FAST-Forward

Randomised clinical trial testing a 1-week course of curative whole breast radiotherapy against a standard 3-week schedule in terms of local cancer control and late adverse effects in patients with early breast cancer

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The Trial Management Group (TMG) will be constituted from members of the Protocol Development Group and principal investigators from a subset of participating centres. A copy of the current membership of the TMG can be obtained from the FAST-Forward Trial Manager within ICR-CTSU.

Protocol Authorised by:

Name and Role	**Date**	**Signature**
Professor Murray Brunt (Chief Investigator)	**24/02/2017**	

This protocol describes the FAST-Forward trial and provides information about procedures for entering patients. The protocol should not be used as a guide for the treatment of other patients. Every care has been taken in the preparation of this protocol, but corrections or amendments may be necessary. These will be circulated to investigators in the trial, but centres entering patients for the first time are advised to contact ICR-CTSU to confirm they have the most recent version. Protocol amendments will be circulated to participating centres as they occur.

This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care and the principles of good clinical practice. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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1. TRIAL SUMMARY

Title	Randomised clinical trial testing a 1-week course of curative whole breast radiotherapy against a standard 3-week schedule in terms of local cancer control and late adverse effects in patients with early breast cancer.
Aim	To identify a 5-fraction schedule of curative radiotherapy delivered in 1 week that is at least as effective and safe as the UK standard 15-fraction regimen after primary surgery for early breast cancer.
Lymphatic Radiotherapy (RT) Sub-Study **(from Protocol Version 3.0)**	The lymphatic RT sub-study (from Protocol Version 3.0 08 July 2015) is an extension to the FAST-Forward trial, which maintains its original design as a phase III randomised clinical trial but whose entry is now restricted to patients prescribed radiotherapy to level I-III axilla and/or level IV axilla (supraclavicular fossa (SCF)) in addition to the breast/chest wall area.
Eligibility Criteria **(Protocol Version 4.0 onwards)**	The eligibility criteria of Fast Forward and the associated nodal sub study were amended in versions 2.0, 2.2 and 3.0 of the study protocol. The criteria below relate to protocol version 4.0 onwards. A summary of historical changes to the eligibility criteria in Versions 1.0 to 3.0 of the protocol is detailed in Appendix 6. **Inclusion criteria (all the following must be met):** • age ≥18 years • female or male • invasive carcinoma of the breast • breast conservation surgery or mastectomy (reconstruction is allowed) • complete microscopic excision of primary tumour • pT1-3 pN1-3a M0 disease) • axillary staging &/or dissection • histological involvement of axillary lymph nodes • indication for radiotherapy to level I-III axilla and/or level IV axilla (SCF) • written informed consent • able to comply with long-term follow up N.B. Concurrent anti-HER2 therapy and/or endocrine therapies are allowed **Exclusion criteria (the patient is ineligible if any of the following are met):** • ipsilateral microinvasive disease and/or non-gradeable tumours • past history of malignancy except (i) basal cell skin cancer, (ii) CIN cervix uteri or (iii) non-breast malignancy allowed if treated with curative intent and at least 5 years disease free • contralateral and/or previous ipsilateral breast cancer, including DCIS, irrespective of date of diagnosis • concurrent cytotoxic chemotherapy (sequential neoadjuvant or adjuvant cytotoxic therapy allowed as long as there is ≥ 2 weeks between therapy and radiotherapy) • any patient with N0 disease • known residual macroscopic nodal disease

	• any positive level IV (SCF) nodes • any requirement for internal mammary chain (IMC) RT* *these patients are excluded because indications for IMC RT are currently unclear.
Study Design	Prospective randomised controlled clinical trial.
Trial Treatment	Patients are randomised to 15 or 5 daily fractions (Fr) to the whole breast or post-mastectomy chest wall/reconstructed breast and from Protocol Version 3.0 to include the lymphatic region (level I-III axilla and/or level IV axilla (SCF)). A sequential tumour bed boost may be added after breast conservation surgery, but dose level (10 Gy or 16 Gy in 2.0 Gy Fr or radiobiological equivalent (from Protocol Version 4.0)) must be declared before randomisation. Each patient will be allocated to one of the following groups: **Control Group**: 40.05 Gy in 15 Fr of 2.67 Gy **Test Group 1**: 27.0 Gy in 5 Fr of 5.4 Gy **Test Group 2**: 26.0 Gy in 5 Fr of 5.2 Gy
Endpoints	**Primary endpoint:** ipsilateral local tumour control **Secondary endpoints:** early and late adverse effects in normal tissues, patient reported outcome measures of late adverse effects and quality of life, health economics, relapse free survival, disease free survival, time to distant metastases and overall survival. From Protocol Version 3.0 the following outcome measures will be collected as part of the lymphatic sub-study. Patient-reported outcomes: arm swelling, shoulder stiffness, upper limb pain, sensorimotor symptoms and arm function. Clinical-reported outcomes*:* upper limb sensorimotor symptoms.
Sample Size **(main trial)**	The sample size is 4,000 patients, with numbers balanced equally in each randomised group. This provides 80% power (1-sided $\alpha = 0.025$ to allow for 1-sided hypothesis and multiple testing) to exclude an increase of 1.6% in the 5-year local relapse rate between each test group and the control, assuming a 5-year rate of 2% in the 40.05 Gy schedule. Stratification will be by centre and risk group (high- < 50 years or grade 3 vs. low - ≥ 50 years and grade 1 or 2). For the photographic and patient reported outcome studies, 2196 patients will provide 80% power to detect an 8% difference in the prevalence of late adverse effects at 5 years between the test groups (assuming a 5-year rate of 35%). The health economics sub-study will involve the same 2196 patients in the photographic and patient reported outcome studies. Acute toxicity was monitored in the first 190 patients in the trial, to exclude a rate of RTOG grade ≥3 acute skin reactions (using a modified RTOG scoring criteria) of over 11% (89% power and 7.9% significance). A second confirmatory acute toxicity study will monitor the acute skin reactions in a further 150 patients using the CTCAE scoring criteria.
Sample size (Lymphatic RT sub-study) from Protocol Version 3.0)	The sample size is 627 patients with numbers balanced equally in each randomised group. This provides 90% power (1 sided $\alpha = 0.025$ to allow for 1-sided hypothesis and multiple testing) to exclude an arm swelling rate of 20% in *each* of the test groups compared to an assumed rate in the control group of 10%, (allowing for 10% attrition due to illness or death based on experience from the START trial). Stratification will be by centre and whether or not the patient has had a level II/III axillary clearance.

Follow Up	Assessment of acute toxicities will be collected by clinical assessments within the now closed acute toxicity sub-studies (Protocol versions 1.0-2.2). Assessment of late toxicities and recurrence by clinical assessment will be incorporated into the annual follow up visits for all patients, with data collected for 10 years from the date of randomisation.
Sub-Studies	
Lymphatic radiotherapy (RT) sub-study (from Protocol version 3.0)	Patients will be asked to participate in the lymphatic RT sub-study to show that a 5-fraction (1 week) schedule of adjuvant RT to level I-III axilla &/or level IV axilla (SCF) is non-inferior to a 15-fraction (3 weeks) standard in terms of patient reported arm swelling & function (primary endpoints of trial extension) and to contribute additional information to the aims of the main trial.
Acute Toxicity Study (in selected centres) **Protocol Versions 1.0-2.2**	One hundred and ninety patients were entered into a sub-study assessing acute toxicity in which a healthcare professional assessed acute skin reactions using a modified RTOG grading system that generated a combined score for moist desquamation and oedema. A second acute toxicity study was conducted in a further 162 patients using the CTCAE scoring criteria.
Photographic AND Patient Reported Outcome Measures (PROMS) **From Protocol Version 2.1**	Photographic sub-study: from Protocol Version 2.1 onwards all patients will be asked to take part in the optional photographic sub-study. Photographs will be taken at baseline and at 2, 5 and 10 years post randomisation in centres with photographic facilities. Patients may decline participation in the photographic sub-study and still take part in the trial. Patient Reported Outcome Measures (PROMS): from Protocol Versions 2.1-2.2 patients will be asked to take part in an optional PROMS sub-study and complete self-assessments of radiotherapy adverse effects and other PROMS at baseline, 3 and 6 months after radiotherapy and 1, 2, 5 and 10 years from randomisation. PROMS will be assessed using the EORTC QLQ-C30 v3.0, the EORTC BR23 breast cancer module, the Body Image Scale (BIS), post-radiotherapy questions and the EORTC FA-13 fatigue module. From Protocol Version 3.0 the PROMS assessments will be mandatory and will include the assessments detailed above in addition to arm swelling, shoulder stiffness, upper limb pain, sensorimotor symptoms and arm function.
Health Economics (all PROMS patients)	Health Economics (HE) will be assessed using the EQ-5D-5L questionnaire and additional health resource use questions completed at baseline, 3 and 6 months post treatment and 1, 2, 5 and 10 years post randomisation. The HE questions will be administered in the PROMS booklets
Translational Studies **(in all centres)**	All patients will be asked to consent to donate a single blood sample and complete a family history questionnaire. This can be collected at any point during the trial. All patients will be asked to consent to the donation of a tissue sample from their original tumour. They will also be asked to consent to the donation of a tissue sample should a recurrence occur.

2. BACKGROUND

The international standard regimen for whole breast radiotherapy delivers a total dose of 50 Gy in 25 fractions (daily doses) over 5 weeks following surgical resection of primary tumour in women with early breast cancer. Attempts to reduce the number of fractions in the 1970s made inadequate downward adjustments to total dose, resulting in unacceptable rates of late complications [1]. These miscalculations inhibited further research in breast radiotherapy fractionation for decades, but interest in fewer larger fractions delivered over a shorter overall treatment time has been rekindled by randomised clinical trials based on a better understanding of normal tissue and tumour responses. Four randomised trials involving a total of >8000 women have compared a lower total dose in fewer larger fractions against 50 Gy in 25 fractions, and all have reported favourable results in terms of local tumour control and late adverse effects [2-6].

The Royal Marsden Hospital/Gloucestershire Oncology Centre and Ontario trials totalling 2644 women with mainly axillary node negative tumours < 5 cm diameter were the subject of a 2008 Cochrane review of altered radiotherapy fractionation in early breast cancer [7]. Radiotherapy fractions larger than 2.0 Gy did not appear to affect: a) local-recurrence free survival (absolute difference 0.4%, 95% CI -1.5% to 2.4%), b) breast appearance (risk ratio (RR) 1.01, 95% CI 0.88 to 1.17; p = 0.86), c) survival at five years (RR 0.97, 95% CI 0.78 to 1.19; p = 0.75), d) late skin toxicity at five years (RR 0.99, 95% CI 0.44 to 2.22; p = 0.98, or e) late radiation toxicity in subcutaneous tissue (RR 1.0, 95% CI 0.78 to 1.28; p = 0.99). The review concluded that the use of unconventional fractionation regimens did not affect breast appearance or toxicity, nor appear to affect local cancer relapse. The results of the UK START trials (N = 4451) were published too late to be included in the overview, but were consistent with the findings. The UK START A trial (N=2236) showed that the estimated absolute differences in 5-year local-regional relapse rates compared with the control schedule of 50 Gy in 2.0 Gy fractions were 0.2% (95% CI -1.3% to 2.6%) after 41.6 Gy and 0.9% (95% CI -0.8% to 3.7%) after 39 Gy. In START A, photographic and patient self-assessments suggested lower rates of late adverse effects after 39 Gy than with 50 Gy, with a hazard ratio for late change in photographic breast appearance of 0.69 (95% CI 0.52 to 0.91, p=0.01). In the UK START B trial (N = 2215) the estimated absolute difference in 5-year local-regional relapse rates for 40.05 Gy compared with 50 Gy was -0.7% (95% CI -1.7% to 0.9%), and the hazard ratio for late change in photographic breast appearance was 0.83 (95% CI 0.66 to 1.04). i.e. the START trials reported similar local tumour control with some evidence of lower rates of late adverse effects

after schedules with fraction sizes larger than 2.0 Gy compared with the international standard 25-fraction regimen [6].

A 15-fraction schedule is now the UK standard recommended by the National Institute for Health and Clinical Excellence (NICE), but it is unlikely to represent the useful limits of hypofractionation for whole breast radiotherapy. There is a history of prescribing once-weekly fractions of whole breast radiotherapy for women too frail or otherwise unable to attend for conventional schedules. In a French series of 115 patients undergoing primary radiotherapy without surgery for non-metastatic breast cancer from 1987 to 1999, the whole breast was treated with 2 tangential fields and received 5 once-weekly fractions of 6.5 Gy [8]. 101 were given additional tumour bed boost doses, 7 with 1 fraction, 69 with 2 fractions and 25 with 3 once-weekly fractions of 6.5 Gy using electrons. Kaplan-Meier estimates of late effects in the breast were 24% grade 1, 21% grade 2 and 6% grade 3 at 48 months. The 5-year local progression-free rate was 78% (95% CI: 66.6-88.4). In a separate French series, 5 once-weekly fractions of 6.5 Gy to the whole breast with no boost were given to 50 women after local tumour excision [9]. Grade 1 or 2 induration was reported in 33% of the patients at a median follow up of 93 months (range 9-140). The 7-year local relapse free survival was 91%. Five fractions of 6.5 Gy are equivalent to 62 Gy in 31 fractions assuming α/β = 3.0 Gy, a significantly higher dose intensity than conventional schedules deliver.

The UK FAST Trial (N = 915) tested two dose levels of a 5-fraction regimen delivering 1 fraction per week against a control schedule of 50 Gy in 25 fractions, defining radiotherapy adverse effects as the primary endpoint [10]. The two test dose levels delivered 5 fractions of 5.7 Gy or 6.0 Gy (total dose 28.5 Gy or 30 Gy), estimated to be iso-effective with the control regimen assuming α/β values of 3.0 Gy or 4.0 Gy, respectively. 915 patients were recruited from October 2004 - March 2007. Mean age was 62.7 years. Only 17 patients (5.2%) developed moist desquamation (12 after 50 Gy, 3 after 30 Gy, 2 after 28.5 Gy) out of 327 with RTOG skin toxicity data available. At a median follow up of 28.3 months (IQR 24.1-33.6), 729 patients had 2-year photographic assessments available, with mild and marked change in breast appearance in 19.3% and 1.7% after 50 Gy, 26.2% and 9.3% after 30 Gy, and 20.3% and 3.7% after 28.5 Gy. Risk ratios for mild and marked change for 30 Gy vs. 50 Gy were 1.48 (95%CI 1.06 -2.05) and 6.06 (2.14 -17.20), $p<0.001$ for trend, favouring 50 Gy; and for 28.5 Gy vs. 50 Gy were 1.07 (0.75 -1.54) and 2.25 (0.70 -7.18), $p=0.26$ for trend, favouring 50 Gy. Any clinically-assessed moderate/marked adverse effects in the breast were increased for 30 Gy compared with 50 Gy (hazard ratio, HR 2.19,

95%CI 1.46 - 3.29, p<0.001), but similar for 28.5 Gy (HR 1.33, 95%CI 0.86 -2.08, p=0.19). At a median follow-up of 37.3 months 2 local tumour relapses had been recorded.

A gain in local tumour control due to shortening treatment time to 1 week is possible. Evidence based on retrospective studies for an influence of treatment time on local tumour control is conflicting with recent systematic reviews drawing different conclusions [11, 12]. Even without a gain in tumour control, accelerated radiotherapy is likely to be more convenient for patients, and may ease scheduling with other treatment modalities. A pilot study (N = 30) tested 30 Gy in 5 fractions of 6.0 Gy in 15 days to the whole breast in terms of acute adverse effects and late effects at 2 years [13]. In this series, 23/30 (77%) patients scored no change in post-operative breast appearance at 2 years, 7/30 (23%) scored mild change and none scored marked change. The acute skin reactions were mild, with no reaction more severe than grade 2 erythema, scored in 9/30 (27%) patients. If the results of the proposed randomised trial support a 5-fraction schedule delivered in 1 week, these will transform international breast radiotherapy practices. In conclusion, it is fair to say that after decades of resistance to evaluating larger radiotherapy fraction sizes in breast cancer, expert opinion is responding to an accumulating body of evidence supporting the safety and effectiveness of this approach.

Against this background, a phase III randomised trial is described with the primary aim of testing local tumour control in women with early breast cancer following a 5-fraction schedule of adjuvant radiotherapy delivered in 1 week. Stratification by treatment centre and by local relapse risk will ensure balanced trial groups (high risk defined as patient age <50 and/or grade 3 tumour; low risk defined as age ≥50 and grade 1 or 2 tumour) [14]. From Version 2 of the protocol (13th Feb 2013) the population of patients with a very low risk of local relapse after breast conservation surgery comprising those aged at least 65 with pT1 G1/2 ER+ HER2- pN0 M0 invasive carcinomas are excluded from the trial following updated analyses by the Early Breast Cancer Collaborative Group [15].

Addition of lymphatic radiotherapy to whole breast/chest wall radiotherapy (from Protocol Version 3.0)

This sub-study to the main trial will test the safety of 5-fraction regimens in the context of lymphatic RT. The model of breast cancer spread dominant in earlier decades envisaged a limited role for regional therapy beyond protection of quality of life, typically secured by surgery. Systematic overviews of RT effects by the Early Breast Cancer

Trialists Collaborative Group (EBCTG) provides level 1A evidence that prevention of local-regional relapse has a major impact on breast cancer mortality [16,17]. An important conclusion to be drawn is that even heavily node-positive axillary patients can be cured by effective local-regional treatment, whether this is achieved by surgery, radiotherapy or systemic therapy [16].The traditional model of breast cancer spread still has some adherents. The Z11 trial, randomised 891 out of a planned 1900 patients with clinically node negative, sentinel node positive disease to axillary clearance versus no further axillary treatment [18, 19]. Twenty seven percent allocated axillary clearance had additional positive nodes. The axillary recurrence rate at 5 years was 0.5% after axillary clearance and 0.9% after no axillary clearance, and there was no difference in breast cancer mortality. For some, this result reinforces the traditional model of breast cancer spread that discounts a role of nodal metastases in determining cancer spread. This interpretation fails to take account that standard post-operative tangential beam RT includes at least lower axillary nodes and may be needed to eradicate residual disease. The same issue has been raised in discussion of the IBCSG 23-01 trial testing axillary dissection vs no further axillary surgery in 929 sentinel node positive patients, 91% of whom were treated by breast conservation followed by whole breast radiotherapy [20]. Disease-free survival events, including axillary recurrences, were non-inferior in the group spared axillary dissection, where standard whole breast radiotherapy will have included at least level I axillary nodes. Although this remains a contested area, there is a wide consensus that control of axillary disease, whether by surgery, systemic therapy or radiotherapy, is an important component of curative therapy.

The recently reported AMAROS trial is informative in determining the role of surgery or radiotherapy for axillary management [21]. The study randomised 1425 patients with positive sentinel nodes to either axillary node dissection in 744 patients or axillary radiotherapy including photon beams to axillary apex and medial supraclavicular fossa (SCF) in 681 patients. Axillary recurrence rates were low in both groups; 1.19% after radiotherapy and 0.43% after surgery, too low to test non-inferiority. The main difference is that clinically reported arm swelling was less of a problem after RT than after surgery; 13.6% vs 28.0%, respectively, at 5 years; $p<0.0001$. The implication is that lymphatic radiotherapy may increasingly be used as an alternative to surgery in this context. Very little internal mammary chain (IMC) RT has been given in the UK in recent decades, but a modest reduction in breast cancer mortality is suggested by the NCIC MA20 trial and confirmed by the EORTC 229922 trial [22, 23]. Both tested IMC/SCF RT, so it is possible that therapeutic effects are attributable solely to the SCF

component. This does not seem likely since, if SCF RT is needed in order to enhance cure of patients with positive IMC nodes, it is reasonable to assume that the latter require managing too. The same argument might apply to the infraclavicular (ICF) nodes (level III axilla), which are usually included in unshielded (rectangular) fields to the SCF. In the EORTC trial, 4004 patients with axillary node positive disease or central/medial tumours with axillary node negative were randomised to receive IMC/medial SCF RT or not. At a median of 10.9 years follow up, the primary endpoint of overall survival improved from 80.75% to 82.3% with the addition of IMC/SCF RT (HR=0.87; CI 0.76-1.00; p=0.0556; p=0.0496 after adjustment). It is not currently clear how these results will impact on practice. In conclusion, there is a need to test the safety of a 5-fraction schedule of lymphatic RT if the FAST-Forward Trial is to remain relevant to the 25% of patients referred for treatment with node positive disease. Whereas most are currently referred following axillary dissection, international and UK practices are changing, and more patients are likely to be referred in future for RT to axillary, SCF/ICF and perhaps IMC lymph node groups. When hypofractionation for breast cancer was first introduced in the 1960s, inappropriate dose regimens and uncertain dosimetry combined to cause unacceptably high rates of brachial plexopathy in patients with early breast cancer [24-36]. Even with hindsight, it is difficult to be sure how much of the morbidity was related to technical factors, especially beam overlap, and how much to dose-time factors. The only series describing brachial plexopathy after total dose ≤50 Gy delivered in 1.8-2.0 Gy fractions to breast and axilla/SCF reported 3/724 (0.6%) affected patients treated between 1968-85, of whom 2 resolved and 1 progressed at 6.5 years median follow up [36]. All patients were treated at the Joint Center, Boston, in a supine treatment position using a 3-field technique with hanging block. A review of all published evidence available in 2005, suggested that brachial plexopathy after local-regional radiotherapy for early breast cancer is uncommon (<1%) at doses <55 Gy in 2.0 Gy equivalents [37]. Dose regimens were normalised using a linear quadratic model, assuming α/β value of 2.0 Gy, see Figure 1.

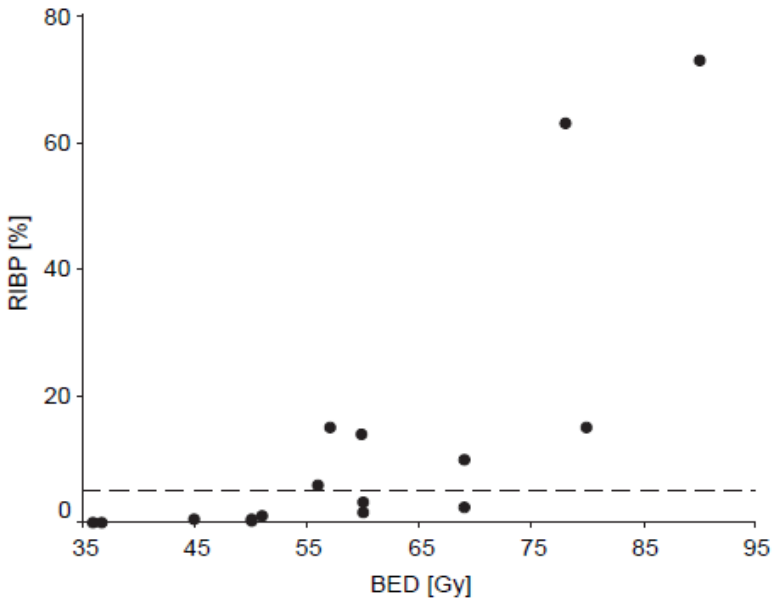


Figure 1: Relationship between incidence of radiation-induced brachial plexopathy and biological equivalent total dose, assuming α/β value=2.0 Gy. The values represent total doses as if delivered in 2.0 Gy fractions [37].

The dose-response relationships are not difficult to reconcile with current practices in head and neck cancer, where total doses of 60 Gy in 30 fractions are standard. One recent example modelled the relationship between total dose in 2.0 Gy fractions and probability of brachial plexopathy in 330 patients systematically screened for evidence of sensorimotor symptoms a median of 56 months (range 6-135) after radical RT for head and neck cancer. Patients treated with definitive RT received a median dose of 70 Gy, and for those treated post-operatively the median dose was 60 Gy. IMRT was used on 62% cases, and 40% had concurrent chemotherapy, usually cisplatin. The brachial plexus was outlined using RTOG criteria on x-ray CT scans [38]. The modelled dose response relationships are shown in Figure 2.

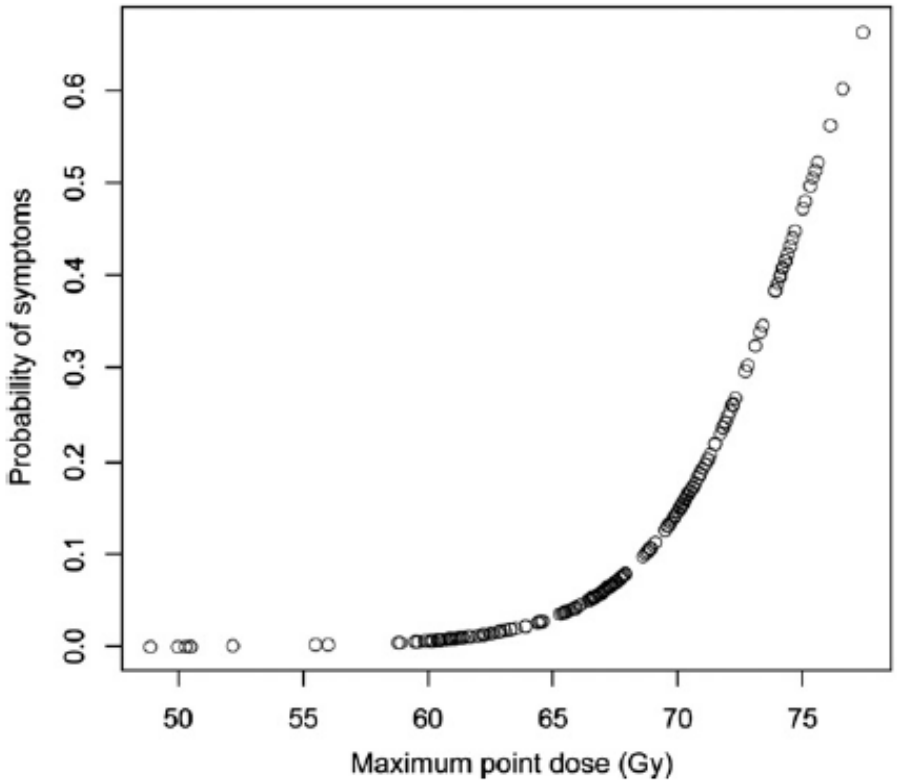


Figure 2: Relationship between probability of developing neuropathic symptoms and maximum brachial plexus radiation point dose (Gy)

Against this background, the FAST-Forward Trial will be extended beyond its target accrual in order to test the safety of hypofractionated lymphatic RT. It is realistic to test only the common dose-limiting adverse effects, including arm swelling and overall arm function. Very uncommon adverse effects, including brachial plexopathy, cannot be formally tested in such a protocol, since a non-inferiority trial wishing to exclude an excess 1% risk with standard statistical power would require tens of thousands of patients. From Protocol Version 3.0 entry into the trial will be restricted to patients who are prescribed radiotherapy to the level I-III axilla and/or level IV axilla (SCF) in addition to the breast/chest wall.

3. AIM

Main Study: to identify a 5-fraction schedule of curative radiotherapy delivered in once-daily fractions, that is at least as effective and safe as the current UK standard 15-fraction regimen after primary surgery for early breast cancer, in terms of local tumour control, adverse effects, patient reported outcome measures (PROMS) and health economic (HE) consequences**.**

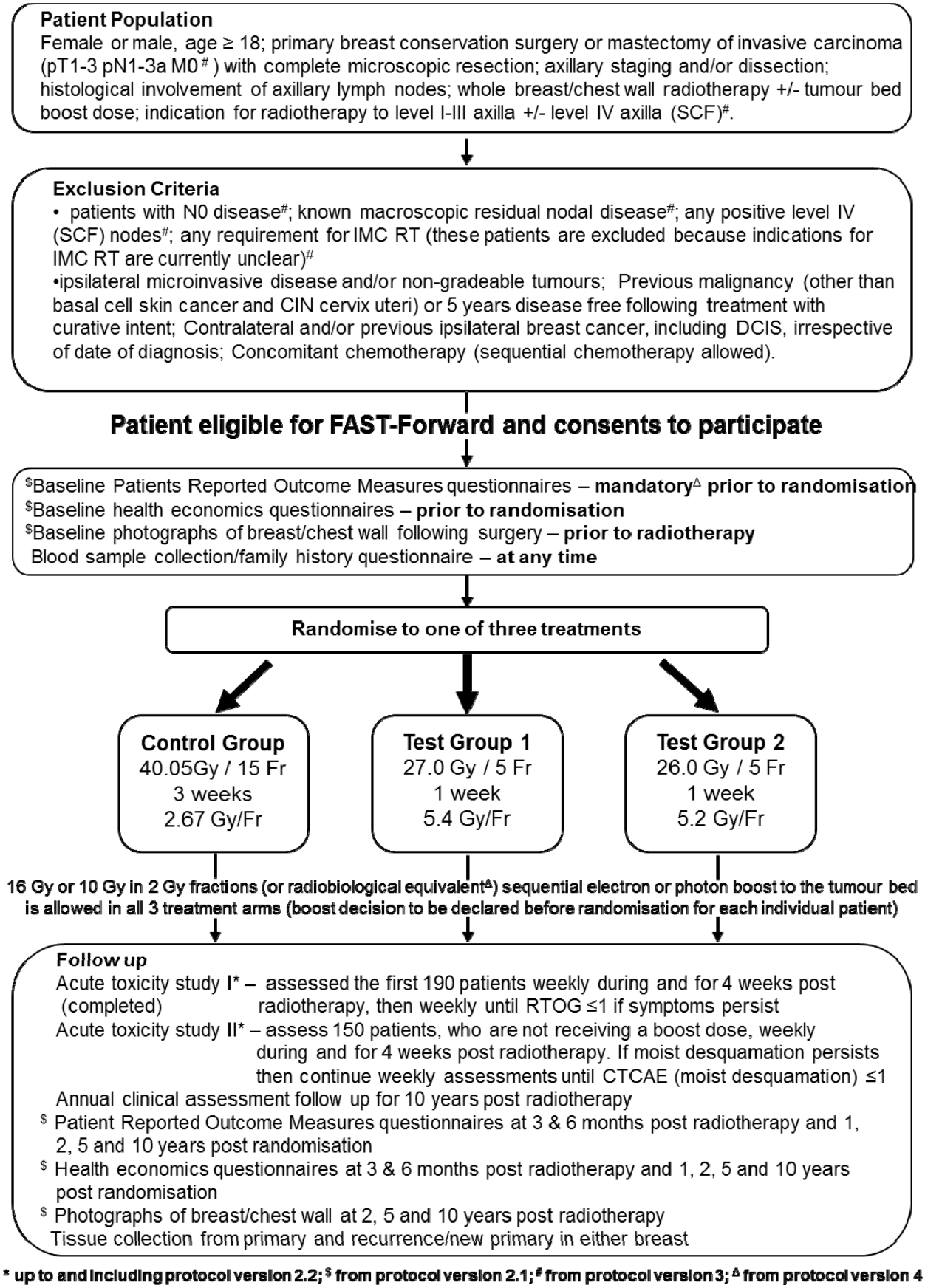
Lymphatic RT sub-study (from Protocol Version 3.0): to show that a 5-fraction (1 week) schedule of adjuvant RT to level I-III axilla and/or level IV axilla (SCF) is non-inferior to a

15-fraction (3 weeks) standard in terms of patient reported arm swelling & function and to contribute additional information to the endpoints of the main trial.

4. TRIAL DESIGN

FAST-Forward is a multicentre phase III randomised controlled trial. Following the implementation of the lymphatic sub-study, from Protocol Version 3.0, 627 patients will be randomised 1:1:1 between the control group and two test groups. In addition to contributing to the main analysis of the primary endpoint (tumour control), this cohort of patients will form the lymphatic sub-study with distinct objectives and analyses.

4.1 FAST-Forward Trial Schema



*** up to and including protocol version 2.2; $ from protocol version 2.1; # from protocol version 3; Δ from protocol version 4**

5. ENDPOINTS

5.1 Primary Endpoint

- Ipsilateral local tumour control.

5.2 Secondary Endpoints

- Acute adverse effects
- Late adverse effects in normal tissues assessed by physicians and patients and from photographs
- Late adverse effects on quality of life assessed by patient reported outcome measures
- Health economics
- Contralateral primary tumours
- Relapse free survival
- Disease free survival
- Time to distant metastases
- Overall survival

Lymphatic RT sub-study

From Protocol Version 3.0 the following outcome measures will also be collected:

Patient-reported outcomes:

- arm swelling
- shoulder stiffness
- upper limb pain
- sensorimotor symptoms
- arm function

Clinical-reported outcomes:

- upper limb sensorimotor symptoms

6. PATIENT SELECTION AND ELIGIBILITY

6.1 Patient Selection

Women and men with complete microscopic resection of early invasive breast cancer following breast conservation surgery or mastectomy for whom local radiotherapy is

recommended (patients undergoing reconstruction are eligible provided the port of a tissue expander is positioned outside the breast).

From Protocol Version 3.0 patients must have an additional requirement for lymphatic RT. Typical examples of indications for lymphatic RT include the following:

• Patients with positive lymph nodes removed by axillary clearance who require RT to level I-III axilla and/or level IV axilla (SCF).

• Patients with sentinel node positive axillary disease not proceeding to axillary dissection and who require RT to level I-III axilla and/or level IV axilla (SCF).

• Patients treated by pre-operative systemic therapy who are recommended post-operative RT to level I-III axilla and/or level IV axilla (SCF).

6.2 Number of Patients

6.2.1 Main study

A total of 4000 patients will be recruited. The proportions of patients accrued in subgroups defined by risk of local recurrence will be monitored during the trial, to ensure reasonable representation of low risk (age ≥50 and grades 1 or 2) and high risk (age <50 and/or grade 3). From Version 2 of the protocol (13 Feb 2013) the population of patients with a very low risk of local relapse after breast conservation surgery comprising those age 65 and over with pT1 G1/2 ER+ HER2- pN0 M0 invasive carcinomas are excluded from the trial following updated analyses by the Early Breast Cancer Collaborative Group [15].

6.2.2 Lymphatic sub-study (from Protocol Version 3.0)

627 patients prescribed radiotherapy to level I-III axilla and/or level IV axilla (SCF) in addition to the breast/chest wall will be recruited into the lymphatic RT sub-study.

6.3 Inclusion Criteria

The eligibility criteria of Fast Forward and the associated nodal sub study were amended in versions 2.0, 2.2 and 3.0 of the study protocol. The criteria below relate to protocol version 4.0 onwards. A summary of historical changes to the eligibility criteria in Versions 1.0 to 3.0 of the protocol is detailed in Appendix 6.

To be eligible, all of the following inclusion criteria must be met:

- age ≥18 years
- female or male
- invasive carcinoma of the breast
- breast conservation surgery or mastectomy (reconstruction is allowed)

- complete microscopic excision of primary tumour
- axillary staging &/or dissection
- pT1-3 pN1-3a M0 disease
- histological involvement of axillary lymph nodes
- indication for radiotherapy to level I-III axilla and/or level IV axilla (SCF)
- written informed consent
- able to comply with follow up

N.B. concurrent anti-HER2 therapy and/or endocrine therapies are allowed

6.4 Exclusion Criteria

The patient is ineligible if any one of the following exclusion criteria is met:

- ipsilateral microinvasive disease and/or non-gradeable tumours
- past history of malignancy except (i) basal cell skin cancer, (ii) CIN cervix uteri or (iii) non-breast malignancy allowed if treated with curative intent and at least 5 years disease free
- contralateral and/or previous ipsilateral breast cancer, including DCIS, irrespective of date of diagnosis
- concurrent cytotoxic chemotherapy (sequential neoadjuvant or adjuvant cytotoxic therapy allowed as long as there is ≥ 2 weeks between therapy and radiotherapy)
- patients with N0 disease
- known residual macroscopic nodal disease
- any positive level IV (SCF) nodes
- requirement for IMC RT*

*excluded because indications for internal mammary chain RT are currently unclear

7. RANDOMISATION

7.1 Randomisation Procedure

An eligibility checklist must be completed and patient consent obtained prior to randomisation.

To randomise a patient, the appropriate centre staff should telephone the ICR-CTSU randomisation line (see below).

Randomisation telephone: 020 8643 7150

Office Hours: 09:00 – 17:00 Monday-Friday

The following information will be required at randomisation:

- name of centre, consultant and person randomising the patient
- patient's full name, hospital number, date of birth, post code and NHS number
- confirmation that an eligibility checklist has been completed and written informed consent has been obtained
- whether the patient has consented to
    - the lymphatic radiotherapy sub-study (from Protocol Version 3.0)
    - photographic assessments
    - blood sample donation and family history questionnaire completion
    - tissue sample donation
    - the use of information held by the NHS and national databases.
- whether a boost is to be given and the dose level

From Protocol Version 3.0 the centres will also be asked the additional questions:

- whether a level II/III axillary clearance has been performed

The caller will be given the patient's unique randomisation number (Trial ID) and the treatment allocation. The Trial ID together with the patient's initials, date of birth and hospital number should be used on all Case Report Forms (CRFs).

7.2 Treatment allocation

Treatment allocation will be 1:1:1 and will use computer-generated random permuted blocks.

Up to and including Protocol Version 2.2 randomisation was stratified by centre and risk group.

From Protocol Version 3.0 randomisation will be stratified by centre and whether the patient has had a level II/III axillary clearance.

A fax will be sent to the randomising centre to confirm the trial number and treatment allocation.

8. TRIAL EVALUATIONS

8.1 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. Patients will have annual clinical assessments for 10 years and annual mammograms for 5 years or until screening age if younger (as per NICE guidelines).

8.2 Treatment-related Endpoints

8.2.1 Early adverse effects (only in centres taking part in the acute toxicity sub-studies, Protocol Versions 1.0-2.2)

Early adverse effects will be assessed in two acute toxicity studies (now closed).

Acute toxicity study I (Protocol Version 1.0 only)

190 patients were entered into a sub-study between November 2011 and April 2012 in order to assess the acute reactions of the skin of the treated breast. This sub- study used a modified RTOG scale (Appendix 1) in which effects for oedema and desquamation were reported in a combined outcome scale. The assessments were carried out weekly during treatment and for 4 weeks following the end of radiotherapy by a health care professional at each centre. Assessments were to continue weekly until any reaction was modified RTOG grade 1 or less.

In addition, patients were asked to report their own acute toxicity of breast radiotherapy (breast soreness, reddening, swelling and blistering) by completing a diary card weekly during treatment and for 4 weeks after the end of radiotherapy. The scores were recorded as “none”, “a little”, “quite a bit” or “very much”. If symptoms persisted then patients were asked to continue scoring their adverse effects on a weekly basis until all scores were graded as “none” or “a little”.

This sub-study was completed in summer 2012 with a review of the data by the Independent Data Monitoring Committee (IDMC) and Trial Steering Committee (TSC). The review highlighted that the data had been collected using a modified RTOG scoring criteria that had not allowed the prospective differentiation between moist desquamation and moderate oedema for those classified with a “grade 3” acute skin reaction and recognised the need to differentiate between these two reactions due to their differential potential to be dose-limiting. Furthermore, the adherence to the intensive weekly follow-up schedule was not as complete as expected with assessments missed both during and after treatment for some patients.

Acute toxicity study II (Protocol Versions 2.1 and 2.2)

The IDMC/TSC requested that a second sub-study be conducted using the CTCAE v4.03 scoring criteria which separately records incidences of moist desquamation and oedema.

The acute toxicity sub-study II was conducted in a subset of centres which have the infrastructure necessary to carry out the weekly toxicity assessments. 162 patients were recruited into the acute toxicity sub-study II which was carried out between April 2013 and January 2014 in the same subset of centres that participated in the first acute toxicity study with the addition of Torbay Hospital.

The acute reactions of the skin of the treated breast were graded for erythema and moist desquamation using standard CTCAE criteria (Appendix 1), and assessed by a healthcare professional at each centre. The assessments were carried out weekly during treatment and for 4 weeks following the end of radiotherapy. If moist desquamation outside skin folds or creases was seen during this time then weekly assessments continued until the reaction has resolved to CTCAE grade 1 or less. If any assessment was missed then the centre was asked to contact the patient by telephone to ascertain the reason for the missed assessment and ask about any acute skin reactions. Patients receiving a boost were excluded from acute toxicity sub-study II, since the objective of this sub-study was to quantify the toxicity of 5-fraction schedules relative to control, effects that are independent and additive to those of the boost.

8.2.2 Late adverse effects (all patients)

The late adverse effects include a range of symptoms and signs, including breast swelling and/or oedema, breast shrinkage, hardness, telangiectasia, pigmentation, skin atrophy, subcutaneous fat necrosis, skin necrosis, pain and tenderness, cardiac injury and lung fibrosis. Late adverse effects will be measured in all patients at the annual clinical assessment and in a subset of patients using photographic assessments and patient-reported outcome measures (PROMS) questionnaires.

From Protocol Version 3.0 all patients recruited into the lymphatic RT sub-study will have both physician and patient reported assessments.

Clinical assessments of late adverse effects (for all patients)

At annual visits for 10 years (from date of randomisation into study) physicians will record the development of breast shrinkage/distortion (including reconstructed breasts), breast induration (outside and inside tumour boost volume), breast pain and breast oedema (for patients receiving radiotherapy following breast conserving surgery) and telangiectasia (tumour boost site only), shoulder stiffness (compared with other side), ischaemic heart disease, rib fracture, costochondritis, symptomatic lung fibrosis, persistent cough and any other severe late event, including any specialist referral for investigation or management of late toxicity.

From Protocol Version 3.0 physicians will also record any indication of upper limb sensorimotor symptoms. A minority of patients are expected to experience these symptoms which will require further investigation and will be reported on CRFs. The symptoms are most commonly due to other causes such as taxane-induced neuropathy, carpal tunnel syndrome induced by aromatase inhibitors, sensory loss and pain secondary to axillary dissection and features of malignant brachial plexopathy. Distinguishing these relatively common diagnoses from very rare cases of radiation-induced nerve damage will be imperative. All such cases of nerve damage and likely aetiology will be recorded. Patients developing sensorimotor symptoms and signs will be investigated using a series of investigations including clinical assessment, MR imaging, nerve conduction studies and neurological referral as appropriate.

Photographic and PROMS assessments of late adverse effects (in the same patients)

Photographic assessments

From Protocol Version 2.1 patients will be asked to take part in the optional photographic sub-study. Digital photographs will be taken at baseline (post-surgery but pre-RT) and at years 2, 5 and 10 after randomisation. 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 coded and stored on a CD to be kept in a secure location. Periodically all CDs will be collected by ICR-CTSU and the images assessed blind by a select group of observers and/or using computer software adapted for the purpose. Change in breast/reconstructed breast/chest wall appearance and distortion compared with the post-surgical baseline will each be scored on a graded scale. Breast size and surgical deficit will each be assessed from the baseline photographs. Reliability and repeatability of the assessments will be verified. The feasibility of and procedures for this scoring mechanism have been established for breast conserving surgery patients in the START trial [39] and assessments for FAST-Forward will build on these existing methods, including validating the method in chest wall patients.

PROMS assessments

From Protocol Version 2.1 patients were asked to take part in an optional PROMS sub-study and to complete self-assessments of radiotherapy adverse effects and other PROMS at baseline, 3 and 6 months after radiotherapy and 1, 2, 5 and 10 years from randomisation. These included the EORTC QLQ-C30 core questionnaire [40], the EORTC BR-23 Breast Cancer module [41], the Body Image Scale [42], the EORTC FA-13 questionnaire [43] and a number of protocol-specific items relating to radiotherapy adverse effects as used in the START and IMPORT trials [44]. Of particular interest is patient self-reporting of symptoms and impact on body image and functioning subscales. The aim is to seek a patient-derived notion of 'radiation tolerance' that can be compared with physician and photographic endpoints, including interpolated estimates of isoeffect.

From Protocol Version 3.0 the PROMS assessments will be mandatory and will include the assessments detailed above in addition to arm swelling, shoulder stiffness, upper limb pain, sensorimotor symptoms and arm function.

9. FOLLOW-UP

After treatment clinical follow up should follow local guidelines, but should include annual visits from date of randomisation.

For the purpose of the study, assessment of acute toxicities will only be performed in the patients consenting to the two acute toxicity sub-studies (see section 8.2.1.).

Assessments of late toxicities using photographs and PROMS will be performed in patients consenting to these sub-studies only (according to the schedule outlined in section 8.2.2.).

Assessment of late toxicities and recurrence by clinical assessment will be incorporated into the annual follow up visits for all patients, with data collected for 10 years from the date of randomisation.

9.1 Withdrawal of Patients from Study Treatment and follow up

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 outcome data will be on the basis of intention to treat. As this is a non-inferiority trial if there is high non-compliance with the test

treatment groups then an analysis of only those compliant with the protocol will also be conducted.

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. If a patient withdraws consent for further follow-up and for PROMS data to be collected, the appropriate form in the CRF should be completed and returned to ICR-CTSU. In the extremely unlikely event that the patient wishes to have their data removed from the trial completely the implications of this should be discussed with the patient to ensure that this is their intent and this should be recorded on the withdrawal of consent CRF. The extent of patient withdrawal should be discussed between the patient and a senior member of the local research team to ensure that the patient understands the extent of withdrawal i.e. from treatment, follow up or consent for the trial. Any request for withdrawal of consent for use of data cannot be applied retrospectively once the trial results have already been published.

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 only data that is routinely collected i.e. disease status, vital status, cause of death will be used on behalf of the trial. Any samples already donated, i.e. 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.

9.2. Schedule of assessments

				Treatment			Follow up (all taken from date of randomisation except where shown)												
Event		Prior to randomisation	Post randomisation pre RT	wk 1	wk 2	wk 3	weekly for 4 weeks post RT	mth 3 Post RT	mth 6 Post RT	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[1]	x[1]													
Radiotherapy verification				**Up to daily during treatment**															
Serious Adverse Event (if applicable)				x	x	x	x	x											
Acute toxicity assessments[#]	Study I (first 190 patients)		x	x	x[1]	x[1]	*												
	Study II (150 patients, no boost)		x	x	x[1]	x[1]	*												
Follow up - annual clinical assessment (all patients)										x	x	x	x	x	x	x	x	x	x
Sub studies																			
PROMS [2]		x (baseline*)						x	x	x	x			x					x
Photographic assessment [2]			x								x			x					x
Health economics - annual		x (baseline*)						x	x	x	x	x	x	x	x	x	x	x	x
Lymphatic radiotherapy including PROMS[3]		x (baseline*)						x	x	x	x	x	x	x	x	x	x	x	x
Blood sample collection and family history questionnaire			**At any time during the trial, ideally by the end of RT**																
CT scan if recurrence				**At the time of recurrence**															
Tissue collection - 1° tumour - recurrence/new 1° tumour			**As requested during the trial**																

[#] up to and including Protocol version 2.2; *Follow up booklets will be sent by post from the ICR-CTSU office; [1] Control group only; CRFs to be completed throughout the trial as indicated in the Trial Guidance Notes; [2] PROMS and photographic assessments are to be offered to the same set of patients; [3] from Procotol version 3 (date)

10. RADIOTHERAPY

Patients are randomised to 15 or 5 daily fractions to the whole breast or post-mastectomy chest wall. From Protocol Version 3.0 patients in the lymphatic RT sub-study also receive treatment, with the same fractionation to the axilla (at least one of levels I/II/III/IV). A sequential tumour bed boost may be added after breast conservation surgery, but dose level (10.0 Gy or 16.0 Gy in 2.0 Gy fractions or radiobiological equivalent (from Protocol Version 4.0)) must be declared before randomisation. Each patient will be allocated to one of the following groups:

Control Group: 40.05 Gy in 15 fractions of 2.67 Gy
Test Group 1: 27.0 Gy in 5 fractions of 5.4 Gy
Test Group 2: 26.0 Gy in 5 fractions of 5.2 Gy

10.1 Dose Prescriptions

10.1.1 Whole breast/chest wall, level I-III axilla and/or level IV axilla (SCF)

Trial group	Total dose (Gy)	Dose per fraction (Gy)	Number of fractions	Fractions per week	Treatment time (weeks)
Control Group	40.05	2.67	15	5	3
[#]Test Group 1	27.0	5.4	5	5	1
[#]Test Group 2	26.0	5.2	5	5	1

[#] Justification for choice of these regimens is found in Appendix 2

10.1.2 Tumour bed boost

If a tumour bed boost dose is recommended, this needs to be declared before randomisation for each patient, together with the dose to be used. The dose prescription can be 10.0 Gy in 5 fractions, 16.0 Gy in 8 fractions or a radiobiological equivalent (from Protocol Version 4.0) to the 100% isodose, treating once-daily, and the boost must follow whole breast radiotherapy without a break. A boost is suggested for all patients under 40 years and for patients aged 40-49 years with either grade 3 tumours and/or lymphovascular invasion. A boost is also suggested for patients aged 50-59 years with one or more adverse prognostic factor, such as grade 3 tumours or lymphovascular invasion. There are no suggested indications for a boost in patients aged ≥60 years. No bolus should be used for boosts.

11. RADIOTHERAPY TARGET VOLUMES, LOCALISATION AND OUTLINING

11.1 Target Volume Definition

Whole Breast Clinical Target Volume (WBCTV)

This is based on the recommendations in the START trial protocol [45]. The CTV includes the soft tissues of the whole breast from 5 mm below the skin surface down to the deep fascia, excluding muscle and underlying rib cage.

Chest Wall Clinical Target Volume (CWCTV)

The clinical target volume encompasses the skin flaps and includes the soft tissues down to the deep fascia, excluding the underlying muscle and rib cage.

Lymph Node Clinical Target Volumes (LN CTVs from Protocol Version 3.0)

The lymph node clinical target volumes (LN CTVs) include the supraclavicular nodes (level IV axilla) and/or the axillary chain. The axillary chain can be treated in its entirety or only the levels specified by the clinician. Detailed guidelines on the outlining of the LN CTV volumes are given in the FAST-Forward planning pack.

Tumour bed

Delineation of the tumour bed is recommended for all patients who had breast conserving surgery as this facilitates appropriate placement of the tangential breast field to maximise target coverage whilst and minimising dose to organs at risk (OAR). Examples are shown in the planning pack.

To assist the delineation, it is strongly advised that titanium clips or gold seeds are implanted into the walls of the tumour excision cavity (tumour bed) at the time of breast conserving surgery as per British Association of Surgical Oncology (BASO) guidelines [46]. The tumour bed may be localised if there is a well-defined seroma in the absence of implanted markers. Either of these localisation methods will be necessary if the boost radiotherapy is to be delivered with a conformal photon plan.

Planning Target Volumes (PTV)

A margin should be added to whole breast/chest wall, lymph node and tumour cavity CTV, taking into account set-up error, breast swelling and breathing; a typical PTV margin is 10 mm for all PTV volumes, however for the level IV axilla (SCF) PTV a maximum of 5 mm margin should be applied medially in order to limit the dose to midline structures. Limited or no expansion may be applied inferiorly depending on the

position of the superior border of the tangential fields. A field-based PTV can be used for the whole breast/chest wall volume only and this method is illustrated in the planning pack.

A margin should be added to whole breast/chest wall and tumour cavity CTV, taking into account set-up error, breast swelling and breathing; a typical PTV margin is 10 mm for both whole breast/chest wall and tumour bed A field-based whole breast/chest wall PTV can be used and this method is illustrated in the planning pack.
From Protocol Version 3.0 a margin should also be added to the lymph nodes (levels I-IV as appropriate). Typically a 10mm margin is added, except for the level IV axilla (SCF) PTV where a maximum of 5 mm margin should be applied medially in order to limit the dose to midline structures. Limited or no expansion may be applied inferiorly depending on the position of the superior border of the tangential fields.

Organs at Risk (OAR)

It is mandatory to contour ipsilateral lung and heart 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. From Protocol Version 3.0 the brachial plexus should be outlined for all patients receiving lymph node radiotherapy, following the guidelines in the FAST-Forward planning pack. Volumes are recorded for the purposes of the trial.

11.2 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 should not be moved between tangential and/or nodal fields.

11.3 Acquisition of Outlines

A full 3D set of outlines covering the whole breast and the organs at risk must be collected with a slice separation of no more than 5 mm. From Protocol Version 3.0 the CT scan used for planning lymphatic RT patients should extend from mid-neck to below the diaphragm. The imaging technology to be used must be x-ray CT only to provide accurate dose-volume histogram (DVH) data for plan assessment.

12. RADIOTHERAPY PLANNING

It is compulsory to outline target volumes and the relevant organs at risk for radiotherapy planning of FAST-Forward patients. All computer planning must be carried out on a 3D dataset, and correction for tissue heterogeneity must be applied.

12.1 Whole breast/chest wall

Usually, a tangential pair beam arrangement is used to encompass the whole breast PTV, minimising the ipsilateral lung and heart in the fields. The treatment plan must be optimised with 3D dose compensation aiming to fulfil the criteria in Table 2 below. From Protocol Version 3.0 the dose constraints below for the whole breast and chest wall PTV should be evaluated using the composite plan.

Upper and lower dose limits for whole breast/chest wall PTV

Lower dose limit	Prescription dose	Upper dose limit
>95% of the volume should receive 95% of the prescribed dose	Use a clinical relevant normalisation point for tangents, seek QA advice for inverse-planned	<5% of the volume should receive ≥105% <2% of the volume should receive ≥107% global max <110% of the prescribed dose

Table 2: Upper and lower dose limits for whole breast/chest wall PTV

12.2 Level I-III axilla and/or level IV axilla (SCF) from Protocol Version 3.0

Matching of the inferior border of the nodal fields to the superior border of the whole breast or chest wall tangential fields should preferably be achieved using non-divergent field edges, with either a single or dual isocentre technique. A single anterior field is recommended, which should be angled as required to avoid the spinal cord and/or any overlap with the tangential fields. The beam should be shaped to cover fully the LN PTV (using an appropriate penumbra margin), but care should be taken to avoid the oesophagus and the trachea medially. In patients with larger separation the use of a higher energy posterior field can be considered, and should be weighted down compared with anterior.

The coverage and hotspots to both breast and nodal target regions must be assessed in the treatment planning system using the composite of the two dose distributions, including all breast and nodal fields.

The dose distribution should meet the ICRU homogeneity criteria and planners should aim to achieve the dose distribution objectives specified in the Lymphatic Radiotherapy Guidelines for the FAST-Forward trial.

12.3 Dose Constraints for Organs at Risk (OAR) – whole breast/chest wall

The dose constraints for ipsilateral lung and heart in whole breast radiotherapy using tangential field arrangements are listed below. If non-tangential fields are used, e.g. inverse planned IMRT for patients with pectus excavatum or very medial tumour bed, then the planner must seek advice of the QA team. These constraints do not take into account the tumour bed boost dose or dose from any nodal fields. Although maximum dose constraints are stated for the heart, the planner should aim to keep any dose to the heart as low as possible.

Control Group

- The volume of ipsilateral lung receiving 12.0 Gy should be less than 15%
- The volume of heart receiving 2.0 Gy and 10.0 Gy should be less than 30% and 5% respectively.

Test Group 1 and 2

- The volume of ipsilateral lung receiving 8.0 Gy should be less than 15%
- The volume of heart receiving 1.5 Gy and 7.0 Gy should be less than 30% and 5% respectively.

Dose per fraction (Gy)	Keep 30 % of dose to < 15 % of ipsilateral lung volume	Keep 25 % of dose to < 5 % of heart volume	Keep 5 % of dose to < 30 % of heart volume
2.67	12.0 Gy	10.0 Gy	2.0 Gy
5.2/5.4	8.0 Gy	7.0 Gy	1.5 Gy

From Protocol Version 3.0 the dose to the ipsilateral lung and heart from the composite plan should be kept as low as reasonably achievable.

12.4 Bolus

Centres should specify prior to randomisation whether or not post-mastectomy (+/- reconstruction) bolus is to be applied, and if so, whether it is to be applied a) to part (e.g. the scar area) or all of the chest wall, b) for all or a specified number of fractions and c) thickness of bolus used for a given photon energy. Either composite plans, or plans with and without bolus are to be sent to the QA team for DVH assessment. Bolus is not applied after breast conservation surgery.

12.5 Beam Energy

Beam energies for treatment as for local practice, usually 6 MV, but a mixture of energies e.g. 6 MV and 15 MV can be used for larger patients. Anterior nodal fields would usually be planned with 6 MV but higher energy photons can be considered if needed.

12.6 Tumour bed radiotherapy

The tumour bed boost treatments can be either delivered by electron or photon beams. 10.0 Gy in 5 fractions, 16.0 Gy in 8 fractions or a radiobiological equivalent (from Protocol Version 4.0) is prescribed to the 100% isodose. Centres should aim to contour the boost volume and, where possible, produce dose distributions on their planning system and send boost plans to the QA team. If clinical mark-up is used for planning, CT information must be used to guide localisation of the tumour bed, for example, using the information on clip position and the use of surface rendered views (if these can be produced from the planning system). Details on minimum requirements for tumour bed boost radiotherapy can be found in the planning pack.

13. TREATMENT SCHEDULING AND GAPS

Treatment can start on any day of the week.

A gap of up to 3 days is acceptable in the event of machine service or breakdown. This is preferable to transferring the patient to a machine on which daily verification imaging is not available. If the treatment machine is unavailable for more than 3 days, please contact the QA team.

14. RADIOTHERAPY VERIFICATION

14.1 Treatment Set-up Verification – Breast / Chest Wall, level I-III axilla and/or level IV axilla (SCF)

Verification is carried out using electronic portal imaging. This can be either MV or kV.

Control Group: Treatment verification is required for at least three fractions in the first week of treatment to determine and correct for any systematic error*. Correction is carried out following local practice as long as this has been approved by the QA team. This correction is applied on fraction 4, and a further image may be taken to confirm the move. A suitable tolerance for the check of the correction is 5 mm. Verification is then once weekly throughout the remaining treatment with a tolerance of 5 mm.

Test Group 1 and 2: Verification imaging is required for each fraction to check for a gross error. A tolerance of not more than 5 mm should be used. Local policy is followed if the check is out of tolerance. A further image may be taken to confirm the correction and this also applies where daily imaging is used to correct couch position before treatment. Best practice is to correct all measured displacements.

If MV tangential fields are used for verification imaging, the method to derive the couch correction follows local practice as long as this has been approved by the QA team.

From Protocol Version 3.0 when applying corrections in set-up for patients receiving lymphatic RT, all necessary precautions should be taken to avoid overlap or under dosage at the match line between the nodal field and the main tangents, regardless of the allocated trial group.

14.2 Treatment Set-up Verification - Boost

Electron Boost

The electron boost set up is verified daily by visual matching to marks on the skin and checks on the gantry and collimator angles required for matching.

Photon Boost

If photon mini-tangent fields are used, the first 2 or 3 fractions are imaged (as appropriate for the fractionation scheme). A correction for the systematic error is made for the remaining fractions*. A check of the correction may be made on fraction 6 for the 16.0 Gy in 8 fraction schedule; a suitable tolerance is 5mm.

Alternatively, as the fractionation schedules are short, daily imaging maybe used as described for the whole breast/chest wall Test Groups 1 and 2.

If a conformal photon boost is used, then daily imaging and correction is recommended for all fractionation options (10.0 Gy in 5 fractions, 16.0 Gy in 8 fractions or a radiobiological equivalent (from Protocol Version 4.0)). Best practice is to correct all measured displacements.

*All systematic errors should be corrected and this is recommended, but if a centre wishes to use a correction tolerance on systematic error it should not be greater than 5 mm, and preferable not more than 3 mm and reported to the QA team

Where the need for more complex treatment planning (e.g. inverse planning or tomotherapy) requires a verification method not described here, centres are requested to discuss this on an individual basis with the QA Team. Similarly, if a centre wishes to use a tighter PTV margin with a more stringent verification protocol, this should be discussed with the QA Team.

14.3 In-vivo Dosimetry

In line with current UK guidelines, all FAST-Forward patients should have in-vivo dosimetry within the first week of treatment. This may be performed using diodes or thermo-luminescent dosimetry (TLD). Other methods may be appropriate for an individual centre and should be discussed with the QA team.

15. RADIOTHERAPY QUALITY ASSURANCE (QA)

A comprehensive QA programme is planned for all centres involved with FAST-Forward (see Appendix 3).

16. SERIOUS ADVERSE EVENT REPORTING

16.1 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 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
6. is otherwise considered medically significant by the Principal Investigator

Related Unexpected Serious Adverse Events: an adverse event that meets the definition of serious and is assessed by the CI or nominative representative as:

- "Related" – that is, it resulted from administration from the research procedure, and "Unexpected" – that is, the type of event is not listed as an expected occurrence

16.2 Reporting Serious Adverse Events

All SAEs should be reported within 24 hours of the investigator becoming aware of the event, by completing the FAST-Forward SAE form and faxing it to the FAST-Forward Trial Manager, Clinical Trials and Statistics Unit, 020 8722 4369 (Monday – Friday 09.00-17.00). The SAE form must be completed, signed and dated by the Principal Investigator or nominated person identified on the centre delegation log. ICR-CTSU will send a fax back to the centre to acknowledge receipt of the SAE.

The Chief Investigator (or a nominated representative) will review all SAEs to assess relatedness and expectedness.

Any relevant follow up information, including final resolution of the event, should be completed on the relevant part of the original SAE form and faxed to the ICR-CTSU, within 15 days of the local investigator becoming aware of this information.

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

SAEs will be collected during the patient's radiotherapy and for three months following treatment.

16.3 Reporting Related and Unexpected SAEs

If an SAE is defined as related and unexpected by the Chief Investigator, 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.

N.B. Patients showing unexpectedly severe late normal tissue responses will be identified on the Follow-up Forms and are not reported as SAEs. These late-occurring reactions include unexpectedly severe late subcutaneous fibrosis, ischaemic heart disease (after both right- and left-sided radiotherapy), rib fracture and symptomatic lung fibrosis.

17. STATISTICAL CONSIDERATIONS

17.1 Choice of Principal Outcomes

Primary outcome is ipsilateral local tumour control, since this is the justification for treatment in the main trial. Other endpoints include normal tissue effects, PROMS and health economic considerations and from Protocol Version 3.0 patient reported arm swelling. It is intended that each endpoint will be analysed separately. If there is discordance between the endpoints in terms of treatment outcome this will allow discussion of clinical trade-offs.

17.2 Methods of Analysis

Survival analysis methods (i.e. Kaplan-Meier analysis and Cox proportional hazards regression) will be used to compare rates of local recurrence between allocated treatments for all randomised patients (i.e. intention to treat). Normal tissue effects will be analysed using methodology developed for the START Trials; i.e. survival analyses of time to occurrence of moderate or marked effects, as appropriate. Analysis of the PROMS data will follow algorithms developed for the PROMS forms (i.e. calculation of standardised sub-scale scores), and will compare treatment groups at individual time points, as well as longitudinal changes from baseline. A generalised linear modelling approach will be used to describe the longitudinal PROMS data, taking into account important prognostic factors such as age, stage of disease, treatment received and other socio-demographic and clinical characteristics. Appropriate adjustments will be made for multiple comparisons in the analysis of the PROMS data by adopting a more stringent cut-off for statistical significance.

The sample size calculations have been based on survival analysis methods. The 5-year figure has been used as the clinically relevant time point and assumes that recurrences before and after five 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.

As this is a non-inferiority trial if there is high non-compliance with the test treatment groups then an analysis of only those compliant with the protocol will also be conducted.

The incidence of uncommon serious complications will be monitored.

Analyses of local tumour recurrence and of normal tissue effects adjusting for adjuvant therapy (chemotherapy, hormonal therapy) will be performed. Analyses of normal tissue effects will also be adjusted for breast size and surgical deficit.

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. Each Test group will be compared with the Control group and treatment effects estimated separately. The inclusion of two test dose levels (Test 1 & 2) allows minor adjustment, for example by interpolation, between test dose levels to identify the fraction size most closely resembling the control schedule in terms of late change in breast/chest wall appearance and other adverse effects. The primary comparison is the rate of local tumour control at this 5-fraction dose level compared to the 15-fraction control. Since local relapse rates are so low, and no measurable difference in local relapse between the two test schedules is expected, interim analyses will also combine the test schedules for comparison with the control for the primary endpoint.

The primary outcome measure for the health economic evaluation will be the cost per quality-adjusted life year (QALY) gained from health resource usage and EQ-5D-5L health status. A decision analytic model will be used to extrapolate the trial results in order to estimate the QALYs and health resource utilisation over a lifetime time horizon, and to express the uncertainty in the estimates of cost-effectiveness. Information from published studies will be incorporated with the trial data to compare

the trial regimens with the current UK standard regimen. In addition the economic evaluation will consider the impact of data relating to convenience of the treatment schedules (e.g. days of work missed, travel time and cost).

17.3 Sample Size

17.3.1 Main Trial

The target sample size is 4000 patients, with numbers balanced equally in each randomised group. This provides 80% power (1-sided $\alpha = 0.025$ to allow for 1-sided hypothesis and multiple testing) to exclude an increase of 1.6% in the 5-year local relapse rate between each test group and the control, assuming a 5-year rate of 2% in the 40.05 Gy schedule (using START data and allowing for reduction in local relapse due to recent adoption of aromatase inhibitors and trastuzumab). As local relapse rates after radiotherapy are low, there is limited potential for reducing this even further when comparing different regimens in a trial. Therefore the aim is to test whether the local relapse rate in the test groups is at least as effective, and not more than 1.6% higher than in the control group. Since no measurable difference in local relapse between the two test schedules is expected, interim analyses will combine the test schedules for comparison with the control for the primary endpoint. This combined analysis will enable an excess of 1.3% in the 5-year local relapse rate of the test groups relative to the control to be excluded (80% power). As follow-up continues and more events accrue, the statistical power to compare each test schedule separately with the control will be higher. The calculations allow for up to 10% loss to follow-up / unevaluable.

17.3.2 Acute toxicity study I (Protocol Version 1.0)

The first 190 patients were entered into the acute toxicity sub-study to be assessed by a healthcare professional for acute skin toxicity up to settling of reaction to modified RTOG grade 1 and at least 4 weeks post radiotherapy. The patients were also asked to complete the Radiotherapy Breast Symptoms Diary Cards for self-assessment of acute toxicity. This would enable a rate of modified RTOG grade≥3 acute skin reactions of 10.9% to be excluded, based on the data from the 50 Gy in 25 fractions control schedule of the FAST trial. From the FAST trial 5-fraction test schedules, the rate of acute skin reactions was expected to be around 2.3% in the test groups of FAST-Forward. Using the Simon single stage design (using exact p-values) with power 89.2% and one-sided alpha of 7.9%, 50 patients per group were required (total 150). In each test group, if 3 or more patients developed grade ≥3 acute skin reactions using

the modified RTOG scale, the IDMC may advise the Trial Steering Committee to consider a change in the test schedule.

This study was completed in summer 2012 and no grounds for undue clinical concern were reported. However, the data were collected in a way that would not allow the prospective differentiation between moist desquamation and oedema.

17.3.3 Acute toxicity study II (Protocol Versions 2.1 and 2.2)

A second acute toxicity study will be conducted using standard CTCAE criteria to score erythema and moist desquamation (see section 8.2.1.). Fifty evaluable patients will be required for each treatment group (total approximately 150). An evaluable patient will be defined as receiving at least one fraction of radiotherapy and with complete or at most one missing toxicity assessment. This sample size will provide sufficient data to estimate the true incidence of acute skin reactions in the control and test schedules.

17.3.4 Photographic, patient reported outcome measures (PROMS) and health economics (HE) sub-studies (from Protocol Version 2.1)

For the sub-studies (photographic assessments, PROMS and HE), 732 patients per group (2196 in total) will provide 80% power to detect an 8% difference in the prevalence of late adverse effects at 5 years between the test groups (assuming a 5-year rate of 35%). PROMS and HE evaluation will be collected as part of the same booklet. Accrual will continue until there are 2196 evaluable patients in both the photographic and PROMS/HE sub-studies. It is also preferred that the patients in the photographic sub-study are the same subgroup as in the PROMS/HE studies, for data comparison. For the HE evaluation, it is expected that the majority of differences between the schedules in terms of quality-adjusted-life-years will be due to the late adverse effects, and so the estimated sample size will be sufficient. The uncertainty in HE outcomes will be reflected using probabilistic sensitivity analysis. The calculations allow for up to 10% loss to follow-up / unevaluable.

17.3.5 Lymphatic RT sub-study (from Protocol Version 3.0)

The sample size is 627 patients, with numbers balanced equally in each randomised group. This provides 90% power (1 sided $\alpha = 0.025$ to allow for 1-sided hypothesis and multiple testing) to exclude an arm swelling rate of 20% in *each* of the test groups compared to an assumed rate of 10% in the control group (allowing for 10% attrition due to illness or death based on experience from the START trial). Stratification will be by centre and whether the patient has had an axillary clearance.

17.4 Interim analyses and Data Monitoring

The Independent Data Monitoring Committee (IDMC) reviewed the data on acute skin reactions on the first 190 patients. Following completion of the acute toxicity study I, the IDMC, together with the TSC, requested a second confirmatory study using the CTCAE scale. This study requires 150 evaluable patients (50 in each group), to provide a robust estimate of the true incidence of radiotherapy dose-dependent acute skin reactions in each of the treatment groups using a standard toxicity scale.

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 the IDMC for confidential review. In the light of the interim analyses, the IDMC will advise the 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 normal tissue responses. 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 PROMS and Health Economics 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.

18. ASSOCIATED STUDIES

At the time of randomisation all patients will be asked to consent to donate a whole blood sample which may be taken at any routine follow up visit, and a formalin-fixed paraffin-embedded (FFPE) diagnostic tumour tissue sample.

Sites will be notified by ICR-CTSU to when the tissue sample collection will commence and no samples should be collected prior to this notification.

18.1 Molecular Correlates of Normal Tissue Injury

It is thought that part of the inter-patient variation in the incidence and severity of late normal tissue responses reflects inter-patient differences in tissue responsiveness to radiotherapy. Common DNA sequence variations (single nucleotide polymorphisms) account for differences in protein expression between individuals that may explain an important component of the variation between individuals. Genome-wide approaches

offer scope to identify patterns of single nucleotide polymorphisms, DNA copy number and methylation status that may distinguish patients at lower and higher than average annual risk of late adverse effects.

Up to 20 ml of whole blood will be collected by venesection into blood tubes and sent to the Institute of Cancer Research, Sutton, Surrey, where it will be stored for future research, in accordance with the Human Tissue Act 2004. The research may be carried out at other centres, including those outside the UK. An aliquot of this blood may also be requested for comparison of genomic DNA with tumour DNA extracted from donated tissue samples (see 18.2). Blood will be collected at the treating hospital. Patients will also be asked to complete a family history questionnaire.

18.2 Molecular Correlates of Fractionation Sensitivity and Local Tumour Relapse

Local tumour relapse remains a clinical problem in a minority of women. The likelihood of local relapse may be influenced by genetically regulated factors, including the extent of intraductal spread and radiation resistance. Genome-wide approaches offer scope to identify DNA sequence differences (mutations and polymorphisms) between tumours that discriminate between patients who suffer a local relapse 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). Genomics offer scope for investigating the genetic relationships between ipsilateral and contralateral tumour relapse and primary tumour in a systematic way that may 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 DNA extracted from the blood samples (see 18.1). For LOH studies, a sample of the donated blood stored at the Institute of Cancer Research, Sutton, Surrey will be requested. It is proposed to establish tissue arrays and to extract DNA and RNA from paraffin blocks of primary tumours and ipsilateral and contralateral relapses/new primaries. 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 analysis. In some centres, samples described above will be fresh frozen and sent to KCL/Guy's and St. Thomas' Hospital Breast Tissue Bank for the same analyses. The KCL/Guy's and St. Thomas' 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.

It is likely that breast cancers are heterogeneous in their sensitivity to fraction size. If so, it may be possible to distinguish subgroups of patients suited to treatment with large or small fractions based on examination of the tumour phenotype. Immunohistochemistry provides measures of tumour proliferation, hypoxia and DNA damage response status and other factors postulated to influence fractionation sensitivity. It is proposed to create tissue arrays from the primary tumour for future analysis of factors predicting sensitivity to radiotherapy fraction size.

18.3 Patient Reported Outcome Measures (PROMS) Study

The original protocol stipulated that the PROMS study would not be implemented until the acute toxicity study (I) had finished. PROMS is an umbrella term given to any data that are reported directly by the patient without an intermediary such as a family member or a healthcare professional [47]. In the main trial, the PROMS measures of interest are the late-occurring normal tissue effects, quality of life and fatigue. From Protocol Version 3.0 the PROMS measures of interest will also include arm swelling, shoulder stiffness, upper limb pain, sensorimotor symptoms and arm swelling.

There is evidence that radiotherapy causes long-term effects on quality of life in terms of altered breast appearance, breast, arm and shoulder symptoms, as well as a possible impact on some general aspects such as fatigue. Results from the START trial have highlighted the value of patients' self-reported post–radiotherapy symptoms in discriminating between radiotherapy (RT) regimens in favour of hypofractionation [44]. Experience of the START trials showed that patient-rated cancer specific PROMS data, obtained with the EORTC QLQ-C30 [39] provided useful data at baseline (for example concerning the effects of surgery) [48] and also made a small contribution to a comparison of the regimens up to 2 years, from which it was found that fewer changes in parameters were observed from 2-5 years (unpublished data 2010). The FAST-Forward PROMS sub-study is planned to provide subjective views of key breast symptoms and body image over 10 years of follow-up, thus to add supportive data in the comparison of a trade-off between local tumour control and adverse effects of treatment. The key effects of radiotherapy on PROMS are hypothesised to be on a range of breast symptoms as reported for the START trial [44] and potentially on body image plus short term general effects such as fatigue.

From Protocol Version 3.0 key patient reported outcomes will be arm and shoulder symptoms such as arm swelling, shoulder stiffness, upper limb pain, sensorimotor

symptoms and overall arm function associated with lymphatic RT. In the START trials these symptoms largely related to prior surgery [44].

The PROMS study is detailed in Appendix 4.

18.4 Health Economics (HE)

Rationale for HE measurement

The health economic analysis will make use of a generic, preference-based measure of HRQoL (health-related quality of life). The objective is to have an index measure of HRQoL where quality of life and absence of morbidity are valued on the same scale as quantity or length of life. This enables the calculation of quality adjusted survival where duration of time spent experiencing certain health states (e.g. receiving radiotherapy, experiencing a local recurrence) is weighted according to the HRQoL value associated with that health state [49, 50]. The health benefits can then be combined with information on health resource usage in order to establish the cost-effectiveness of a 5-fraction schedule of curative radiotherapy in comparison to current UK practice. This is measured by using health resource usage questions and EQ-5D-5L (http://www.euroqol.org/about-eq-5d/valuation-of-eq-5d/eq-5d-5l-value-sets.html).

Timing of assessments

EQ-5D-5L and resource usage questions will be collected at: baseline, 3 and 6 months post radiotherapy and 1, 2, 5 and 10 years post randomisation.

The Health Economics study is detailed in Appendix 5.

19. TRIAL MANAGEMENT

19.1 Trial Management Group

A Trial Management Group (TMG) will be set up and will include the Chief Investigator, Chief Clinical Co-ordinators, ICR-CTSU Scientific Lead and identified collaborators, the Trial Statistician 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 have operational responsibility for the conduct of the trial. Where possible membership will include at least one lay/consumer representative. The Committee's terms of reference, roles and responsibilities will be

defined in a charter issued by ICR-CTSU and based on MRC Good Clinical Practice (MRC GCP).

19.2 Trial Steering Committee

A Trial Steering Committee (TSC) will be set up and will 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 one or two Principal Investigators. It is the role of the TSC to monitor progress of the trial and to ensure there is adherence to the protocol and the principles of Good Clinical Practice. The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSU and based on MRC GCP.

19.3 Independent Data Monitoring Committee

An IDMC will be instigated to monitor the progress of the trial. Membership of the IDMC will be proposed by the TMG and approved by the TSC. The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSU and based on MRC GCP. The IDMC should meet in confidence at regular intervals, and at least annually. A report of the findings and recommendations will be produced following each meeting and a summary of the minutes will be submitted to the TMG and TSC, and if required, the main REC.

The IDMC reserve the right to release any data on outcome or side-effects through the TSC to the TMG (and if appropriate to participants) if it determines at any stage that the combined evidence from this and other studies justifies it.

20. RESEARCH GOVERNANCE

20.1 Sponsor Responsibilities

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 principles of Good Clinical Practice (GCP).

The following responsibilities have been delegated to:

The Chief Investigator:

- selection of Investigators
- taking appropriate urgent safety measures

The Chief Investigator or a named deputy delegated in his absence:

- prompt decision as to which related adverse events are related unexpected SAEs and prompt reporting of that decision to ICR-CTSU for onward reporting to the main REC

The Institute of Cancer Research (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.

The responsibilities of ICR-CTSU for the day-to-day management of the trial will include the following.

- ensuring an appropriate ethics opinion has been sought, and any amendments have been approved
- giving notice of amendments to protocol, make representations about amendments to the Main REC
- giving notice that the trial has ended
- randomising patients
- raising and resolving queries with local investigators
- issuing and collating PROMS questionnaires returned by post
- logging clinical and PROMS data received; raising queries
- keeping records of all serious adverse events (SAEs) reported by investigators
- notifying the Main REC and Investigators of related Serious Adverse Events

The Participating Centres

- putting and keeping in place arrangements to adhere to the principles of GCP
- keeping a copy of all 'essential documents' (as defined under the principles of GCP) and ensuring appropriate archiving and destruction of documentation once the trial has ended
- taking appropriate urgent safety measures

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 FAST-Forward QA programme (see Appendix 3).

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.

21. TRIAL ADMINISTRATION AND LOGISTICS

21.1 Protocol Compliance

The FAST-Forward 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 principles of GCP. Before activating the trial, participating centres are required to sign an agreement between an individual participating centre and The Institute of Cancer Research. Centres may commence recruitment once centre agreements have been signed by both parties, trial documentation is in place and a site initiation (visit or teleconference) has taken place. Site initiation visits will be conducted at centres where the Principal Investigator has requested one or where ICR-CTSU deems it is appropriate.

21.2 Protocol Amendments

Proposed protocol amendments will be submitted to the TMG by the Chief Investigator. 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.

21.3 Investigator Training

Training and advice will be provided via a trial launch meeting, training workshops, site initiation and QA feedback to identified key individuals in each participating centre by members of the Trial Management Group. 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.

21.4 Data Acquisition

The clinical data should be recorded on the FAST-Forward case report forms (CRFs) and the relevant pages forwarded to ICR-CTSU in a timely manner. The Trial Management Group reserves the right to amend or add to the CRFs as appropriate. Such changes do not constitute a protocol amendment, and revised or additional forms should be used by centres in accordance with the guidelines provided by ICR-CTSU. Where appropriate, data may need to be collected retrospectively if an additional question has been added to the CRF.

By participating in the FAST-Forward trial, the Principal Investigators at each centre are 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
- original consent forms are dated and signed by both patient and investigator and are kept together in a central log together with a copy of the specific patient information sheet(s) given at the time of consent
- all essential documents must be retained after the trial ends to comply with current legislation
- staff will comply with the protocol and Trial Guidance Notes for FAST-Forward

On receipt at ICR-CTSU, CRFs will be recorded as received and any missing forms will be reported to the originating centre. Illegible forms may be returned to the centre for clarification.

21.5 Central Data Monitoring

ICR-CTSU will review incoming CRFs for compliance with the protocol, and for inconsistent or missing data. Should any missing data or data anomalies be found, queries will be sent to the relevant centre for resolution. Following initial review, the CRF data items will be entered into the clinical study database held at ICR-CTSU.

Data will be further reviewed for data anomalies / missing data, by central statistical monitoring. Any systematic inconsistencies identified may trigger monitoring visits to centres.

21.6 On site Monitoring

If a monitoring visit is required, ICR-CTSU will contact the centre to discuss dates of proposed visit. Once a date has been confirmed, the centre should ensure that the relevant patient notes are available for monitoring.

If any problems are detected in the course of the monitoring visit, ICR-CTSU will work with the Principal Investigator to resolve issues and, if necessary, to determine the centre's future participation in the study.

ICR-CTSU staff conducting on-site monitoring will review essential documentation and carry out source data verification to confirm compliance with the centre agreement and trial protocol to ensure the protection of patients' rights as detailed in the Declaration of Helsinki 1964 as amended October 1996.

21.7 End of Study

The study end date is deemed to be the date of the last data capture and is expected to be at least 10 years after the last patient is entered.

21.8 Archiving

Essential documents are documents that individually and collectively permit evaluation of the conduct of the trial and substantiate the quality of the data collected. Essential documents will be maintained at ICR-CTSU in a way that will facilitate the management of the trial, audit and inspection. They should be retained for a sufficient period (at least 15 years) for possible audit. Documents should be securely stored and access restricted to authorised personnel.

Essential documents should also be archived at each participating centre in accordance with current legislation.

22. PATIENT PROTECTION AND ETHICAL CONSIDERATIONS

22.1 Risk Assessment

This study has been formally assessed for clinical risk using the ICR-CTSU risk assessment tool.

22.2 Patient Confidentiality

Patients will be asked to consent to their full name being collected at randomisation in addition to their date of birth, hospital number, postcode and NHS number (CHI in Scotland). This will allow tracing through the GP and national records to assist with long term follow up and to permit linkage with routinely collected NHS data. The personal data recorded on all documents will be regarded as confidential, and any information which would allow individual patients to be identified will not be released into the public domain.

Patients consenting to the PROMS and HE study are asked to provide their name, address and telephone number as well as the address and phone number of their GP to ICR-CTSU. These details will only be used for the purposes of the PROMS and HE

sub-studies. 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 patients and will not reproduce or disclose any information by which patients could be identified. Representatives of ICR-CTSU and the Radiotherapy QA team will be required to have access to patients notes for QA purposes but patients should be reassured that their confidentiality will be respected at all times. In the case of special problems, it is also necessary to have access to the complete study records provided that patient confidentiality is protected.

22.3 Ethical Considerations

This trial has been approved by the South East Coast Kent Research Ethics Committee. Before entering patients, the Principal Investigator at each centre is responsible for gaining Site Specific Assessment and Research and Development approval for this study.

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 (PIS) according to national guidelines.

There were 4 separate PIS in this study up to and including Protocol Version 2.2.

i) for centres who are taking part in all sub-studies
ii) for centres taking part in acute toxicity study I
iii) for centres taking part in acute toxicity study 2
iv) for centres who are not taking part in the PROMS and photographic sub-studies.

From Protocol Version 3.0 there is a single PIS which includes details of the lymphatic RT sub-study.

All PIS contain details of the optional sub-studies: photographic assessments and collection of biological samples. Patients will be encouraged to participate in the associated studies but if they decline, this will not exclude them from the trial.

All consent forms must be countersigned by the Principal Investigator or a designated individual. A record listing the designated individuals and the circumstances under which they may countersign consent forms must be clearly documented at the centre as part of the Delegation of Responsibilities Log. This log, together with original copies of all signed patient consent forms, must be available for inspection.

22.4 Data Sharing

Data arising from this research will be managed and made available to maximise public benefit. Data sharing will be in a timely and responsible manner. Appropriate regulatory permissions relating to the ethical use of data must be in place before the data can be shared.

22.5 Data Protection Act (DPA)

ICR-CTSU will comply with all aspects of the DPA 1998. Any requests from patients for access to data about them held at ICR-CTSU should be directed to the Trial Manager in the first instance who will refer the request to the Data Protection Officer at The Institute of Cancer Research.

22.6 Liability/Indemnity/Insurance

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

23. FINANCIAL MATTERS

The trial is investigator designed and led and has been approved by National Institute for Health Research Health Technology Assessment programme (NIHR-HTA) 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.

The trial has received funding from the NIHR-HTA. If further funding is received from any other source this will be made apparent in the patient information sheet and to the approving Main REC and NIHR-HTA, but will not require a protocol amendment.

The trial is part of the NIHR Clinical Research Network portfolio and NIHR Cancer Research Network resources should be made available for FAST-Forward specific research costs.

24. PUBLICATION POLICY

The main trial results will be published in the name of the trial in a peer-reviewed journal, on behalf of all collaborators. The manuscript will be prepared by a writing group, appointed from amongst the Trial Management Group and participating clinicians. All participating centres and clinicians will be acknowledged in this publication together with staff from the ICR-CTSU. All presentations and publications relating to the trial must be authorised by the Trial Management Group, on whose behalf publications should usually be made. Authorship of any secondary publications will reflect the intellectual and time input into these studies, and will not be the same as on the primary publication. No investigator may present or attempt to publish data relating to the FAST-Forward trial without prior permission from the Trial Management Group.

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APPENDIX 1: Acute skin reactions scoring scale

Modified RTOG scale (acute toxicity study I)

Grade	Description
Grade 0	No visible change
Grade 1	Faint/dull erythema
Grade 2	Tender/bright erythema +/- dry desquamation
Grade 3	Patchy moist desquamation, moderate oedema
Grade 4	Confluent moist desquamation, pitting oedema

CTCAE version 4.03 (acute toxicity study II)

Grade	Description
Grade 1	Faint erythema or dry desquamation
Grade 2	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin fold and creases; moderate oedema
Grade 3	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion
Grade 4	Life threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated
Grade 5	Death

APPENDIX 2: Selection of Test Dose Levels for FAST-Forward

Assuming i) that the fractionation sensitivity of late normal tissue effects (NTE) is well-described by an α/β value of 2.8, based on the results of the START A & FAST trials, ii) the slope of the dose response for NTE is well described by a γ value of 1.4, based on the START A trial and iii) complete repair of sublethal damage between daily fractions, the estimated equivalent total doses delivered in 2.0 Gy fractions assuming an α/β value of 2.8 Gy ($EQD_{2.8Gy}$) are shown below in a table that includes 50.0 Gy in 25 fractions as a reference schedule:

Fractionation regimen	$EQD_{2.8Gy}$ (Gy)	*ΔNTE (%)
50 Gy/25Fr/5Wk (2.0 Gy/Fr)	50.0	reference
40.05 Gy/15Fr/3Wk (2.67 Gy/Fr)	45.6	-12.3
27 Gy/5Fr/1Wk (5.4 Gy/Fr)	46.1	-11.1
26 Gy/5Fr/1Wk (5.2 Gy/Fr)	43.3	-18.8
* Negative values indicate estimated NTE rates lower than after 50 Gy in 25 fractions		

Where tumour response is concerned, applying an α/β value of 4.6 Gy generated by the START pilot and START A trials and γ = 0.2 based on START A, the estimated equivalent total doses delivered in 2.0 Gy fractions ($EQD_{4.6Gy}$) are shown below in a table that includes 50 Gy in 25 fractions as a reference schedule:

Fractionation regimen	$EQD_{4.6Gy}$ (Gy)	*ΔTumour Relapse (%)
50 Gy/25Fr/5Wk (2.0 Gy/Fr)	50.0	reference
40.05 Gy/15Fr/3Wk (2.67 Gy/Fr)	44.1	+2.4
27 Gy/5Fr/1Wk (5.4 Gy/Fr)	41.0	+3.6
26 Gy/5Fr/1Wk (5.2 Gy/Fr)	38.6	+4.6
* Positive values indicate higher estimated levels of tumour relapse than after 50 Gy in 25 fractions		

Note that a 2.4% excess tumour relapse rate was excluded with >97% confidence in START B, where the HR for local relapse after 40.05 Gy in 15 fractions compared to 50.0 Gy in 25 fractions was 0.79 (95% CI=0.48-1.29). In other words, the local relapse rate was, if anything, slightly lower, not higher, after 15 compared to 25 fractions [1]. If treatment time explains part

or all of this effect, local relapse in the 1-week schedules will be lower than those estimated above.

Acute skin reactions

Data on acute skin reactions in humans suggest that acute skin reactions will be milder in the test groups, since acute reactions are much less sensitive to fraction size than to total dose (which is reduced from 40.05 Gy to <30 Gy in the test groups). A 1 week schedule is too short to stimulate repopulation in the epidermis and radiosensitisation due to re-assortment. This expectation is consistent with the results of a pilot study in 30 patients receiving 30 Gy to whole breast in 5 fractions of 6.0 Gy over 15 days, in which there were 3 cases of grade 1 and 1 case of grade 2 moist desquamation (no cases of grade 3 or 4) [2].

Incomplete repair during a 24-hour inter-fraction interval

Turesson showed that a 24-hour inter-fraction interval is more sparing of late damage (telangiectasia) than a 4-hour interval. The difference was equivalent to 11% difference in fraction size [3]. Estimates of recovery half-time ($T_{½}$) for late endpoints in humans are based on the CHART head and neck trial: $T_{½}$ for telangiectasia was 3.8 hours and for fibrosis was 4.4 hours [4]. It is likely that repair beyond a 24-hours is very limited, and that no adjustment is needed to fraction size when moving from a 7-day to 1-day inter-fraction interval. The 2-year results of the FAST pilot study raised no concerns that an inter-fraction interval of 2 or 3 days leads to excessive late effects [2]. The $EQD_{2.8Gy}$ of the 5-fraction regimen delivered as one fraction per week in the FAST trial was estimated to be 54 Gy, but no marked change in breast appearance at 2 years was recorded in any of 30 patients treated with 30 Gy in 5 fractions over 15 days [2].. An element of incomplete repair at 24 hours (relative to 7 days) after 4 out of 5 test group fractions might lead to an estimated 1% increase in NTE, as illustrated for Test group 1 below if the second, third, fourth and fifth fractions follow on consecutive days and each deliver 5.5 Gy of absorbed dose instead of prescribed 5.4 Gy.

Fractionation regimen	$EQD_{2.8Gy}$ (Gy)	*ΔNTE (%)
5.4 Gy x 1	9.2	-
5.5 Gy x 4	38.0	-
5.4 Gy x 1 plus 5.5 Gy x 4	47.2	-10
** 5.4 Gy x 5	46.1	-11

* Estimated NTE rates relative to 50 Gy in 25 fractions
** Test group 2, assuming 100% repair between fractions

Despite a lack of evidence suggesting need for dose modification taking account of incomplete repair and/or a lower α/β value for late NTE than that estimated in the START A and FAST trials, a second test dose level (26.0 Gy in 5 fractions of 5.2 Gy) is included, as applied in START A. This allows interpolation, if required, in order to identify a 5-fraction schedule iso-effective with 40.05 Gy in 15 fractions.

Appendix 2 references

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APPENDIX 3: Quality Assurance (QA) 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/chest wall and nodal region arise from the geometry and proximity of the associated treatment volumes–with important radiation sensitive structures underlying the breast, chest wall and nodal region including the lung, myocardium and brachial plexus.

Careful localisation, computerised planning, accurate verification of beam position and meticulous attention to alignment and matching during treatment are essential.

A QA 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 [1, 2].

In this multi-centre randomised trial the QA 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 outcomes emerge.

In this way the definition of QA as “all those planned and systematic actions necessary to provide adequate confidence that a produce will satisfy given requirements of quality” [3] 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 trials. This has provided an element of consensus in radiotherapy technique amongst radiotherapy centres. FAST-Forward 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 QA programme will follow the guidelines set out by the EORTC [2] and will be co-ordinated by an experienced QA team based at Mount Vernon Hospital [4, 5]. It is based on anticipated accrual by around 40 RT centres over a three and a half to four year period. From Protocol Versions 1.0-2.2 the QA programme applied to whole

breast/chest wall radiotherapy. From Protocol Version 3.0 onwards centres will need to gain additional QA approval for lymphatic RT.

The 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 creation of an ideal plans and outlining of target volumes as defined by trial protocol to be produced by each centre, where not already assessed for another trial.
From Protocol Version 3.0 each centre PI will be credentialed for lymphatic nodal outlining as part of the QA approval process.

2.2 A visit by the QA team may be performed 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.
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 [6].
vii) Measurements across the treatment volume within a purpose-made phantom, if not performed for the same technique within the last 3 years.
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 FAST-Forward 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.
From Protocol Version 3.0 new centres will need to gain QA approval for both whole breast/chest wall and lymphatic radiotherapy.

4. Analysis of QA programme

The data from the QA 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) Systematic errors of technique in any stage of treatment from planning through to implementation.

The detailed analysis of the QA 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 outcomes:

- 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.

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APPENDIX 4: Patient Reported Outcome Measures (PROMS)

Patient reported outcome has become an important measure in breast cancer research over the past decade. It is an umbrella term coined for any subjective report from the patients on outcomes such as quality of life, self-perceived functional well-being and satisfaction of treatment received. There is evidence that radiotherapy causes long-term effects on quality of life in terms of altered breast appearance, breast, arm and shoulder symptoms, as well as a possible impact on some general aspects such as fatigue. Results from the START trial have highlighted the value of patients' self-reported post–radiotherapy symptoms in discriminating between radiotherapy (RT) regimens in favour of hypofractionation [1]. The START trials also showed that patient-rated cancer specific PROMS data, obtained with the EORTC QLQ-C30 [2] provided useful insight of patient experience at baseline (for example concerning the effects of surgery) [3] and made a small contribution to a comparison of the regimens up to 2 years, with fewer changes in parameters observed from 2-5 years (unpublished data 2010). The FAST-Forward PROMS sub-study is planned to provide subjective views of key breast symptoms and body image over 10 years of follow-up, with the aim to add supportive data in the comparison of a trade-off between local tumour control and adverse effects of treatment. The key effects of radiotherapy on PROMS are hypothesised to be on a range of breast symptoms as reported for the START trial [1] and potentially on body image plus short term general effects such as fatigue. From Protocol Version 3.0 key patient reported outcomes will be arm and shoulder symptoms such as arm swelling, shoulder stiffness, upper limb pain, sensorimotor symptoms and overall arm function associated with lymphatic RT. In the START trials these symptoms largely related to prior surgery [1].

Rationale for PROMS measurement

The evaluation strategy is based on standardised measures that will provide data and allow comparison with other relevant trials. The scales selected include specific measures for evaluating breast cancer therapies, body image, protocol-specific post RT symptoms, fatigue and psychological distress together with a general cancer health related quality of life scale; all have been used in the START and IMPORT radiotherapy trials. Assessment will be carried out over at least 5 years of follow-up.

Measures

The EORTC QLQ-C30 [2] comprises 5 functional sub-scales, 2 symptoms subscales and additional symptoms items and questions about global health and global quality of life.

The EORTC BR23 breast cancer module is a 23-item scale designed for use in breast cancer treatment [4]. It consists of 6 subscales: breast symptoms, arm symptoms, body

image, systemic side effects, sexual functioning, sexual enjoyment and items on hair loss and future perspective. This will be supplemented by 6 items specific to post-treatment effects evaluating change in skin appearance, change in overall appearance of the breast, breast shrinkage and hardening, position of the nipple and difficulty getting a bra to fit. An additional item measures shoulder stiffness. From Protocol Version 3 onwards patients will be asked a further six questions relating to potential side effects from the lymphatic RT.

The 10-item Body Image Scale (BIS) (of which 4 items are already incorporated in the BR23) was designed for use with cancer patients [5] and has been widely used in national breast cancer treatment trials.

The EORTC 13-item Fatigue module (EORTC QLQ-FA-13 (revised version Phase III) [6,7] will be used in this trial as detailed data are required to assess the short and longer term impact of RT. Relevant permission to use this scale has been obtained.

The PROMS evaluations are designed to complement the photographic assessments of breast appearance and clinical ratings of late normal tissue effects, and to capture the medium and long-term sequelae of breast radiation therapy on fatigue and psychological distress as important components of quality of life. The long-term PROMS sub-study is both comparative and descriptive: sample size considerations are addressed where appropriate.

The timing and mode of administration of PROMS questionnaires is based on experience from the START trials plus the need to assess adverse effects due to RT at an earlier time point (3 months). The PROMS data will be collected in a subset of centres participating in the FAST-Forward trial who wish to participate in the PROMS sub-study; this is the same strategy that was used in the START and IMPORT trials. All patients at PROMS participating centres will be invited to participate in the PROMS sub-study, but if they would prefer not to they may still be randomised into the main trial.

The PROMS outcomes 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 PROMS domain: the aim is to provide information from all PROMS domains as appropriate.

1) Normal tissue effects and body image

The proportion of patients suffering breast, arm and shoulder symptoms together with specific post-RT symptoms will be assessed at baseline, 3 and 6 months post-treatment and 1, 2, 5

and 10 years post-randomisation. Relevant symptoms from the breast cancer module (EORTC BR23) and protocol-specific post RT symptoms, all scored as 'quite a bit' or 'very much' will be used as an indicator of adverse effects. Body image concerns will be summarised for comparison between regimens, and where appropriate, individual items will also be compared.

2 General PROMS outcomes

1) The EORTC QLQ-C30 and the Fatigue module (EORTC QLQ-FA-13 revised Version Phase III) will be analysed according to EORTC guidelines and results compared between regimens for short and longer-term effects and differences.

2) Sexual function and sexual enjoyment (BR23)

Whilst we would not assume that these parameters are influenced primarily by RT, these domains are interrelated and may reflect the general impact of treatment. We will therefore be able to explore these domains within regimen and describe levels of dysfunction and distress across regimens. Formal statistical comparisons will be considered if differences emerge which warrant testing, but these are not expected. .

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 outcomes. We will <u>not</u> attempt to produce a summary score representing a PROMS outcome 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

All patients who:

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

Sample Size

732 patients per group (total 2196) will provide 80% power to detect differences of ≥ 8% in the prevalence of specific normal tissue effects. Sample size estimate assumes a 2-sided significance level of = 0.025 (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 PROMS 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 PROMS sub-study in all or a specific subgroup of patients. 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. Evaluation points are designed to allow comparison with the START and IMPORT LOW and HIGH trial PROMS outcomes.

Baseline Patient Reported Outcome Measures (PROMS): All measures: EORTC QLQ-C30 and BR23, protocol specific pre-RT items, Body Image Scale (BIS) and EORTC Fatigue module. A designated member of staff, trained in PROMS administration, should hand out questionnaires in the clinical centre. Patients will be asked to complete the questionnaires after a full explanation of the study and after giving informed consent but **before** the randomisation is known, to avoid the possibility of bias.

Patient Reported Outcome Measures (PROMS) Follow-up: Results of the START trials indicated a rise in breast symptoms at the 6-month evaluation and more precision is needed in estimating these effects closer to treatment. All PROMS measures (EORTC QLQ-C30 and BR23, Protocol specific post–RT breast symptoms, BIS, EORTC Fatigue module) will therefore be mailed to patients from the FAST-Forward Trials Office at 3 and 6 months post radiotherapy, 1 and 10 years post randomisation. A smaller set of PROMS measures

(EORTC BR23, BIS, protocol specific post-RT breast symptoms) will be mailed to patients from the FAST-Forward Trials Office at 2 and 5 years post randomisation.

Follow-up - general aspects of PROMS: administered by the Trials Office, will be made as follows:

Due care will be taken to check the physical status of all patients prior to questionnaire mailing. This will be done through email or telephone contact with the hospital department and/or GP as appropriate. The follow-up questionnaires will be sent out by the FAST-Forward Trials Office to the patients' home requesting completion within the week. If the questionnaires have not been returned 2 weeks after having been sent out, a letter will be sent to the patients enclosing another booklet requesting completion and return in the usual way. The 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 PROMS assessments. Full explanation of the PROMS 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.

PROMS Study Management

Trials Office

The Study Co-ordinator, based in the FAST-Forward Trials Office, will be responsible for overall co-ordination of the study. The Co-ordinator will liaise closely with those responsible

for the PROMS study in each participating centre and with the expert psycho-oncologist and clinicians involved in the project. The Co-ordinator 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 PROMS protocol. This person will explain the study to the patient, ensuring that the patient understands how to complete the PROMS questionnaire, and forward the first set of completed questionnaires to the Study Co-ordinator. He or she will maintain close liaison with the Study Co-ordinator in the FAST-Forward Trials Office and be responsible for organising cover in times of holiday or other planned absence.

PROMS Data Management

The Study Co-ordinator will be responsible for checking the data for consistency and completeness, for providing reminders for overdue questionnaires 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 PROMS questionnaires 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 [8]. The treatment groups will be compared at the individual time points with appropriate adjustments being made for multiple comparisons. Normal tissue effects will also be analysed using methodology developed for the START Trials i.e. survival analyses of time to occurrence of moderate or marked effects (scored ‘quite a bit’ or ‘very much’). 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 [9,10]. 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 socio-demographic and clinical characteristics.

Informed Consent and Ethical Issues

Details for the main trial are outlined in section 20.1. 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 PROMS assessment.

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APPENDIX 5: Health Economics (HE)

Rationale for HE measurement

The primary outcome measure for the health economic evaluation will be the cost per quality-adjusted life year (QALY) gained informed from health resource usage and EQ-5D-5L health status. The objective of the health economic evaluation is to establish whether a 5-fraction schedule of curative radiotherapy is cost-effective relative to current UK practice.

The health economic analysis will make use of a generic, preference-based measure of HRQoL (health-related quality of life). The objective is to have an index measure of HRQoL where quality of life and absence of morbidity are valued on the same scale as quantity or length of life. This enables the calculation of quality adjusted survival where duration of time spent experiencing certain health states (e.g. receiving radiotherapy, experiencing a local recurrence) is weighted according to the HRQoL value associated with that health state [1, 2].

Short term study

All patients in the PROMS study will complete the EQ-5D-5L assessment at 3 months in order to compare HRQoL 'off treatment' between treatment groups. This would provide information about how soon HRQoL may improve following radiotherapy and provide information on whether any differences between treatment arms persist beyond the end of treatment.

Long term study

Comparison of HRQoL at one year would provide information to test the assumption that there are no long-term differences in HRQoL directly resulting from different radiotherapy fractionation schedules. Repeated follow-up of EQ-5D-5L could potentially be used to estimate the impact of ever having had a long-term adverse event and/or recurrence on HRQoL. However, as recurrences are likely to be rare, data on the HRQoL impacts of recurrence may be supplemented or obtained from literature review. Such published data may be limited for the long-term adverse events associated with radiotherapy.

Resource use data

The aim of this part of the HE evaluation would be to compare the treatment groups in terms of resource implications for the NHS. This would primarily entail comparing the costs of providing each radiotherapy regimen and the costs of treating adverse events (short and long term) and further breast cancer events. The trial may well detect hospitalisations associated with adverse events or further breast cancer events. Questions relating to resource use outside of inpatient care, such as the use of specialist nurses, GP visits, medication and outpatient visits for treating adverse events and side effects from treatment will be added to the PROMS questionnaires, as in the IMPORT LOW trial. Information on the resource use

associated with recurrent breast cancer events may be supplemented or obtained from literature review. These data may be limited for long-term adverse events associated with radiotherapy. In previous studies expert opinion has been utilised to provide estimates of the resource use that would typically be associated with common adverse events, which is then applied to the number of such events observed in the trial.

Measures

The **EQ-5D-5L** is a standardised instrument designed for self-completion in an adult population [3]. The questionnaire asks patients to describe their current health status by specifying one of five levels of severity (no problems, slight problems, moderate problems, severe problems and unable to/extreme problems) across five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). The preference based health related quality of life weights for each of the health states described by the EQ-5D-5L are currently being estimated and will be available before the end of the trial. Currently EQ-5D-5L health states can be valued using a cross-walk algorithm from a set of preferences established on the basis of a UK general population survey [4].

The resultant EQ-5D-5L scores will be compared between each regimen at each time point and will inform the health economic analysis in calculating quality adjusted survival for patients receiving each regimen. Where appropriate, the EQ-5D-5L scores will be subject to regression analysis to identify the impact on health related quality of life of having experienced an adverse event or recurrence. In order to extrapolate beyond the trial these data will be supplemented by a literature search of previous studies of the health related quality of life impact of treatment and events in patients with breast cancer.

The EQ-5D-5L will enable the calculation of quality adjusted life years that would be consistent and comparable with those routinely used in the economic evaluation of health care technologies by the National Institute for Health and Clinical Excellence in the UK [5].

Resource use questions:

1. How many times have you **been visited** by your GP for any reason (even if **not** related to your breast cancer)?
2. How many times have **you visited** your GP for any reason (even if **not** related to your breast cancer)?
3. How many times have you **been visited** by a district nurse?
4. How many times have you **been visited** by a MacMillan nurse?
5. How many days have you spent in hospital **related to your breast cancer**?
6. How many days have you spent in hospital **for other reasons**?
7. How many hospital outpatient visits have you had **related to your breast cancer**?

8. How many hospital outpatient visits have you had **for other reasons**?

Timing of assessments

EQ-5D-5L and resource used questions will be collected at: baseline 3 and 6 months post radiotherapy and 1, 2, 5 and 10 years post randomisation.

Methods

A decision analytic model describing a series of health states and health events experienced by patients with early breast cancer will be developed [6]. This model will be used to synthesise information from the trial and other published studies in order to estimate costs and quality adjusted survival over an appropriate time horizon from the perspective of the UK NHS and PSS. Uncertainty around the values used in the decision analytic model will be characterised using probabilistic sensitivity analysis. The trial regimens will be evaluated using standard cost-effectiveness analysis. If one strategy is not found to be dominant (i.e. less costly and more effective) in comparison to the other, then an incremental cost-effectiveness ratio (ICER) will be determined [7]. The ICER will be based on the mean costs and mean QALYs estimated within the probabilistic sensitivity analysis of the decision model. Uncertainty around cost-effectiveness will be described using cost-effectiveness acceptability curves which describe the probability that an intervention is cost-effective.

Appendix 5 references

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APPENDIX 6: Summary of Inclusion/exclusion criteria for the trial

Eligibility Criteria						
Inclusion Criteria		**Version 1 27/05/2011**	**Version 2 13/02/2013**	**Version 2.2 02/05/2013**	**Version 3 08/07/2015**	**Version 4 24/02/2017**
1	Age ≥18 years	✓	✓	✓	✓	✓
2	Female or male	✓	✓	✓	✓	✓
3	Invasive carcinoma of the breast	✓	✓	✓	✓	✓
4	Breast conservation surgery or mastectomy (reconstruction allowed but not with implant. Tissue expanders with distant metal ports are allowed)	✓	N/A	N/A	N/A	N/A
4	Breast conservation surgery or mastectomy (reconstruction allowed)	N/A	✓	✓	✓	✓
5	Axillary staging &/or dissection	✓	✓	✓	✓	✓
6	Complete microscopic excision of primary tumour	✓	✓	✓	✓	✓
7	pT1-3 pN0-1 M0 disease (superseded)	✓	✓	✓	N/A	N/A
7	pT1-3, pN1-2, M0 disease (superseded)	N/A	N/A	N/A	✓	N/A
7	pT1-3 pN1-3a M0 disease	N/A	N/A	N/A	N/A	✓
8	Histological involvement of axillary lymph nodes	N/A	N/A	N/A	✓	✓
9	Indication for radiotherapy to level I-III axilla and/or level IV axilla (SCF)	N/A	N/A	N/A	✓	✓
10	Written informed consent	✓	✓	✓	✓	✓
11	Able to comply with follow up	✓	✓	✓	✓	✓
12	Concurrent trastuzumab and hormone therapy is allowed	✓	✓	✓	✓	✓

Eligibility Criteria						
Exclusion Criteria		**Version 1 27/05/2011**	**Version 2 13/02/2013**	**Version 2.2 02/05/2013**	**Version 3 08/07/2015**	**Version 4 24/02/2017**
1	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	✓	✓	✓	✓	✓
2	Contralateral breast cancer, including DCIS, irrespective of date of diagnosis (superseded)	✓	N/A	N/A	N/A	N/A
2	Ipsilateral and contralateral breast cancer, including DCIS, irrespective of date of diagnosis (superseded)	N/A	✓	N/A	N/A	N/A
2	Contralateral and/or previous ipsilateral breast cancer, including DCIS, irrespective of date of diagnosis	N/A	N/A	✓	✓	✓
3	Breast reconstruction using implants	✓	N/A	N/A	N/A	N/A
4	Concurrent cytotoxic chemotherapy (sequential neoadjuvant or adjuvant cytotoxic therapy allowed as long as there is ≥ 2 weeks between therapy and radiotherapy)	✓	✓	✓	✓	✓
5	Radiotherapy to any regional lymph node areas (excepting lower axilla included in standard tangential fields to breast/chest wall)	✓	✓	✓	N/A	N/A
6	Age ≥65 years and pT1G1/G2 ER+HER2-pN0 M0 invasive disease	N/A	✓	✓	N/A	N/A
7	Ipsilateral microinvasive disease and/or non-gradeable tumours	N/A	✓	✓	✓	✓
8	Any patient with N0 disease	N/A	N/A	N/A	✓	✓
9	Known residual macroscopic nodal disease	N/A	N/A	N/A	✓	✓
10	≥10 positive axillary nodes	N/A	N/A	N/A	✓	N/A
11	Any positive level IV (SCF) nodes	N/A	N/A	N/A	✓	✓
12	Any requirement for internal mammary chain (IMC) RT because indications for IMC RT are currently unclear	N/A	N/A	N/A	✓	✓