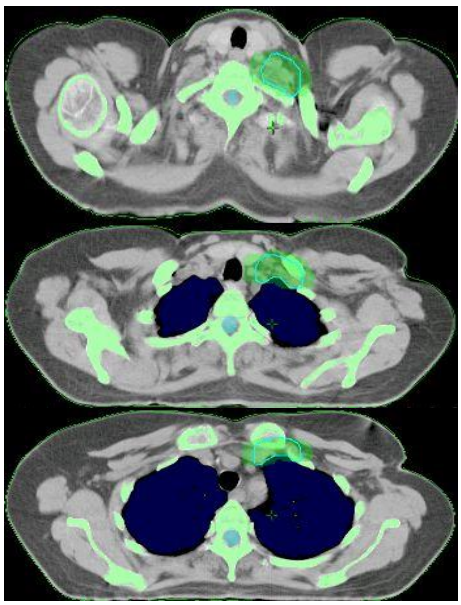


Figure 2
Axial CT views of SCF region showing CTV outline in blue and green shaded PTV: top, superior; middle, central; and bottom, inferior CT slices.

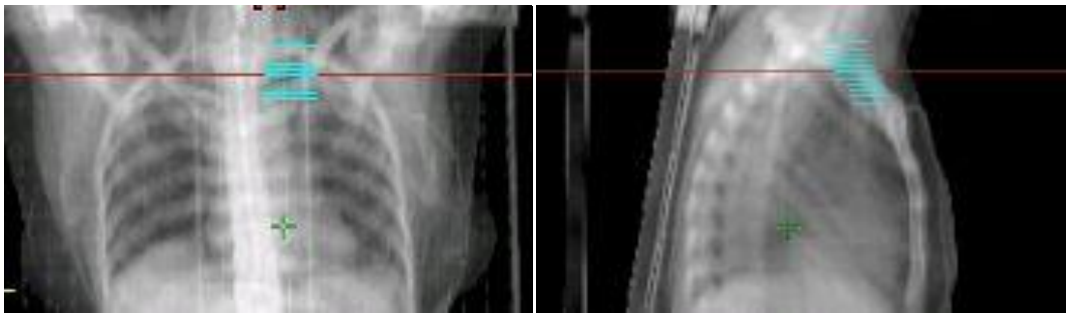


Figure 3 : Digitally reconstructed radiographs showing PTV on coronal and sagittal views.

9. RADIOTHERAPY PLANNING

All computer planning should be carried out using 3D algorithms and correction for tissue heterogeneity should be applied. It is essential that the planned boost volumes are comparable across all 3 groups. Therefore, the use of photons for boost planning in ALL patients is obligatory. The justification for this is set out in Appendix 3. Oncology Centres participating in this trial will receive a radiotherapy planning pack, which will give practical pointers for planning with worked examples.

9.1 Control group

9.1.1 Whole breast fields with sequential photon boost

Planning target volume

See Section 8.1, and Table 2.

Treatment technique

For the control group, the whole breast should be encompassed by a tangential pair of fields with a non-divergent back edge. The planner should aim to place the field so that the maximum lung distance and maximum heart distance does not exceed 2cm and 1cm respectively. The treatment plan should aim to fulfil the criteria in table 3 below. This may be achieved for some patients with a standard wedged pair, but others will require 3D compensation. (See radiotherapy planning pack).

Sequential photon boost can be forward or inverse planned, details of suggested techniques can be found in the radiotherapy planning pack. The overall plan assessment will be done using a composite plan.

9.2 Test Groups: Whole breast, partial breast and concomitant photon boost

(See planning pack)

Planning target volume

See Section 8.1, and Table 2.

Treatment technique

For the test groups, inverse planning is recommended, but forward planned IMRT is acceptable. The majority of the whole breast dose can be delivered by a tangential pair of fields with a non-divergent back edge. The planner should aim to place the field so that the maximum lung distance and maximum heart distance does not exceed 2 cm and 1 cm respectively. The treatment plan should aim to fulfil the criteria in table 3. Details of suggested techniques can be found in the radiotherapy planning pack.

Upper and lower dose limits

Control Group

Volume	Lower dose limit	Reference Dose	Upper dose limit
PTV_{WB} - PTV_{TB}	**> 90% of the volume should receive 36Gy**	**median dose = 40Gy**	**< 5% of the volume should receive > 56Gy**
PTV_{TB}	**> 95% of the volume should receive 53.2Gy**	**median dose = 56Gy**	**< 5% of the volume should receive > 60Gy**

Test Group 1 / 2

Volume	Lower dose limit	Reference Dose	Upper dose limit
$PTV_{WB} - PTV_{PB}$	**> 90% of the volume should receive 32.4Gy**	**median dose = 36Gy**	**< 5% of the volume should receive > 40Gy**
$PTV_{PB} - PTV_{TB}$	**> 90% of the volume should receive 36Gy**	**median dose = 40Gy**	**n/a**
PTV_{TB}	**> 95% of the volume should receive 45.6Gy / 50.4Gy**	**median dose = 48 / 53Gy**	**< 3% of the volume should receive > 51.4 / 56.7Gy with a global max < 52.8 / 58.3 Gy**

Table 3

9.3 Dose constraints for organs at risk

- The volume of ipsilateral lung receiving 18 Gy should be less than 15%
- The volume of contralateral lung receiving 2.5 Gy should be less than 15%
- The volume of heart receiving 13 Gy should be less than 10%
- The mean dose to the contralateral breast should be less than 0.5 Gy although an upper limit of 1.5 Gy is acceptable for trial entry

9.4 Bolus to scar

No bolus should be applied to the skin, including excision scar.

9.5 Beam energy

Beam energies for treatment as for local practice, usually 4 - 6 MV, but a mixture of energies e.g. 6 MV and 15 MV can be used to improve dosimetry.

9.6 Lymph nodes

Beam arrangement

A single anterior field encompassing the planning target volume is recommended. Posterior fields may only be used if the nodal region is CT planned, and if the nodal fields and breast fields are matched or there is a gap between the nodal fields and breast fields. Fields may be angled as required to avoid treating the spinal cord and to avoid any overlap with the tangential fields. If there is no gap then a match should be obtained between the inferior border of the supraclavicular field and the superior border of the tangential fields. The method of matching will be checked by the QA team. ICRU recommendations on dose homogeneity should be adhered to if possible and in no case should the maximum dose (either inside or outside the PTV) exceed 110% of the prescribed dose. Segment fields and/or mixed energy beams may be necessary to achieve this. The plan should be assessed as a composite of all beams, including all breast fields and nodal fields.

10. RADIOTHERAPY VERIFICATION

10.1 Treatment Set-up Verification

Control Group: Whole Breast Fields

Treatment verification is required for at least three fractions in the first week of treatment to determine and correct for any systematic error. Verification is then once weekly throughout the remaining whole breast field treatment. Verification is carried out with MV electronic portal imaging. A tolerance of 5 mm is recommended. The whole breast treatment fields are appropriate for this verification.

Control Group: Sequential Photon Boost

Test Groups: Whole Breast, Partial Breast and Concomitant Photon Boost

The control group and the test groups comprise a conformal boost to the tumour bed and so, the verification approach suggested is common to both and more rigorous than that required for the control group whole breast fields. Tumour bed markers are mandatory unless the position of a clearly defined seroma can be verified daily with volumetric imaging.

An established patient set-up correction protocol is essential. These protocols fall into two classes : on-line and off-line. The use of either is sufficient.

An example of an off-line protocol is the 'No Action Level' model of de Boer (49). This was extended to create the eNAL system which corrects for time-trends (49). These methods correct for the systematic error component which contributes approximately three-quarters of the total margin. Both protocols have been applied to partial breast irradiation (50). The use of the NAL protocol reduced the population mean systematic error to less than 2mm in all directions for both tumour bed and the whole breast. A further reduction to 1mm was obtained using the eNAL protocol.

An on-line protocol with daily set-up correction compensates for both systematic and random error but introduces a time penalty and additional imaging dose.

Centres are encouraged to measure their own treatment set-up errors in order to help establish how frequently set-up correction should be required.

Either 2D or 3D imaging technology may be used to determine the patient set-up corrections from the movements of the implanted markers. Both MV (planar EPID or tomotherapy) or kV (2D planar or cone beam CT) imaging may be used. Treatment fields are used where possible for MV planar images, however low dose verification only fields may be necessary if the treatment fields are not appropriate. Whatever the choice of imaging technology the additional imaging doses to be used are to be optimised so that they are as low as possible whilst still enabling sufficient information for an accurate correction to be made.

10.2 In-vivo Dosimetry

The use of in-vivo dosimetry within the first week of treatment is encouraged for patients in IMPORT HIGH.

11. RADIOTHERAPY QUALITY ASSURANCE

(see Appendix 6)

A comprehensive quality assurance programme is planned for all centres involved with IMPORT HIGH.

12. CHEMOTHERAPY

Chemotherapy and radiotherapy must be separated by a minimum of 2 weeks. Patients receiving neo-adjuvant chemotherapy are not excluded.

13. FOLLOW-UP

A Case Report Form (CRF) booklet for each patient including a radiotherapy form, adjuvant treatment form, and follow up forms will be provided for each patient following randomisation. The follow up forms should be completed annually for at least 10 years, or until death should this occur before the end of the 10 year follow-up period.

IMPORT HIGH Schedule of Assessments

Event	Prior to randomisation	Post randomisation pre RT	Treatment wk 1	wk 2	wk 3	wk 4	wk 5	Follow-up mth 3	mth 6	yr 1	yr 2	yr 3	yr 4	yr 5	yr 6	yr 7	yr 8	yr 9	yr 10
Eligibility checklist	**x**																		
Informed consent	**x**																		
Randomisation checklist	**x**																		
Radiotherapy QA			**Prior to centre initiation and throughout the trial recruitment period**																
3D radiotherapy planning		**x**																	
Radiotherapy treatment			**x**	**x**	**x**	**x[1]**	**x[1]**												
Radiotherapy verification			**Up to daily during treatment**																
Clinical assessment										**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Photographic assessment		**x**										**x**		**x**					
Family history questionnaire			**At any time during the trial, associated with blood sample collection [2]**																
Blood sample collection			**At any time during the trial , ideally by the end of RT**																
Tissue collection,1° tumour Tissue collection, recurrence/new 1° tumour			**As requested during the trial**																
Serious Adverse Event (if applicable)			**x**	**x**	**x**	**x**	**x**	**x**											
CT scan if recurrence			**At the time of recurrence**																
Quality of life study	**x (baseline*)**								**x**	**x**		**x**		**x**					

***** *Follow up booklets will be sent by post from the ICR-CTSU office*

[1] *Control group only*

[2] *Questionnaire to be completed at the time of blood sample collection.*

CRFs to be completed throughout the trial as indicated in the Trial Guidance Notes

14. ENDPOINTS

The primary endpoint is local recurrence. Secondary endpoints include palpable induration inside the boost volume of the irradiated breast, other late adverse effects in normal tissues assessed by physicians and patients, (including quality of life and photographic assessments in a sub-set of patients), Location of tumour relapse in breast, contralateral primary tumours, regional and distant metastases and overall survival will also be collected as secondary endpoints.

14.1 Tumour-related endpoints

Ipsilateral tumour relapse and contralateral primary tumour must be confirmed by cytological/histological assessment. Metastases will be determined by an appropriate combination of clinical, haematological, imaging and pathological assessment, recognising that pathological confirmation is not always possible.

The location of any ipsilateral tumour relapses will be compared with the original radiotherapy volumes for each individual patient. Appendix 8 describes the procedures for achieving this. The simplest method is for the breast quadrant in which the relapse occurs to be identified on a diagram for comparison with a surface rendered image of the treatment fields from the radiotherapy treatment planning system. This will indicate in a simple way, in which treatment field the relapse was located.

More accurate methods involve the use of ultrasound and CT to locate the size and position of relapse in relation to the surrounding breast tissue. These methods enable registration with the patient's original 3D planning scan using the radiotherapy tattoos on the patient. It will therefore be possible to ascertain in which 3D radiotherapy isodose the relapse is located.

Ipsilateral tumour relapse

Ipsilateral tumour relapse will be localised as follows:

A. Breast parenchyma/skin within boost volume (all trial groups).
B. Breast parenchyma/skin within volume receiving 40 Gy in 15 fractions (all trial groups).
C. Breast parenchyma/skin within volume receiving 36 Gy in 15 fractions (test groups only).
D. Marginal relapse in skin or subcutaneous tissue/breast on border or just outside (within 2cm) of whole breast volume (all trial groups).

Additional Endpoints

Contralateral primary breast cancer.
Other primary cancer (site specified).
Regional metastases (axilla, supraclavicular fossa, internal mammary chain).
Haematogenous metastases (only details of the first relapse are required).
Death.

These events will be recorded, but do not constitute primary endpoints.

14.2 Treatment-related endpoints

Late adverse effects will be measured using a combination of clinical and photographic assessments and patient self-assessments. Photographic assessments will be supplemented by annual physician assessments of the breast, and outcome will be correlated at 3 and 5 years.

Physician assessments of late adverse effects

At annual visits, physicians will record the development of breast shrinkage/distortion, breast induration (outside and inside tumour boost volume), telangiectasia, (tumour boost site only), breast oedema, arm oedema, shoulder stiffness (compared with other side), ischaemic heart disease, brachial plexopathy, rib fracture, symptomatic lung fibrosis, persistent cough and any other severe late event, including any specialist referral for investigation or management of late toxicity, including ischaemic heart disease.

Patient self-assessments of late adverse effects

A sub-set of patients will be asked to complete self-assessments of quality of life at baseline, 6, 12, 36 and 60 months after randomisation. These will include the EORTC QLQ-C30 core questionnaire, the EORTC BR-23 Breast Cancer module, the Body Image Scale and the Hospital Anxiety and Depression Scale (HADS). Of particular interest will be patient self-reporting of symptoms and impact on body image and functioning subscales. The aim will be to seek a patient-derived notion of 'radiation tolerance' that can be compared with induration and photographic endpoints, including interpolated estimates of isoeffect.

Photographic assessments of late adverse effects (in all centres with local facilities)

Digital photographs will be taken at baseline, following breast conserving surgery, and at years 3 and 5 after radiotherapy treatment in a sub-set of patients. Timing of assessments is based on experience from the START trial, with the aim to maximise the information collected whilst minimising the assessment burden. Two frontal views of the chest will be taken, one with hands on the hips and the other with hands raised as far as possible above the head. Both photographs will exclude the patient's head.

All photographs will be taken and retained locally in the first instance. Digital images will be anomomised and stored on a CD to be kept in a secure location. Periodically, all CDs will be collected and the images assessed blind by a select group of observers. Change of breast appearance compared with the post-surgical baseline will be scored on a three-point graded scale together with an assessment of breast size and surgical deficit. Reliability and repeatability of the assessments will be verified. The feasibility of and procedures for this scoring mechanism have been established in the START trial and assessments for IMPORT HIGH will build on these existing methods.

14.3 Serious Adverse Events

(See Appendix 9)

All Serious Adverse Events (SAEs) must be reported within 24 hours of the investigator or member of their team becoming aware of the event using the **IMPORT HIGH** SAE form. The form must be sent by FAX to the Institute of Cancer Research Clinical Trials and Statistics Unit on 020 8722 4368. This form must be completed, signed and dated by the Principal Investigator or nominated person identified on the site delegation log. The Chief Investigator or nominated representative will review all SAEs to assess the 'relatedness' and 'expectedness' of the event.
SAEs will be reported during the patient's radiotherapy treatment and for three months following the last RT treatment. Patients showing unexpectedly severe early or late normal tissue reactions will be identified on the Follow-up Forms. These reactions include unexpectedly severe late subcutaneous fibrosis, ischaemic heart disease (after both right- and left-sided

radiotherapy), rib fracture, symptomatic lung fibrosis and pneumonitis. Principal Investigators are asked to inform the IMPORT Trials Office within 8 weeks of any patient presenting with sensori-motor symptoms in the ipsilateral upper limb, regardless of aetiology.

Pregnancy during treatment is not in itself an SAE however, any new pregnancy that occurs during the SAE timeframe should be reported on the SAE form within 2 weeks of the investigator or member of their team becoming aware of the event. The pregnancy must be followed up to determine outcome including spontaneous or voluntary termination, details of the birth and the presence of birth defects or congenital abnormalities. The outcome must be submitted on a follow up SAE form.

15. STATISTICAL CONSIDERATIONS

15.1 Choice of principal endpoints

The primary endpoint is local relapse at five years following radiotherapy treatment. An important secondary endpoint is palpable induration in the ipsilateral breast at three years following radiotherapy treatment. This is based on the fact that palpable breast induration discriminated between randomised electron boost vs. no boost in the RMH/GOC Breast Fractionation Trial at 3 years, whereas breast photography only detected changes after 5 years of follow up, see Section 14.4. There are several other secondary endpoints including photographic change, other physician-assessed normal tissue effects, patient assessed normal tissue effects and quality of life (QL). It is intended that each endpoint will be analysed separately.

15.2 Methods of analysis

Local relapse

The question of primary importance is to ensure patient safety in terms of the efficacy of delivering a concomitant boost and as such there will be two primary comparisons to ensure there are not significantly more local recurrences in either test group.

Analyses of the primary endpoint will be based on the intention to treat principle and therefore include all randomised patients regardless of whether they deviated from the protocol. Survival analysis methods (i.e. Kaplan-Meier analysis and Cox proportional hazard regression) will be used to compare local relapse of the control group and each test group separately. The log-rank test will be used to compare groups. Estimates of the treatment effect will be presented with a one-sided 95% confidence interval (as non-inferiority design). Information will be presented on both absolute and relative effects. Primary analyses will be unadjusted. The Cox proportional hazards model will be used to produce adjusted treatment effect estimates, adjusting for important known prognostic factors (including adjuvant chemotherapy, hormonal therapy and use of lymphatic radiotherapy). For all time to event analyses, time will be measured from randomisation. The assumptions underlying the Cox proportional hazards model will be explored.

If non-inferiority is confirmed with both test groups, the IDMC will be able to request further non-inferiority analyses by combining the two test groups (at interim and final analyses as appropriate). By combining the test groups there will be more power to rule out a smaller difference between the control and test groups.

If non-inferiority for the test groups compared with control is confirmed, analyses will also be presented for comparison of the control group with each test group with two-sided 95% confidence intervals. A comparison will also be made between the two test groups. As an example, with 856 patients in each test group there would be 85% power to detect a 3% difference in local relapse rate
(2.5% alpha two-sided test) assuming a 5% local relapse rate at 5 years in test group 1.

Secondary endpoints

For palpable induration, the main comparison will be between the two test groups; the data from the control group will be used to estimate the dose-volume trade-off between whole breast versus tumour bed ('boost') irradiation. Analyses will estimate the size of treatment effect with a confidence interval for the estimated difference between schedules. Information will be provided on both the absolute and relative treatment effect.

Survival analysis methods (i.e. Kaplan-Meier analysis and Cox proportional hazards regression) will be used to compare rates of late radiation effects on normal tissues between allocated treatments for all randomised patients (i.e. intention to treat). Normal tissue effects will be analysed using methodology developed for START, i.e. time to any adverse event or marked adverse event will be analysed using appropriate survival analysis methods. Pair-wise comparisons will be made between the control group and each test group separately and between the two test groups. The impact on QL of expected differences in the rates of normal tissue effects between treatment groups will also be investigated. It is likely that clinically relevant differences in QL parameters that cannot be inferred from clinical or photographic assessments will be detected between treatment groups. Improvement in symptom status is expected in the test groups due to protection of the pectoralis muscle and underlying ribcage from high doses delivered to patients in the control group. Analysis of the QL data will follow algorithms developed for the QL forms (i.e. calculation of standardised subscale scores), and will compare treatment groups at individual time points, as well as longitudinal changes from baseline. Repeated measures analysis of variance will be used to describe the longitudinal data. The QL analysis will take into account important prognostic factors such as age, stage of disease, treatment received and other socio-demographic and clinical characteristics using generalised linear models. Appropriate adjustments will be made for multiple comparisons in the analysis, by adopting a more stringent cut-off for statistical significance e.g. $\alpha = 0.01$.

The 3-year figure for induration has been used as the clinically relevant time point and assumes that events before and after three years will be included in the analysis accordingly (i.e. patients will be followed from randomisation until it becomes impractical to do so further, and patients will only be censored in the analysis upon death or if lost to follow-up). Analyses will incorporate the time to an event as well as the occurrence of that event.

The incidence of uncommon complications will be monitored.

Analyses of normal tissue effects will be performed, adjusting for adjuvant therapy (chemotherapy, hormonal therapy), use of lymphatic radiotherapy, for breast size and surgical deficit using multivariate statistical models.

15.3 Interpretation of results

If non-inferiority is confirmed the radiobiology of the two test groups will be explored to estimate if there is a dose-response for tumour control. This is in a similar manner to the IMPORT LOW

and FAST-Forward trials. Using previous data it is estimated that the absolute difference in local relapse rates between test group 1 and test group 2 could be between 2% and 5%. The dose response for tumour control after whole breast radiotherapy in the START pilot trial (39 vs 42.9Gy) generated a gamma of 0.5 (50). It is reasonable to assume that the majority of the effect of whole breast radiotherapy is achieved within the relatively large and accurately localised tumour bed boost volumes used in IMPORT HIGH. As such, 0.5 represents the highest point estimate of gamma to be expected in IMPORT HIGH. The EORTC boost trial (51) generated a gamma value of 0.2, based on a smaller electron boost volume. Therefore, 0.2 is regarded as the lower limit of gamma for IMPORT HIGH. It is therefore possible that test group 2 could be superior to test group 1 in terms of local control.

Palpable induration in the ipsilateral breast

The test dose that is isoeffective with the Control group in terms of normal tissue tolerance (primarily induration) will be estimated by interpolation between Test groups 1 and 2, and this will provide a measure of how much tolerance for boost dose escalation is gained by reducing the whole breast dose from 40 Gy to 36 Gy in 15 fractions. In practice, the degree of dose sparing will be estimated from a multivariate analysis of individual patient data ('direct analysis'). For example, if the normal tissue effects of the control schedule are close to 48 Gy in 15 fractions (Test group 1), it means that a dose reduction equivalent to 6 Gy in 2 Gy fractions (the difference between 40 Gy and 36 Gy in 15 fractions) has no impact on dose-limiting adverse effects (e.g. induration, photographic appearance, patient symptoms etc). If the effects of the control schedule are close to Test group 2, it means that a dose reduction equivalent to 6 Gy in 2 Gy fractions (the difference between 40 Gy and 36 Gy in 15 fractions) allows an additional 9 Gy in 2 Gy fractions, or its equivalent in larger fractions, to be safely given to the tumour bed (9 Gy in 2 Gy fractions is the difference between 48 Gy and 53 Gy in 15 fractions assuming an α/β value of 3.0 Gy). More likely, the point of equivalence will lie in between and will be determined as described above. If, against expectations, the Control group lies outside the dose range covered by Test groups 1 & 2, a very limited amount of projection or extrapolation will be possible, assuming linearity of dose-response.

As a result of the IMPORT HIGH Trial, it will be possible to specify the additional dose to the boost volume that can be safely delivered using IMRT in exchange for a defined dose reduction to the remaining breast tissue regardless of fraction number i.e. 25, 15 or 5 fractions.

15.4 Sample size

The sample size is estimated based on a non-inferiority design to ensure the safety of delivering a concomitant boost in terms of efficacy. The IMPORT HIGH non-inferiority trial is powered to exclude no more than a 3% increase in local relapse with either test group compared to the control group. This non-inferiority margin is consistent with the magnitude of potential excess risk being evaluated in other related trials. It is assumed that 5 year local relapse rate in the control group is 5% (51-52). To exclude a local relapse rate of no more than 8% in either test group with 80% power and 2.5% alpha (one-sided) requires 856 patients per group. Based on experience from the START trials, an allowance of 7% drop-out (at the time of the principal analysis of the primary endpoint) due to patients being non-evaluable (predominantly due to death from metastatic disease without a local recurrence) has been incorporated in to the calculation The total sample size is 2,568 patients.

The sample size assumes a total of 6 years of recruitment and allows for a staggered start to recruitment (assuming 5%, 10%, 15%, 20%, 25% and 25% of total recruitment in years 1, 2, 3, 4, 5 and 6 respectively).

The original sample size for the trial was based on a primary endpoint of palpable induration inside the boost volume of the irradiated breast at three years post radiotherapy. This required 840 patients (280 per group) and was estimated using data from the RMH/GOC Breast Fractionation Trial. In this trial, randomisation of 940 patients to 39.0 Gy or 42.9 Gy in 13 fractions to whole breast over 5 weeks resulted in 3-year absolute risks of breast induration of 8.5% and 25.5%, respectively, a difference of 17% (30).

The dose difference between 39.0 Gy and 42.9 Gy is equivalent to 8.0 Gy in 2.0 Gy fractions, assuming an α/β value of 3.0 Gy for late normal tissue effects (53). Thus, the risk of breast induration increases by 2% per Gy of whole breast radiotherapy. The same trial also tested a randomised electron boost dose of 16.0 Gy in 2.0 Gy equivalents in 723 patients. The 3-year rates of breast induration were 20% and 13% in patients randomised to boost and no boost, respectively. The rate of induration increased by only 0.44% per Gy, suggesting a clear volume response (electron boost volumes are typically 10-20% of the whole breast volumes). The dose difference between 48 Gy and 53 Gy in 15 fractions under test in the IMPORT HIGH Trial is equivalent to 8.5 Gy in 2.0 Gy fractions. An adjustment, which assumes linearity between 15% (electron boost) and 100% (whole breast photons) for the volume response, has been made to allow for the fact that the photon boost volume in IMPORT HIGH will be up to double a conventional electron boost volume, up to 300cc for photons compared with up to 150cc for electrons (54). This predicts that the two test groups in IMPORT HIGH will differ by about 7% in the rate of induration at 3 years. A 20% rate of clinically significant induration at 3 years is assumed for Test group 2, and the difference in boost dose between Test groups 1 and 2 of 9 Gy in 2 Gy fractions is, therefore, estimated to result in a 3-year induration rate in Test group 1 of 13%. 280 patients per group, i.e. a total of 840 patients in the trial, will provide 80% power to detect a reduction of 7% in palpable induration at 3 years in Test group 1 compared with Test group 2 (assuming 20% rate of induration in Test group 2 and 1-sided $\alpha = 0.05$). A 5% rate of loss to follow-up by 3 years has been allowed for, from experience with the START Trial.

Analyses of palpable induration will be carried out after the first 840 patients have completed their three year clinical assessment. This analysis will focus on the comparison between the two test groups, but the interpolated dose (using the Control group) will provide a measure of the partial volume dose sparing effect, depending on whether the Control group is isoeffective with Test group 1 or Test group 2. The study has not been powered to test for significance between the Control group and each of the test groups, but will enable interpolation and estimation of the experimental dose equivalent to the Control group, together with an estimate of precision. With 280 patients per group, the differences in rates of normal tissue effects between the groups can be estimated to within 6% (95% confidence interval).

Photographic assessments and patient self-assessments of late normal tissue effects and quality of life will be carried out in 840 patients. The above sample size will provide sufficient power to detect clinically important differences between treatment groups for these endpoints.

15.5 Interim analyses and data monitoring

Interim analyses of local tumour control, normal tissue responses, radiotherapy side effects and the other endpoints will be conducted at yearly intervals and presented to an Independent Data Monitoring Committee (IDMC) for confidential review.

In the light of the interim analyses, the IDMC will advise the Trial Steering Committee (TSC) if, in their view, the trial has indicated 'proof beyond reasonable doubt' that one of the schedules is clearly indicated or contraindicated in terms of local tumour control and/or induration in the ipsilateral breast. In reviewing the evidence, the IDMC will also consider any available data from other randomised trials involving similar comparisons. The TSC may then consider modification or termination of the study. Unless such a situation arises, the Trial Management Group (TMG), the collaborators and the central administrative staff (except the statistician who prepares the analyses) will remain unaware of the interim results. The IDMC may recommend continuation beyond the planned number of patients in the main trial, the Quality of Life study or in the number of patients having photographic assessments, if it is felt that further information is required to address reliably the hypothesis in question.

16. RESEARCH GOVERNANCE

16.1 Trial Administration and Logistics

The Institute of Cancer Research (ICR) is the agreed Sponsor of this study in accordance with the Research Governance Framework for Health and Social Care and the principals of Good Clinical Practice (GCP).

16.1.2 Responsibilities of ICR-CTSU

ICR-CTSU has overall responsibility for facilitating and coordinating the conduct of the trial and is also responsible for collating data obtained, and undertaking and reporting interim and final analyses.

16.1.3 Responsibilities of participating centres

Centres wishing to recruit to this study will be asked to provide evidence that they can deliver protocol treatment. This will include the successful completion of the IMPORT QA programme (see appendix 6).

Responsibilities are defined in an agreement between an individual participating centre and The Institute of Cancer Research, which must be signed and in place before recruitment can commence.

16.2 Investigator training

Prior to commencing trial recruitment, training will be provided to identified key individuals in each participating network by the Chief Investigator. Training will include discussion on the background to the study and discussion on the issues of clinical equipoise. Experience developed from successfully recruiting centres and information from associated qualitative studies will be provided to participants at their initial training and subsequently on a regular basis. Participating centres will be asked to maintain a screening log to monitor randomisation

acceptance rates, and additional support/training will be offered when lower than anticipated rates are encountered.

16.3 Case Report Forms

Case Report Forms (CRFs), which are in the form of a booklet, should be completed for all patients in accordance with the Trial Guidance Notes. CRFs are in duplicate. The completed top copy must be sent to ICR-CTSU as soon as they are due. The bottom copy must be retained in the booklet held by the Principal Investigator. If information is not known it must be clearly stated as such on the CRF. CRFs should not be made available to third parties.

The Trial Management Group reserves the right to amend or add questions to the CRFs as appropriate. Such changes do not constitute a protocol amendment, and revised or additional forms will be circulated to the centres and should be used with immediate effect. Where appropriate, data may need to be collected retrospectively if an additional question has been added to the CRF.

16.4 Protocol compliance/on site monitoring

The IMPORT HIGH trial is being conducted in accordance with the professional and regulatory standards required for non-commercial research in the NHS under the Research Governance Framework for Health and Social Care and the principals of GCP.

Participating centres may be monitored by ICR-CTSU and possibly by Health Authorities to carry out source data verification, and confirm compliance with the protocol. By participating in the IMPORT HIGH trial the Principal Investigator at each centre is confirming agreement with his/her local NHS Trust to ensure that:

- Sufficient data is recorded for all participating patients to enable accurate linkage between hospital records and CRFs;
- Source data and all trial related documentation are accurate, complete, maintained and accessible for monitoring and audit visits;
- All staff at their centre who are involved with the trial are trained and briefed appropriately
- All original Consent Forms should be dated and signed by the patient, the person taking consent (if different to the researcher) and the researcher (the principal investigator at that site), and kept in a central log together with a copy of the specific patient information sheet(s) they were given at the time of consent.
- Copies of CRFs are retained for 20 years to comply with international regulatory requirements;
- Staff will comply with the Trial Guidance Notes for the IMPORT HIGH trial.

ICR-CTSU will monitor receipt of CRFs. They will also check incoming CRFs for compliance with the protocol, inconsistencies or missing data.

ICR-CTSU will contact centres to discuss dates of any proposed on site monitoring visits. Once a date has been confirmed a list of names of patients whose notes will be monitored during the visit will be sent to the centre. This list will be sent out in advance to give sufficient time for the notes to be made available. It is likely that a random sample of notes will be selected for limited source document verification.

16.5 Archiving

Essential documents are documents that individually and collectively permit evaluation of the conduct of the trial and the quality of the data produced, for example CRFs. These documents will be maintained in the ICR-CTSU archive and at the local centres in a way that will facilitate the management of the trial, audit and inspection. They will be retained for a sufficient period (at least 20 years) for possible audit and inspection by the regulatory authority. Documents will be securely stored with security designed to meet the necessary regulatory requirements and access will be restricted to authorised personnel. An archive log will be maintained to track archived documents.

16.6 Financial Matters

The trial is investigator designed and led, and has been approved by the Clinical Trials Awards and Advisory Committee (CTAAC). It is endorsed by Cancer Research UK and meets the criteria for R&D support as outlined in the Statement of Partnership on Non-Commercial R&D in the NHS in England.

Research costs (to ICR-CTSU) are being funded by Cancer Research UK. If additional financial support is received from any other source, this will be made apparent to the approving Main REC and CTAAC, but will not require a protocol amendment.

No individual per patient payment will be made to trusts or investigators, but National Cancer Research Network (NCRN), or regional equivalent, resources should be made available as the trial is part of the NCRN portfolio by virtue of its approval by CTAAC**.**

16.7 End of Study

For the purposes of ethics approval, the study end date is deemed to be the date of the last data capture and is expected to be 10 years after the last patient is entered.

17. TRIAL MANAGEMENT

17.1 Trial Management Group

A Trial Management Group (TMG) will be set up and will include the Chief Investigator (Professor John Yarnold) and the Chief Clinical Co-ordinator (Dr Charlotte Coles), co-investigators and identified collaborators, the trial statisticians and the trial managers. Principal investigators and key study personnel will be invited to join the TMG as appropriate to ensure representation from a range of centres and professional groups.

Notwithstanding the legal obligations of the Sponsor and Chief Investigator, the TMG has operational responsibility for the conduct of the trial.

17.2 Trial Steering Committee

A Trial Steering Committee (TSC) will be set up to monitor and supervise the progress of the trial on behalf of the Sponsor and funding body. In particular, the TSC will concentrate on the progress of the trial, reported adherence to the protocol, patient safety and the consideration of new information. Day-to day management of the trial is the responsibility of the Chief Investigator and TMG.

Membership will be limited and include an independent Chairman (not involved directly in the trial other than as a member of the TSC), not less than two other independent members, the Chief Investigator and the trial statistician.

Where possible membership will include a lay/consumer representative. Trial co-ordinators and other key members of the TMG will attend meetings (as observers) as appropriate. Observers from the funding body and Sponsor will be invited to all meetings. The TSC will meet at least annually.

17.3 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be established to oversee the safety and interim efficacy of the trial. This committee will be constituted with guidance from MRC principals of Good Clinical Practice (MRC GCP). The IDMC will meet on a regular basis as they see fit, but no less than annually. Following each meeting, the IDMC will report their findings and recommendations to the TSC and to the TMG.

18. PATIENT PROTECTION AND ETHICAL CONSIDERATIONS

18.1 Risk assessment

This study has been formally assessed for clinical risk using a generic risk assessment matrix.

18.2 Liability/Indemnity/Insurance

This study is an investigator-led trial endorsed by the Clinical Trials Awards and Advisory Committee (CTAAC) of Cancer Research UK.

The trial is sponsored by The Institute of Cancer Research. Any potential legal liability of the Sponsor for harm to participants arising from the management of the research will be covered by The Institute's public liability insurance, provided by Zurich Municipal. The study has been designed by employees of the NHS and The Institute of Cancer Research. Any potential legal liability of the Sponsor or employer for harm to participants arising from the design of the research will be covered by the NHS Litigation Authority Schemes for NHS employees and by the public liability insurance provided by Zurich Municipal for Institute employees.

Indemnity for participating hospitals is provided by the usual NHS indemnity arrangements.

18.3 Patient Confidentiality

Patients will provide their full name, date of birth, hospital number and NHS number to ICR-CTSU at randomisation to allow tracing through national records. The personal data recorded on all documents will be regarded as confidential, and to preserve each subject's anonymity, only their initials and date of birth and trial number will be recorded on subsequent Case Report Forms. Patients consenting to the Quality of Life study will provide their name, address and telephone number and also address and phone number of their GP to ICR-CTSU. These details will only be used for the purposes of the Quality of Life study. The principal investigator must keep a separate log of patients' trial numbers, names, and hospital numbers. The principal investigator must maintain in strict confidence trial documents, which are to be held in the local centre (e.g. patients' written consent forms). The principal investigator must ensure the patient's confidentiality is maintained.

ICR-CTSU will maintain the confidentiality of all subject data and will not reproduce or disclose any information by which subjects could be identified, other than reporting of serious adverse events. Representatives of the trial team will be required to have access to patient notes for quality assurance purposes but patients should be reassured that their confidentiality will be respected at all times. In the case of special problems and/or competent authority queries, it is also necessary to have access to the complete study records, provided that patient confidentiality is protected.

18.4 Ethical Considerations

It is the responsibility of the Chief Investigator to obtain a favourable ethical opinion (main REC approval). It is the responsibility of the Principal Investigator at each participating centre to obtain R+D approval of the trial protocol and any subsequent amendments. All correspondence with R+D should be filed by the Principal Investigator in the Site Investigator File.

It is the responsibility of the Principal Investigator to give each patient, prior to inclusion in the trial, full and adequate verbal and written information regarding the objective and procedures of the trial and the possible risks involved. Sufficient time (a minimum of 24 hours) should be allowed for the patient to decide on trial entry. Patients must be informed about their right to withdraw from the trial at any time. Written patient information must be given to each patient before enrolment. The written patient information is an approved patient information sheet according to national guidelines. This also outlines the Quality of Life study, the photographic assessment study and the collection of biological specimens. Patients will be encouraged to participate in these associated studies but if they decline, this will not exclude them from the main trial.

It is the responsibility of the Principal Investigator or designated representative, to obtain signed informed consent from all patients prior to inclusion in the trial.

This trial has been approved by Cambridgeshire 4 Research Ethics Committee on 30/04/2008.

18.5 Patient Information

The importance of providing a high level of information to patients is recognised. Patients will be informed of the services offered by cancerbackup in the patient information sheet. Local leaflets on radiotherapy should be provided by each centre. Each patient invited into the trial will receive a patient information sheet, which will include details of the Quality of Life Study and other sub-studies. They will be encouraged to participate in these studies but if they decline, this will not exclude them from the main trial. In addition, the long-term side effects of radiotherapy to the breast area and the likelihood of these developing post treatment will be explained.

19. WITHDRAWAL OF PATIENTS FROM STUDY TREATMENT

Patients who do not receive their allocated treatment for any reason should be treated at the discretion of their clinician. Unless the patient requests otherwise, all CRFs, including long term follow up, should be completed, regardless of treatment actually received. A trial deviation form should be completed to record details of deviation from treatment allocation. Analyses of all endpoint data will be on the basis of intention to treat.

Patients are asked prior to randomisation to consent to follow up should they withdraw from the treatment allocation (see patient information sheet and consent form), and any patient unwilling to give that assurance prior to trial entry should not be randomised. Patients are however free to

reverse that decision at any time without giving a reason. A trial deviation form should be completed for any patient who withdraws consent for further follow up.

Should a patient become incapacitated at any point during the trial they will be withdrawn for their own protection. If this were to happen during the course of the patient's radiotherapy their treatment should be reviewed as a clinical decision by the Principal Investigator at their centre. No further trial procedures will be carried out and no further data or tissue samples will be collected on behalf of the trial. Any samples already donated ie: blood and tissue will be retained and used for the original research purpose. These procedures are fully explained in the patient information sheet and patients are asked to consent to this prior to randomisation. A trial deviation form should be completed for any patient withdrawn from the trial for this reason.

20. PROTOCOL AMENDMENTS

Proposed protocol amendments will be submitted to the TMG by the Chief Investigator and Chief Clinical Coordinator. The TMG will agree protocol amendments prior to acceptance and submission to the Main REC. Once approved the Principal Investigator at each centre will be informed of the change and sent all the associated documentation. It is the Principal Investigator's responsibility to submit amendments to their R+D department for approval. Confirmation that this has been done must be provided to ICR-CTSU.

21. PUBLICATION POLICY

All publications and presentations relating to the trial will be authorised by the TMG. A Writing Committee may be appointed. Authorship will be determined by the TMG and will include the Chief Investigator, co-investigators, trial co-ordinators and trial statisticians. Further authorship will be determined by centre accrual. All participating centres will be acknowledged in the final manuscript according to patient accrual.

22. ASSOCIATED STUDIES

22.1 Molecular correlates of normal tissue injury

It is hypothesized that part of the inter-patient variation in the incidence and severity of late normal tissue responses to radiotherapy reflect inter-patient differences in the expression of specific proteins (involved in DNA repair, tissue remodelling, growth factors, extracellular matrix components etc). Recent work suggests that common DNA sequence variations (single nucleotide polymorphisms) within the controlling regions or coding sequences of genes account for differences in protein expression between individuals that may explain an important component of the variation between individuals in late normal tissue responses to radiotherapy. Genome-wide approaches offer scope to identify patterns of single nucleotide polymorphisms that distinguish patients at lower and higher than average risk of late adverse effects.

Twenty mls of whole blood will be collected by venesection into blood tubes and sent to the Cancer Research UK/MRC Tissue Bank at Ninewells Hospital, Dundee, where it will be stored for future research. The research may be carried out at another centre. An aliquot of this blood may also be requested for comparison of genomic DNA with tumour DNA extracted from donated tissue samples (see section 21.2).

Blood will be collected at the treating hospital. Patients will also be asked to complete a family history questionnaire.

22.2 Molecular correlates of local recurrence and new primary tumours

Local tumour recurrence remains a clinical problem in a minority of women. The likelihood of local recurrence may be influenced by genetically regulated factors, including the extent of intraductal spread and factors influencing radiation resistance. Genome-wide approaches offer scope to identify DNA sequence differences (mutations and polymorphisms) that discriminate between patients who suffer a local recurrence and those who remain disease-free. Relapses that occur close to the site of the primary tumour are assumed to be true local recurrences (sharing the same gene mutations), whereas those occurring elsewhere in the breast and often at a later point in time are assumed to be new primaries (with differences in mutations compared to the primary tumour). Genome-wide approaches offer scope for investigating the genetic relationships between ipsilateral tumour relapse and primary tumour characteristics in a systematic way that may lead to a more accurate stratification into risk groups and/or guide future local therapies.

It is also possible to investigate loss of heterozygosity (LOH) in breast cancer by comparing DNA extracted from the tumour samples with genomic DNA extracted from the blood samples (see 21.1)

It is proposed to establish tissue arrays and also extract DNA and RNA from paraffin blocks of primary tumours and both ipsilateral and contralateral relapses/new primaries in as many patients as possible for future comparative studies of the cancer genome of original tumour and recurrence. Paraffin blocks containing the primary tumour and any subsequent recurrence/new primary from either breast will be sent to KCL/Guy's and St. Thomas' Hospital Breast Tissue Bank, London, where they will be stored for future creation of tissue microarrays and DNA and RNA extraction. The KCL/Guy's and St. Thomas' Hospital Breast Tissue Bank is a Human Tissue Authority licensed facility. After tissue cores and sections have been taken the tumour paraffin blocks will be returned to the relevant pathology laboratory.

For LOH studies a sample of the donated blood stored at the Cancer Research UK/MRC Tissue Bank at Ninewell's Hospital, Dundee will be requested.

22.3 Quality of Life Study

Please see Appendix 7

22.4 IGRT Study

Testing the benefits of image-guided radiotherapy the IGRT substudy

Background

Current RT 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. Accurate localisation of the tumour bed is required if the expected gains of advanced radiotherapy techniques such as IMPORT HIGH are to be realised. More accurate imaging technique will facilitate smaller safety margins and hence

reductions in the tumour bed planned target volume. 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. Modern treatment machines with on-line x-ray imaging facilities monitor accurately the position of internal organs within the radiotherapy beam on a daily basis. The hypothesis under test in the IGRT sub-study is that if the tumour bed is imaged directly during treatment, the margin of healthy tissue (tumour bed boost volume) can be reduced, leading to a smaller volume of healthy tissue irradiated and fewer chronic adverse effects. Alternatively, in women at highest risk of local recurrence, it will allow safe dose escalation to the tumour bed, with better local cancer cure rates. IMPORT HIGH patients are expected to have titanium clips fastened to the excision cavity wall during surgery allowing the tumour bed to be imaged during radiotherapy delivery using the treatment machines' low energy x-ray facility.

IGRT substudy

It is not considered feasible to randomise patients to IGRT versus no IGRT. On the other hand, the lack of empirical evidence justifying the widespread use of IGRT means that resources to implement IGRT as routine practice are not available and that equipment is left idle. 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 verification, it will be possible to estimate, based on literature sources partly generated by randomised trials conducted by members of our collaboration, the expected reductions in late adverse effects. 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 success of the IGRT sub-study 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) and other relevant endpoints.

This is an observational study embedded within IMPORT HIGH. The IGRT sub-study described above will use the planning and verification data taken for IMPORT HIGH from 180 patients treated at the following 5 RT centres: The Royal Marsden, Addenbrooke's, Ipswich, Cheltenham General and Clatterbridge Cancer Centre.

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APPENDICES

APPENDIX 1 : Definitions of Radiotherapy Target Volumes

1. Clinical Target Volumes (CTV)

Tumour bed (Boost) CTV

The tumour bed CTV should be identified using a recommended imaging modality. Using surgical implanted markers (clips or gold seeds), this would consist of the markers and any change in surrounding tissue architecture, as defined by the William Beaumont group (55). Using ultrasound or MRI, this would consist of the tumour cavity. The CTV margin may be increased depending on the surgical procedure and localisation technique e.g. if surgical margins are less than 5 mm or ultrasound localisation is used (this imaging modality tends to produce smaller volumes when directly compared to clip localisation – see Appendix 2).

Partial Breast (Quadrant) CTV

The partial breast CTV is not a precise anatomical entity, but is intended to approximate a quadrant of the breast. It relies heavily on Holland's whole organ sectioning of 130 mastectomy specimens with unifocal tumours up to 2 cm diameter, in which a 5% frequency of intraduct and a 5% frequency of invasive foci of disease > 4 cm were found beyond the pathologically estimated edge of primary tumour (rates were 7% and 4% respectively in 264 patients with tumours up to 4 cm diameter) (56). It was stated that a 2 cm or smaller tumour, with a margin of 4 cm, would produce a total diameter of 9 - 10 cm, which is on average, the size of a breast quadrant. These pathological correlates are supported by the NSABP B-06 and Milan randomised trials of conservation breast surgery with or without post-operative radiotherapy; 86% and 79% of tumour recurrences occurred in or close to the reference quadrant (15, 57).

In practice, a *minimum* CTV margin of 15 mm should be added around the surgical cavity: this is used by the William Beaumont group, who have a large partial breast radiotherapy cohort and low recurrence rates (55). When added to the surgical bed, the CTV should approximate to the volume of a breast quadrant and therefore reflect the conceptual CTV margin around the tumour.

CTV should be modified according to the individual breast anatomy. This will limit the dose to the surrounding organs at risks (OARs). For example, the posterior margin should not extend beyond the deep fascia (unless clearly breached by the tumour) and therefore, exclude the underlying muscle and ribs. Accurate visualisation of the position of the deep fascia is dependent on the quality of the imaging modality, e.g. multi-slice CT or MRI compared with limited slice simulator-CT images. If the anatomy of this region cannot be easily visualised, the posterior margin should not extend beyond 5 mm anterior to the lung/chest wall interface (this has been adopted as standard practice in other institutions) (58). The CTV should not extend radially beyond the edges of the visible/palpable breast. The anterior extent of the CTV should be limited to 5 mm below the skin surface to reduce late normal tissue skin changes. The actual CTV around the tumour bed should approximate to the volume of a breast quadrant and therefore reflect the conceptual CTV margin around the tumour.

Whole Breast CTV

This should include the soft tissues of the whole breast down to the deep fascia. This is based on the recommendations from the START (Standardisation of breast radiotherapy) Trial (44).

2. Planning Target Volumes (PTV)

A margin should be added to each CTV, which takes into account set-up error and patient movement (including breast swelling and breathing). Several studies have used electronic portal imaging devices to quantify the extent of positional errors and patient movement for breast radiotherapy (59-62). Three studies calculated a weighted standard deviation of the central breast distance (reflecting movement in the anterior-posterior direction) of 4.5 mm, 4.6 mm and 2.2 mm respectively for the systematic component of set-up error (60-62). Four studies calculated a weighted average standard deviation of 3.9 mm, 6.1 mm, 2.0 mm and 4.7 mm respectively for systematic variation in set-up error for the cranio-caudal distance (reflection movement in the superior-inferior direction) (59-61, 63). Due to the variation in reported measurements, Hector *et al* adopted a value of +/- 3 mm for displacement in both directions, to model the effect of set-up error and breast volume change on conventional and intensity modulated breast radiotherapy (IMRT) (64). They found that whilst IMRT was slightly more susceptible to movement than conventional radiotherapy, the final dose distribution was always superior, hence justifying the use of IMRT in the presence of set-up errors. Another study found that a vac-fix immobilisation device was superior to a breast board as it improved transfer of the planned set-up from the simulator to the treatment unit (65). It was felt that implementation of the vac-fix device was not justified for standard tangential breast radiotherapy, but may be important for more complex techniques such as IMRT.

It is difficult to determine from the portal imaging studies exactly which part of the displacement was due to set-up error and which was due to patient movement. Hector *et al* showed that the average increase in breast volume during treatment was 5%, and this peaked between fractions 5 and 8 and then decreased back below the initial volume (62). It has been stated that the effects of breathing motion are in general about half the size of the effects of set-up error (64). Breathing motion may be particularly important in dynamic-MLC IMRT techniques, and a study has shown that dosimetric errors are dependent on the speed of the travelling leaves relative to the speed of the target motion (66). Some centres may wish to implement methods to limit breathing motion such as gated radiotherapy and breath-holding techniques (67).

One institution developing 3D-CRT for partial breast irradiation, measured the impact of patient set-up error and breathing motion to establish CTV to PTV margins (58). This was then tested clinically for adequate coverage of treatment. The CTV-PTV margin for 'breathing only' was calculated by measuring the displacement of surgical clips during 3 types of CT scan: free breathing, and breath holding at the end of normal inhalation and at the end of normal expiration using an active breathing control device. A margin of 5 mm was subsequently selected to completely account for breast motion during quiet breathing. The combined uncertainty of random patient set-up error and respiratory motion, and the distribution of systematic error across all fields and all patients, were measured. This was achieved by measuring the movement of the chest wall/ribs with portal imaging, as a surrogate for the tumour bed. A margin for set-up uncertainties of 5 mm was proposed from this data, producing a total CTV-PTV margin of 10 mm, which was tested in 9 patients. 98 - 100% of the CTV was covered by the 95% isodose surface at the extremes of normal inhalation and exhalation using the 'breathing only' margin of 5 mm. The total CTV-PTV margin of 10 mm also seemed to provide coverage for most patients. The authors state that there is still uncertainty regarding the stability of the tumour cavity relative to the chest wall and that this may vary more in patients with larger breasts. Therefore, slightly larger CTV-PTV margins may be needed in this group of patients.

Given the reports from the literature, a typical PTV margin may be 10 mm. The margins for PTVs should ideally be determined by each centre to reflect accuracy of set-up and estimation of patient movement for that institution (there may be existing information available from the START QA team). 3D growing algorithms should be used where possible and centres may wish to develop asymmetric volume growth if it is felt that one direction is more prone to inaccuracies than others. A margin should be added to the whole breast and partial breast (quadrant) CTV, taking into account set-up error, breast swelling and breathing; a typical PTV margin is 10 mm. A smaller 5 mm PTV margin should be be added to the boost CTV, as volume definition and planning studies have shown that 95% isodoses for the boost and partial breast volume begin to approximate as the boost volume PTV increases. A modified PTV: PTV_{DVH}, will be used for reporting purposes, and will stop 5 mm beneath the skin surface in order to preserve skin sparing.

3. Organs At Risk (OAR)

It is recommended that both lungs, the heart and contralateral breast are contoured for dose volume histogram assessment. The heart should be outlined from the inferior aspect above the diaphragm, to the superior aspect below the pulmonary arch. These volumes should be recorded for the purposes of the trial.

APPENDIX 2 : Localisation of the post-operative breast tumour cavity

Planning of the radiotherapy boost treatment to the tumour bed requires an assessment of the location of the post-operative tumour cavity. In general, this has been done using a combination of information: pre-operative radiological imaging, surgical annotation, clinical palpation of the surgical defect and position of the breast scar, and patients' recollection of the site of the mass. In the past, the position of the scar has been heavily relied upon to assist with locating the tumour bed. However, breast surgical technique has subsequently changed, with the scar frequently being placed some distance from the site of the tumour in order to achieve a better cosmetic result. This has prompted some institutes to compare traditional 'clinical' methods of boost planning with various imaging techniques.

1. Implanted surgical markers for localisation of the tumour cavity

Several studies have reported the superiority of using surgical clips to locate the tumour bed compared with clinical methods (36-37, 68-72). All studies showed that the tumour cavity would have been under-dosed using traditional planning techniques. The clinical method could also result in a substantial volume of normal tissue being irradiated unnecessarily (36). In addition, it was also reported that medially and laterally located tumour cavities could also be missed by the tangential fields (37, 69).

Detailed descriptions of the planning techniques using surgical clips have been reported using both computed tomography (CT) scanning and simulator films (73-74). A consistent policy of clip placement at the time of surgery is necessary. An example of this is to place a clip at the medial, lateral, superior and inferior extent of the tumour bed, and a fifth clip at the deepest extent of the tumour bed in the direction of the surgical excision (73).

An alternative method is the use of 2mm diameter gold seeds, which are sutured into the tumour cavity. These are currently being investigated as part of a multicentre NCRN study on behalf of the IMPORT group (75).

2. Ultrasound for localisation of the tumour cavity

Breast ultrasonography has also been exploited as a method of localising the tumour bed for radiotherapy planning. A study compared clinical methods with ultrasound localisation and found that the full extent of the tumour cavity was underestimated in 87% of women, and the chest wall depth was incorrectly estimated in 90% using traditional methods (76). Another study reached similar conclusions: conventional electron boost planning resulted in 55% of patients having areas of under-treatment and 20% of patients received significant over-treatment (77). The location and appearance of the tumour cavity has been found to be highly reproducible on repeated scans, with a mean depth difference between scans of 2 mm (38).

Several studies have commented that the tumour cavity was more difficult to localise using ultrasound as the time from surgery increased. One study reported that it was difficult to visualise the cavity after 8 weeks from surgery (76). This view was reflected by another study, which found that the optimal time for radiotherapy planning was within 60 days post-operation (78). A third study, concluded that best accuracy of localisation when the ultrasound scan was carried out within 100 days from surgery (79). In addition, this study compared both ultrasound and surgical clips localisation methods within the same cohort and found that the mean volume was less with ultrasound. This finding should be taken into consideration when adding 3D margins for the clinical target volume (CTV).

Radiotherapy techniques such as a brachytherapy interstitial implant or a concomitant photon boost to the tumour bed using intensity modulated radiotherapy (IMRT), require more detailed 3D information than is possible with 2D ultrasound alone. However, more 3D information can be achieved by using a combination of ultrasound examination and placement of radio-opaque skin markers and measurement of cavity depth, followed by CT scanning in the same position (80). Another novel method is to use a high definition 3D ultrasound scanning technique, which has been investigated at Addenbrooke's Hospital, Cambridge and has since been developed commercially. A position sensor is used to continually track the position of an array of infrared-emitting diodes attached to the transducer. Thus both the ultrasound image and associated spatial information are recorded simultaneously. A 3D volume of the tumour cavity can then be produced, which is imported into the radiotherapy planning system.

3. Magnetic Resonance (MR) imaging for localisation of the tumour cavity

Magnetic resonance (MR) provides excellent definition of the breast and surrounding tissues. Its use in breast radiotherapy planning, however, has been very limited. This has largely been due to a combination of limited MR resources and the difficulty of scanning the patient in the treatment position. The Bristol Haematology and Oncology Centre have experience in the use of a low-field open MR scanner for breast radiotherapy planning, which allows imaging in the treatment position. This group has demonstrated with MR imaging, that conventional breast radiotherapy planning of the boost and sometimes the tangential fields, can result in under-treatment of the target. In addition, greater sparing of surrounding organs at risk can be achieved with MR-assisted planning. Potential problems with MR radiotherapy planning include image distortion and co-registration with radiotherapy planning systems.

4. Tumour bed localisation methods for IMPORT HIGH

4.1 Implanted surgical markers

The use of implanted surgical markers is recommended unless 2D/3D ultrasound or MRI is used for localisation. Six 2-3 mm diameter gold seeds may be sutured into the tumour bed, marking the anterior, posterior, medial, lateral, superior and inferior margins. The seeds can be seen clearly on megavoltage portal imaging, which will assist on-treatment image-guided radiotherapy (IGRT). Alternatively, 6 pairs of titanium clips can be used. These are less easily seen on megavoltage portal imaging, but can be visualised with kilovoltage portal imaging. The clips protocol provided in the Site Investigator File should be used.

4.2 Ultrasound

A combination of 2D ultrasound and CT scanning is a reliable alternative to visualise the tumour cavity without the use of surgical clips. Three-dimensional ultrasound may also be used, either in combination with CT or optical breast contouring system. However, the ability to clearly define the cavity decreases with increasing time from surgery.. Therefore, it is advised to restrict the use of ultrasound to patients planned within 3 months of surgery.

4.3 MR imaging

MR imaging can be used to obtain anatomical information of the tumour cavity and surrounding tissues. Ideally, this should be available electronically in the radiotherapy planning system.

4.4 General recommendations

The patient must be scanned in the treatment position for all imaging modalities. Each centre must develop its own localisation protocol according to which of the 3 methods is available. Centres with established methods could assist with this development process. A central Quality Assurance team must assess and approve all localisation techniques.

APPENDIX 3: Justification for standardising boost volumes across all groups

The START & FAST Trial results have enabled accurate estimates of concomitant boost doses in 15 or 5 fractions (F) that are equivalent to standard sequential boost schedules delivered in 2.0 Gy fractions. No time correction is needed for late adverse effects in changing from sequential to concomitant boost; only the fraction size affects the calculation. IMPORT LOW will quantify the normal tissue sparing effects of reducing the dose intensity to whole breast from 40 Gy to 36 Gy/15 F (Control vs. Test group 1 of IMPORT LOW). There is an opportunity to combine these two elements in the IMPORT HIGH Trial in order to quantify how much tolerance is gained for concomitant boost dose escalation by reducing the dose intensity to low risk areas. If the boost volumes in control and test groups are standardised, the trial design will be as robust as it can be. This means that electrons cannot be used to deliver sequential boost.

Since the IMPORT HIGH trial design standardises boost volume across all groups, the Test Group 1 boost dose is exactly equivalent to the Control Group boost dose in terms of late adverse effects (40 Gy/15 F + 16 Gy/8 F and 48 Gy/15 F are each equivalent to 60 Gy/30 F assuming α/β value of 3.0 Gy). If the frequency and severity of induration in the boost volume is the same in Test Group 1 and Control Group, this suggests that the whole breast dose of 36 Gy/15 F in Test Group 1 does not spare the tissues inside the boost volume (although patient self-assessments may pick up relevant differences in symptoms outside the boost volume). If there is no dose sparing of tissues inside the boost volume in Test Group1, this means that the Test Group 2 boost dose of 53 Gy/15 F will be equivalent to 69 Gy in 2.0 Gy fractions. Although this sounds high, the Netherlands is currently comparing 50 Gy/25 F whole breast plus 16 Gy/8 F vs 26 Gy/13 F electron boosts in high risk women i.e. 76 Gy/38 F in the test group. If Test Group 2 is comparable to the Control Group in IMPORT HIGH, this suggests a large and quantifiable dose sparing effect of reducing the dose to low risk volumes from 40Gy to 36Gy in 15F. The outcome is likely to fall somewhere in between. Whatever the result, the data will inform the trial design of a subsequent Phase III trial independent of fractionation schedule (25, 15 or 5 fractions).

Since all eligible patients will require accurate localisation of GTV, CTV and PTV, it is highly likely that treatment volumes in the Control Group will increase compared to current clinical methods regardless of which modalities (photons or electrons) are used to deliver the boost. For example, if a small GTV localised using titanium clips on CT scan is 3 cm in diameter (it might be more), the protocol specifies a margin of 1.5 cm for CTV and a 1.0 cm margin for PTV. This describes a PTV of 8 cm diameter, requiring a 10cm applicator in the normal course of events using electrons. In the EORTC trial of boost versus no boost, photon boost volumes in 753 patients were larger than electron boost volumes (mean 288 cc compared with 144 cc), although no difference in the rate of moderate/marked fibrosis was detected in the two groups of patients (54). In conclusion, a sequential photon boost has advantages in the Control Group of IMPORT HIGH, even in cases where electrons *would* encompass a properly planned and localized PTV.

APPENDIX 4 : Evidence for dose constraints

IMPORT HIGH requires the use of more complex radiotherapy techniques, including inverse and forward planned Intensity Modulated Radiotherapy (IMRT). In addition, the photon boost requires several beams which will pass through normal tissue. Therefore, it is inadequate to state only the "traditional" simple normal tissue dose-volume restrictions, such as the maximum heart/lung distance within the treatment field. Dose constraints to the Organs at Risk (OARs) were determined from evidence from the literature and dose-volume histogram analysis in the IMPORT planning study. Three major normal tissue structures were considered and discussed below and in table 4:

(i) Contralateral breast

The 2007 recommendations from the International Commission on Radiological Protection (ICRP) estimated the risk of radiation-induced breast cancer as follows (81): Given that there is a 5% risk of cancer per sievert (Sv), and the weighting factor for breast is 0.12 (0.06 per breast), then a mean dose to the breast of 1 Gy = 0.06 sievert (Sv), which gives a less than 0.5% risk of cancer. The IMPORT HIGH planning study showed that a mean dose of less than 1 Gy could be achieved in the majority of cases, but occasionally this was exceeded, particularly with very medial tumour beds. Subsequent analysis has shown 50% of plans can achieve a mean dose of 0.5 Gy or less, with a potential halving of any possible second cancer risk. Therefore, the current IMPORT HIGH recommendations are to aim for a contralateral breast mean dose of less than 0.5 Gy where possible, but a mean dose of less than 1.5 Gy would be acceptable for trial entry.

(ii) Lung

There is good evidence in non-small cell lung cancer that if V20 (volume receiving 20 Gy) is < 22% for *total* lung, there is no risk of pneumonitis (80). A breast radiotherapy study showed that V20 < 30% for the *ipsilateral* lung resulted in very few cases of pneumonitis (82). IMPORT HIGH dose constraints for the lung are set at a lower threshold, to take into account possible increased toxicity with systemic therapy and account for the slightly higher dose per fraction. Therefore, the IMPORT HIGH recommendations are for no more than 15% of the ipsilateral lung to receive 18 Gy, and no more than 15% of the contralateral lung to receive 2.5 Gy.

(iii) Heart

Gagliardi et al have reported that only the dose level above 30 Gy to the heart is important to the calculated risk of cardiac toxicity, whereas the curve is almost constant below 30 Gy (83). This is also supported by the results from long-term survivors of Hodgkin's disease receiving RT (84). IMPORT HIGH dose constraints for the heart are set at a lower threshold, to take into account possible increased toxicity with systemic therapy and account for the slightly higher dose per fraction. Therefore, the IMPORT HIGH recommendations are for no more than 10% of the heart to receive 13 Gy.

	Keep ipsilateral lung volume </= 15%	**Keep contralateral lung volume </= 15%**	**Keep heart volume </= 10%**	**Contralateral mean breast dose**
Dose (Gy)	**18**	**2.5**	**13**	**Aim </= 0.5 Accept </= 1.5**

Table 4: summary of IMPORT HIGH dose constraints for Organs at Risk

APPENDIX 5 : Equivalent total doses used in the IMPORT HIGH trial

Trial group	Target volume	Fx	Prescribed dose per fraction (Gy)	Late effects [a]EQD_2 (Gy)	Tumour [b]EQD_2, no repop.(Gy)	Tumour [c]EQD_2 with repop. (Gy)
Control 15 fractions	Whole breast volume	15	2.67	45.2	44.5	52.9
	Tumour bed[d] (photons)	±8	2.0	61.2	60.5	61.7
Test Group 1 15 fractions	Low dose (whole breast) volume	15	2.4	38.8	38.4	46.8
	Standard dose (partial breast) volume	15	2.67	45.2	44.5	52.9
	Tumour bed (photons)	15	3.2	59.1	57.6	66.0
Test Group 2 15 fractions	Low dose (whole breast) volume	15	2.4	38.8	38.4	46.8
	Standard dose (partial breast) volume	15	2.67	45.2	44.5	52.9
	Tumour bed (photons)	15	3.5	67.6	65.6	74.0

Table 5 : Equivalent doses for centres using 15 fractions (plus boost in the control group):

EQD_2: Equivalent total dose delivered in 2.0 Gy fractions.

[a] Assuming α/β = 3.2 Gy for late effects.

[b] Assuming α/β = 4.0 Gy for local tumour control and no time factor (D_{prolif} = 0 Gy/day).

[c] Assuming α/β = 4.0 Gy for local tumour control and time factor (D_{prolif} = 0.6 Gy/day).

[d] The tumour bed receives the whole breast dose + a sequential photon boost.

All schedules normalised to an overall treatment time of 5 weeks.

NOTE: the assumed fractionation sensitivities (α/β values) for late normal tissue effects and for tumour control are based on data from the Royal Marsden Hospital/Gloucestershire Oncology Centre Breast Fractionation Trial that are now incorporated into the START Trial dataset. They are incorporated here with the permission of the START Trial Steering Committee and with the approval of the START Trial Data Monitoring and Ethics Committee.

APPENDIX 6 : Quality Assurance Programme

1. Background

The complex nature of modern radiotherapy carries inherent problems both in ensuring reproducibility and accuracy within a radiotherapy unit and, more particularly, when carried out on a multi-centre basis. Specific issues in the treatment of the breast and lymph node pathways arise from the geometry of the treatment volume which varies in contour in all three planes with important radiation sensitive structures underlying the breast and chest wall including the lung and myocardium. Careful localisation, computerised planning, accurate verification of beam position and meticulous attention to alignment and matching during treatment are essential

A quality assurance programme is “a mandatory prerequisite when aiming at high dose, high precision radiotherapy” and is an integral component of any radiotherapy trial as defined by the EORTC guidelines for trial protocols in radiotherapy (85-86).

In this multi-centre randomised trial the quality assurance programme will enable confirmation that technical guidelines within the protocol have been understood and implemented correctly by participants and that the dose prescription is delivered according to protocol together with appropriate documentation of technique and patient related data. This will ensure that clinical observations in terms of tumour control and normal tissue damage reflect differences in the randomised schedules rather that departures from trial protocol. Techniques used will be documented, this data will be available should differences in observed endpoints emerge.

In this way the definition of quality assurance as “all those planned and systematic actions necessary to provide adequate confidence that a produce will satisfy given requirements of quality” (87) can be satisfied and the scientific worth of the parent trial be validated.

The QA programme will build on that developed for the START and IMPORT LOW trials. This has provided an element of consensus in radiotherapy technique amongst radiotherapy centres. IMPORT will necessitate the implementation of new technology in some centres where the use of intensity-modulated radiotherapy or image-guided radiotherapy has not been used previously.

2. Plan of investigation

The quality assurance programme will follow the guidelines set out by the EORTC (86) and will be co-ordinated by an experienced QA team based at Mount Vernon Hospital (88-89). he programme will proceed as follows:

2.1 An initial questionnaire establishing precise details of technique to be used within the centre, together with specimen patient outlines to be used for ideal plans to be produced by each centre.

2.2 A visit by the quality assurance team prior to a centre entering the study to validate independently the technique in use against the information given in the questionnaire. In particular, the following parameters will be assessed:

i) Target volume and treatment technique used together with methods of beam matching where appropriate.

ii) Confirmation of IMRT/compensator implementation .

iii) Planning of radiation distributions across the treatment volume for homogeneity and prescription points.

vi) Routine QC performed by the centre will be assessed and compared with current IPEM guidelines (90).

vii) Measurements across the treatment volume within a purpose-made phantom.

viii) The imaging verification technique and protocol will be assessed.

2.3 All plans together with corresponding CT data sets will be collected electronically. Data should be anonymised with the patient's trial number and initials prior to sending to the QA team. Verification images will also be collected for the first 3 patients.

3. Quality control by department for IMRT

Where a centre has an established IMRT programme which has been previously credentialed by members of the NCRI trials QA team for another trial, some aspects of the IMPORT HIGH QA programme may be omitted. Where an established IMRT programme is not set up, additional QC may be required such as verification of fluence maps for each field.

4. Analysis of QA programme

The data from the quality assurance programme will be analysed separately from the main trial. Major discrepancies from trial protocol will be notified to participating centres. These will include:

i) Discrepancies in documentation, dose prescription and dose recording.

ii) Failure to meet upper and lower dose limits for treatment volumes.

iii) Hot spots (> 100%) at field matchlines.

iv) Inclusion of > 2 cm of lung and > 1cm of heart in the treatment volume.

v) Systematic errors of technique in any stage of treatment from planning through to implementation.

The detailed analysis of the quality assurance data will produce quality information covering the following areas:

i) Variations in breast radiotherapy practice in participating centres

ii) A comparison of methods used for IMRT (multiple static fields, dynamic fields)

iii) An assessment of the emerging technologies and their quality control

iv) Quantification of dose uniformity during the treatment period

v) Correlation of physical parameters of radiation with trial endpoints:

- The association between dose variation across the treatment volumes and tumour control.
- Dose variation, machine energy and skin surface doses in relation to moderate/severe fibrosis and breast shrinkage.
- Variations in dose homogeneity with rib pain, fracture and necrosis.

APPENDIX 7 : Quality of Life Studies

Rationale for QL study

There is evidence that radiotherapy causes long-term effects on quality of life in terms of altered breast appearance, breast and other physical symptoms, notably fatigue. In this trial comparing different radiotherapy approaches, women's subjective views of their body image and other QL parameters together with their experience of relapse if it occurs, need to be ascertained in order to compare the trade off between local tumour control and adverse effects of treatment. The key effects of treatment and relapse on QL are hypothesised to be on breast symptoms, body image and psychological distress as well as general symptoms such as fatigue, and physical functioning.

Rationale for QL measurement

The main priority guiding the evaluation strategy is to select standardised QL scales and subscales that will answer the research questions of importance in this study and allow comparison with other relevant trials. The scales selected include a general cancer QL scale, plus specific measures for breast cancer, body image and psychological distress.

Measures

The EORTC QLQ-C30 (91) is a purpose-developed self report scale for use with cancer patients, which has been well tested psychometrically and is being widely used in clinical trials. The EORTC BR23 breast cancer module is a 23-item scale designed for use with the core instrument in breast cancer treatment (92). A 10-item Body Image Scale (BIS) designed for use with cancer patients will also be included (93), which has been used in other national breast cancer trials, and for which extensive reference data are available. Psychological distress will be measured by the Hospital Anxiety and Depression Scale (HADS) (94) which has been widely used in clinical trials to date and provides clinically interpretable endpoints.

The QL endpoints are designed to complement the external assessments of breast appearance and other late normal tissue effects, and to capture the medium- and long-term sequelae of breast radiation therapy on health-related quality of life. The QL study is both descriptive and comparative: sample size considerations are addressed where appropriate.

Feedback from compliance data and interim analysis in the START trial will guide the optimal timing and mode of administration of QL questionnaires, especially at the time of relapse. A suitable policy will then be adopted for IMPORT HIGH QL data. This protocol will be available to all centres participating in the IMPORT HIGH trial. A subset of patients will be asked to participate in the QL study, but if they would prefer not to they may still be randomised into the main trial.

The QL evaluation is described below for 2 endpoints: normal tissue effects and tumour-related effects. The QL endpoints will be summarised in a form that can be used by clinicians to inform patients and other stakeholders e.g. providers and commissioners of health care. No weighting will be given to prioritise any particular QL domain: the aim is to provide information from all QL domains as appropriate.

Normal tissue effects

1) Breast appearance and body image

The impact of different radiotherapy fractionation regimens will be assessed using 10 items relating to body image.. Data on body image will be summarised at 3 and 5 years. Associations between altered body image and psychological distress will be explored using all available data.

2) Other radiotherapy-induced adverse effects

The proportion of patients suffering lymphoedema, shoulder stiffness, breast pain and brachial plexopathy will be assessed at 3 and 5 years. Relevant symptoms from the breast cancer module of the EORTC QLQ-C30 scored as 'quite a bit' or 'very much' will be used as an indicator of adverse effects. Limitations on functional status will be assessed using the following subscales of the EORTC QLQ-C30: physical functioning (items 1-5), role functioning (items 6,7), social functioning (items 26, 27). Again, limitations scored 'quite a bit' or 'very much' will be used as a basis for comparison between regimens.

3) Sexual functioning, psychological distress and global quality of life

Whilst we would not assume that these parameters are influenced primarily by treatment, these domains may reflect the impact of tissue damage on altered body image - we will therefore explore these domains within regimen and describe levels of dysfunction, distress and global quality of life. Formal statistical comparisons will be considered if differences emerge which warrant testing, but these are not expected. Global QL will be measured using items 29 and 30 from the EORTC QLQ-C30. Sexual functioning will be assessed from relevant questions from the EORTC Breast Cancer Module BR23. Anxiety and depression will be assessed using the accepted threshold scores on the Hospital Anxiety and Depression Scale (HADS).

Tumour-related effects

We hypothesise that local recurrence will be associated with increased psychological distress. However, there are expected to be too few events in the current trial to allow formal statistical testing of treatment differences between trial groups.

Summary of results to reflect favourable and unfavourable effects

In order to aid clinicians in an appraisal of the results we shall summarise the major findings, positive and negative, of the above endpoints. We will <u>not</u> attempt to produce a summary score representing a QL endpoint for each regimen, but will report results for each domain under consideration. Results for medium and long-term effects will be presented in tabular form with accompanying explanatory paragraphs.

This will be a particularly important way of trying to provide a resume of a large study, which will help clinicians and others consider and discuss factors that influence a 'trade-off' of (psychosocial) cost and benefit, should this arise, the main one being considered to be enhanced cosmesis at a greater risk of local relapse.

Eligibility

subset (840) of patients who:

- are entered into the IMPORT HIGH trial;
- are not taking part in a QL study as part of another trial;
- consent to be part of the QL study and are available for follow up;
- are willing and able to complete the self-report QL questionnaires.

Sample Size

Quality of Life evaluations will be carried out on 840 patients in the main trial. 280 patients per group will provide at least 80% power to detect differences of ≥ 15% in the prevalence of specific normal tissue effects (e.g. lymphoedema, shoulder stiffness, breast pain) and anxiety and depression. Sample size estimate assumes a 2-sided significance level of = 0.01 (to allow for multiple testing) and allowing for 10% attrition due to illness or death (based on experience from the START trial).

The significance level chosen allows, to some degree, for the multiple testing involved in analysing individual sub-scales of the QL questionnaires. The numbers identified above also allow for some degree of attrition due to illness or death (10% non-completion). Experience from the START trial has shown compliance to be high. Particular care will be taken when approaching patients in the trial known to have relapsed, as although it is vital to collect these data, it may be requested at a sensitive point.

Patients will be stratified by centre and due representation geographically will be considered. The IDMC may recommend extending recruitment in the QL study in all or a specific subgroup of patients (e.g. those receiving axillary irradiation). Such extension will take into account the attrition rate observed during follow-up in the study to date.

Timing of Assessments

The emphasis is on the long-term assessment of different treatment policies so that the number of questionnaire administrations is limited in the first year.

Baseline

A designated member of staff, trained in QL administration, will hand out questionnaires in the clinical centre. Patients will be asked to complete the forms after a full explanation of the study and after giving informed consent but **before** the randomisation is known, to avoid the possibility of bias.

Subsequent assessments will be mailed directly to the patient from the IMPORT HIGH Trials Office at the following times after randomisation: 6 months, 1 year, 3 years, 5 years.

Due care will be taken to check the physical status of all patients prior to questionnaire mailing. This will be done through telephone contact with the hospital department and/or GP as appropriate. The follow-up questionnaires will be sent out by the IMPORT HIGH Trials Office requesting completion within the week. If the forms have not been returned 2 weeks after having been sent out, there will be a telephone call to advise the patient that the forms have been sent, to check that they have been received and to prompt their completion and return. Such a mechanism also provides the opportunity to clarify any missing data with the patient on the forms which have been returned with incomplete responses. The annual follow-up assessments will be sent out shortly after the patient attends the hospital for routine annual follow-up, thereby ensuring that information on the patient's health status is up to date.

Missing data

All reasonable efforts will be made to ensure correct completion of the QL assessments. Full explanation of the QL study will be given by the responsible research nurse/member of breast care team prior to administration of the baseline questionnaires. On collection, the questionnaires will be briefly checked for completeness. The follow-up questionnaires will

include instructions for completion. When individual items are missing, procedures, which have been used in similar studies, will be adopted:

- where the missing item is a single item measure this is simply recorded as a missing value;
- where the missing item forms part of a sub-scale a prorating procedure will be used depending on the total number of items on the scale and the number appropriately completed:
- where fewer than 50% of the items of the sub-scale have been completed correctly then this constitutes a missing case for that sub-scale;
- where at least 50% of the items of the sub-scale have been completed then the mean score obtained for the completed items can be inserted.

QL study management

Trials Office

The Study Co-ordinator, based in the IMPORT HIGH Trials Office, will be responsible for overall co-ordination of the study. The Co-ordinator will liaise closely with those responsible for the QL study in each participating centre and with the expert psycho-oncologist and clinicians involved in the project. The Coordinator will verify the status of the patient and send out the follow-up questionnaires. Any queries regarding the patient or the patient's management will be referred to the responsible person in the centre.

Centre

It is necessary for each participating centre to identify a person responsible for the conduct of the QL protocol. This person will explain the study to the patient, ensure that the patient understands how to complete the QL questionnaire, and forward the first set of completed forms to the Study Co-ordinator. He or she will maintain close liaison with the Study Co-ordinator in the IMPORT HIGH Trials Office and be responsible for organising cover in times of holiday or other planned absence.

QL Data Management

The Study Co-ordinator will be responsible for checking the data for consistency and completeness, for providing reminders for overdue forms to the responsible persons in the centres and for entering the data onto the central database for the trial.

Statistical Analysis Plan

The algorithms developed for use with the QL forms will be used to measure the parameters of interest. Groups of patients will be compared at agreed time points and overall for differences in these parameters (95). The treatment groups will be compared at the individual time points with appropriate adjustments being made for multiple comparisons. Because of the longitudinal nature of the data, an analysis which takes into account the repeated measures is also needed. A generalised linear modelling approach will be adopted (39, 96-97). This will allow the appropriate error distribution to be used and will enable the analysis to take account of important factors such as age, stage of disease, treatment received and other sociodemographic and clinical characteristics.

Informed Consent and Ethical Issues

Details for the main trial are outlined in the Clinical Protocol. Principal Investigators participating in the QL Study will obtain local Ethics Committee approval for the study. The principal investigator or his/her delegated representative is responsible for obtaining each patient's signed informed consent prior to the administration of the baseline QL assessment.

Patients obtaining clinically significant scores on the HADS should be further assessed clinically. This will be explained in the Patient Information Sheet and patients will be specifically asked to consent to information about high HADS anxiety/depression scores being passed on to their doctor. The cut-off HADS score for the subscales combined used for identifying probable cases is 19, 75% of people with a score of this magnitude are found on interview to have clinically significant anxiety and/or depression which could be relieved for the majority of them by psychotherapeutic and/or pharmacological intervention. If a patient scores 19 or above on the HADS scale the IMPORT HIGH QL Co-ordinator will contact her clinical oncologist.

Endpoints and measures

Measures to be used

EORTC QLQ-C30 (Academic Users Agreement obtained.)
EORTC BR-23 Breast Cancer Module (Academic Users Agreement obtained).
Body Image Scale (BIS) (Published).
The Hospital Anxiety & Depression Scale (HADS) (Published).

Quality of Life, The EORTC QLQ-C30 and Breast Cancer Module (BR23)

The QLQ-C30 is a 30-item questionnaire comprising 5 functional scales (physical, role, cognitive, emotional and social), a global QL scale, and 3 symptom scales (fatigue, pain, nausea & vomiting) and a number of single item measures.

The breast cancer specific module consists of 23 items of specific relevance to patients with breast cancer, namely side effects of breast surgery, chemotherapy, endocrine therapy and radiotherapy, body image, sexuality and future perspective.

Body Image

External (photographic) and subjective (patient self-report) assessments will be carried out prospectively.

1) Photographic Assessments

Digital photographic assessments will be undertaken post-surgery and at 3 and 5 years post-treatment, using two views, with hands on hips and hands raised as far as possible over the head. Change of breast appearance compared with the post-surgical baseline will be scored on a three-point scale by 'blinded' investigators, to define clinically relevant groups, namely no/minimal change; marked/gross change and an in-between group.

2) Patient Self-Assessment

The 10-item Body Image Scale is sensitive to change over time and discriminates between patients treated with mastectomy and conservative surgery. Four items are already incorporated in the BR23 and will be summed with the 6 additional items to form the full scale. Three protocol specific items not covered by the EORTC breast cancer module or Body Image Scale will also be included to complete the evaluation of cosmesis and radiation effects.

The Hospital Anxiety & Depression Scale - HADS

This is a 14-item scale (7 items anxiety, 7 items depression) designed to measure psychological distress in cancer patients. Threshold scores have been derived that enable the prevalence of clinically significant levels of anxiety and depression to be evaluated. A comparison of 3 screening measures suggested that the HADS was the best scale when compared against a diagnostic psychiatric interview, in patients who were disease-free or stable, and hence is the preferred measure for this trial (98).

APPENDIX 8 : Recommendations for Recurrence Mapping

The primary endpoint of IMPORT HIGH is local recurrence and an important secondary endpoint related to this is the position of any recurrence in relation to the treatment volumes. The highest quality data will be obtained by relating the 3-dimensional (3D) position of tumour recurrences/new primaries to the original radiotherapy plan.

The management of recurrences/new primaries varies from centre to centre. Also, it is important that the mapping techniques are practical to enable the maximum value from the information gathered. For this reason some suggested recurrence mapping recommendations have been devised with a variety of complexity This takes into account that technology would be rapidly improving over the lifetime of the trial.

The patient information sheets and case report forms, plus a leaflet explaining how to contact the local radiotherapy centre, if a lump is detected, will be used to alert the patient and health care professionals of the IMPORT HIGH trial if a recurrence/new primary occurs.

Patients who proceed to Surgery without the involvement of the local Radiotherapy Centre

The surgeon indicates on a form with a simple schema the quadrant of the breast in which the recurrence/new primary occurs. The data are used to estimate where the recurrence/new primary is located with respect to the radiotherapy fields which may be visualised using a surface rendered image from the radiotherapy treatment planning system.

Patients who proceed to Surgery with the involvement of the local Radiotherapy Centre

It is expected that all patients would have a mammogram and ultrasound as part of standard diagnosis of a recurrence/new primary.

The recommendations are for optical, ultrasound and CT systems. Magnetic Resonance (MR) imaging is an alternative, with the advantage of being an accurate method of demonstrating tumour recurrence without additional radiation. The use of MRI, or other methods, for the recurrence mapping should be discussed with the imaging working party and QA team prior to use.

Simple mapping method using ultrasound and optical systems

- Patient is set-up in the radiotherapy simulator/treatment room in the original radiotherapy position.
- The light fields will be set-up to show position of the whole breast and partial breast radiotherapy fields.
- 2D ultrasound will record the centre, diameter and depth of the tumour and the position will be marked on the skin.
- If possible, the centre of gravity of the original tumour bed will be recorded from imaging the clips/seeds.
- It will be recorded whether the recurrence/new primary is inside the original tumour bed field, outside the tumour bed field but inside the partial breast field, outside the partial breast field, or in a borderline region (within 1 cm of the partial breast field edge).

- An estimate of the distance of the recurrence/new primary from the original tumour bed will be made if possible.

N.B. pre- and post-radiotherapy photographs of the patient's breast (including a linear scale) will give a score for the degree of breast shrinkage, and thus the level of accuracy of the above method.

Mapping using Computed Tomography

- Recurrences should be marked by means of a CT-visible coil or clip marker either at biopsy or once diagnosis has been confirmed. This should be discussed and arranged in co-operation with the breast imaging team.
- Patient will be set-up in the CT-simulator in the original radiotherapy position and CT-scanned.
- This CT scan will be co-registered with the original CT planning scan.
- The centre of gravity co-ordinates of the tumour recurrence (coil) and original tumour bed (clips/seeds) will be recorded.
- It will be recorded whether the recurrence/new primary is inside the original tumour bed field, outside the tumour bed field but inside the partial breast field, outside the partial breast field, or in a borderline region (within 1 cm of the partial breast field edge).
- The distance of the tumour recurrence from the original tumour bed will be recorded.

N.B. pre- and post-radiotherapy photographs of the patient's breast, and change in CT breast contour, will indicate the degree of breast shrinkage, and thus the level of accuracy of the above method.

APPENDIX 9 : Serious Adverse Event reporting

Definitions:

Adverse Event (AE): Any untoward medical occurrence in a patient or clinical trial subject administered a research procedure; events do not necessarily have a causal relationship with the procedure.

Related Adverse Event: An adverse event assessed by the Principal Investigator or Chief Investigator or nominated representative as reasonably likely to be related to the administration of a research procedure.

Serious Adverse Event (SAE): an untoward occurrence that:

1. results in death
2. is life-threatening
3. requires hospitalisation or prolongation of existing hospitalisation
4. results in persistent or significant disability or incapacity
5. consists of a congenital anomaly or birth defect; or
6. is otherwise considered medically significant by the principal investigator

Related Unexpexted Serious Adverse Events: An adverse event that meets the definition of serious and is assessed by the Chief Investigator or nominated representative as:
"Related" – that is, it resulted from administration of the research procedure, and "Unexpected" – that is, the type of event is not listed as an expected occurrence as detailed in section 14.3

Reporting procedure

1. All SAEs must be reported within 24hrs of the Investigator or member of their team becoming aware of the event using the specific SAE form. This must be completed, signed and dated by the Principal Investigator or delegate named on the delegation form.

2. The SAE form must be faxed to the IMPORT trials office at the ICR-CTSU on:

   020 8722 4368

3. The IMPORT Trials office will send a fax to acknowledge receipt of the SAE.

4. The Chief Investigator or nominated representative will review all SAEs to assess the "expectedness" and "relatedness" of the event

5. If an SAE is defined as related and unexpected by the Chief Investigator or nominated representative, the ICR-CTSU will report the SAE to the main REC within 15 days from the date the ICR-CTSU became aware of the event. Any subsequent reporting will be carried out as appropriate.

6. Follow-up information should be completed on the relevant part of the original SAE form within 15 days of the initial report and faxed to the ICR-CTSU.

7. Centres should continue to send follow-up SAEs until the event is resolved e.g recovered, recovered with sequelae, or died**.**

8. The final resolution of the event should be completed on the relevant part of the original SAE form and faxed to the ICR-CTSU as soon as possible.

9. The Site SAE log should be completed and the SAE form filed in the Site Investigator File.