NETSCC, HTA

15th September 2011

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

Chief Clinical Coordinators:	Dr Murray Brunt (University Hospital of North Staffordshire) Dr Duncan Wheatley (Royal Cornwall Hospital)
Chief Investigator:	Professor John Yarnold (The Institute of Cancer Research/ The Royal Marsden NHS Foundation Trust)
Sponsor:	The Institute of Cancer Research
Funders:	National Institute for Health Research - Health Technology Assessment programme.
Coordinating Trials Unit:	ICR Clinical Trials and Statistics Unit (ICR-CTSU) The Institute of Cancer Research, Sutton.

PROTOCOL

Version 1: 27/05/2011

ICR-CTSU Protocol Number: **ICR-CTSU/2010/10026**

Main REC Reference Number: **11/LO/0958**

Funder Reference Number: **09/01/47**

ISRCTN19906132

The FAST-Forward trial has been scientifically approved and funded by National Institute for Health Research Health Technology Assessment programme.
The FAST-Forward trial is part of the National Institute for Health Research Clinical Research Network Trial Portfolio

ADMINISTRATION

1. Clinical Coordination

Chief Clinical Co-ordinators	Chief Investigator
Dr Murray Brunt University Hospital of North Staffordshire Stoke-on-Trent ST4 6QG Tel: 01782 672565 Email: murray.brunt@uhns.nhs.uk Dr Duncan Wheatley Royal Cornwall Hospital Truro TR1 3LJ Tel: 01872 258303 Email: duncan.wheatley@rcht.cornwall.nhs.uk	Professor John Yarnold The Institute of Cancer Research Royal Marsden Hospital Downs Road Sutton, Surrey SM2 5PT Tel: 020 8661 3388 Fax: 020 8643 8809 Email: john.yarnold@icr.ac.uk

2. Biological Co-ordination

Blood Sample Collection	Tissue Sample Collection
Mark Sydenham The Institute of Cancer Research Sutton, Surrey SM2 5NG Tel: 020 8722 4104 Email: mark.sydenham@icr.ac.uk	Mark Sydenham The Institute of Cancer Research Sutton, Surrey SM2 5NG Tel: 020 8722 4104 Email: mark.sydenham@icr.ac.uk

3. Trial Coordination

ICR Clinical Trials & Statistics Unit (ICR-CTSU), Section of Clinical Trials,
The Institute of Cancer Research,
Sir Richard Doll Building, Cotswold Road, Sutton, Surrey SM2 5NG

ICR-CTSU (a UKCRC registered and NCRI accredited clinical trials unit) is responsible for the day to day conduct of the trial

ICR-CTSU Scientific Lead : Judith Bliss
Tel: 020 8722 4297
Email: judith.bliss@icr.ac.uk

FAST-Forward Trial Manager: Mark Sydenham
Tel: 020 8722 4104
Email: mark.sydenham@icr.ac.uk

ICR-CTSU Senior Statistician: Jo Haviland
Tel: 05602 848697
Email: jo.haviland@icr.ac.uk

Any questions relating to this protocol should be addressed in the first instance to the FAST-Forward Trial Manager within ICR-CTSU:

Email: fastforward-icrctsu@icr.ac.uk **General enquiries:** 0208 722 4104
Fax: 0208 770 7876

Protocol Development Group

Rajiv Agrawal, Royal Shrewsbury Hospital; Abdulla Alhasso, Beatson Oncology Centre; Peter Barrett-Lee, Velindre Hospital; Jane Beety, Norfolk and Norwich Hospital; Judith Bliss, ICR-CTSU, Sutton; Peter Bliss, Torbay Hospital; David Bloomfield, Royal Sussex County Hospital; Jo Bowen, Cheltenham General Hospital; Murray Brunt, University Hospital of North Staffordshire; Mark Churn, New Cross Hospital, Wolverhampton; Laura Ciurlionis, NCRI QA Team, Mount Vernon Hospital; Suzy Cleator, St Mary's Hospital, Paddington; Charlotte Coles, Addenbrooke's Hospital; John Dewar, Ninewells Hospital; Ellen Donovan, RMH Sutton; Paul Dyson, Cumberland Infirmary; Marie Emson, ICR-CTSU, Sutton; Andrew Goodman, Torbay Hospital; Susan Griffin, Centre for Health Economics, York; Sam Guglani, Cheltenham General Hospital; Adrian Harnett, Norfolk and Norwich University Hospital; Jo Haviland, ICR-CTSU, Sutton; Penny Hopwood, ICR-CTSU, Sutton; Judith Mills, ICR-CTSU, Sutton; Sarah McKenna, Independent Cancer Patients Voice; Carolyn Morris, Independent Cancer Patients Voice; Helen Passant, Velindre Hospital, Cardiff; Christine Rawlings, Torbay District General Hospital; Anne Robinson, Southend General Hospital; Elinor Sawyer, Guy's and St Thomas' Hospital; Mark Sculpher, Centre for Health Economics, York; Judith Sinclair, Charing Cross Hospital; Navita Somaiah, Radiobiology Institute, University of Oxford; Emma Staples, Queens Hospital, Romford; Georges Sumo, ICR-CTSU; Mark Sydenham, ICR-CTSU, Sutton; Isabel Syndikus, Clatterbridge Centre for Oncology; Jean Tremlett , Royal Sussex County Hospital; Yat Tsang, NCRI QA Team, Mount Vernon Hospital; Karen Venables, NCRI QA Team, Mount Vernon Hospital; Duncan Wheatley, Royal Cornwall Hospital, Treliske; John Yarnold, Royal Marsden Hospital, Sutton

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 John Yarnold (Chief Investigator)	**27.05.2011**	

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.

TABLE OF CONTENTS

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.
Eligibility Criteria	*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 allowed but not with implant. Tissue expanders with distant metal ports are allowed) • axillary staging &/or dissection • complete microscopic excision of primary tumour • pT1-3 pN0-1 M0 disease • written informed consent • able to comply with follow up N.B. Concurrent trastuzumab and hormone therapy is allowed *Exclusion criteria (the patient is ineligible if any of the following are met):* • 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 • contralateral breast cancer, including DCIS, irrespective of date of diagnosis • breast reconstruction using implants • concurrent cytotoxic chemotherapy (sequential neoadjuvant or adjuvant cytotoxic therapy allowed) • radiotherapy to any regional lymph node areas (excepting lower axilla included in standard tangential fields to breast/chest wall)
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. 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) must be declared before randomisation. Each patient will be allocated to one of the following groups: **Control**: 40.05 Gy in 15 Fr of 2.67 Gy **Test 1**: 27.0 Gy in 5 Fr of 5.4 Gy **Test 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, quality of life, contralateral primary tumours, regional and distant metastases and survival.

Sample Size	The sample size is 4,000 patients, with numbers balanced equally in each randomised group. This provides 80% power (1-sided α = 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, quality of life studies, 2196 patients would 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%). Acute toxicity will be monitored in the first 150 or so patients in the trial, to exclude a rate of RTOG grade ≥3 acute skin reactions of over 11% (89% power and 7.9% significance).
Follow Up	Clinical follow up is as per local practice with annual follow up for recurrence for at least 10 years from date of randomisation. Acute toxicity will be assessed by a healthcare professional in the first 150 patients recruited to the trial using a modified RTOG grading system. This will be carried out weekly during radiotherapy and for 4 weeks after treatment. If symptoms persist the patients will be assessed weekly until their reaction settles to RTOG grade 1 or less.
Photographic study	Photographs will be taken at baseline and at 2, 5 and 10 years post randomisation in centres with local facilities. This study will start once the acute toxicity study has finished/ 150 patients have been recruited to the trial.
Quality of Life Study	Quality of Life (QL) will be assessed using the EORTC QLQ-C30 v3.0, EORTC BR23 breast cancer module, BIS and HADS scales and the EORTC FA-13 fatigue module. This study will start once the acute toxicity study has finished/ 150 patients have been recruited to the trial. QL questionnaires will be completed at baseline, 3 and 6 months, 1, 2, 5 and 10 years post randomisation. The QL study will be undertaken in a subset of centres in the trial. All patients in these centres will be asked to take part in the QL study.
Translational Studies	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. Patients will also be asked to consent to the donation of a tissue sample should a recurrence occur. A sample of the original tumour will also be collected at this time.

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].

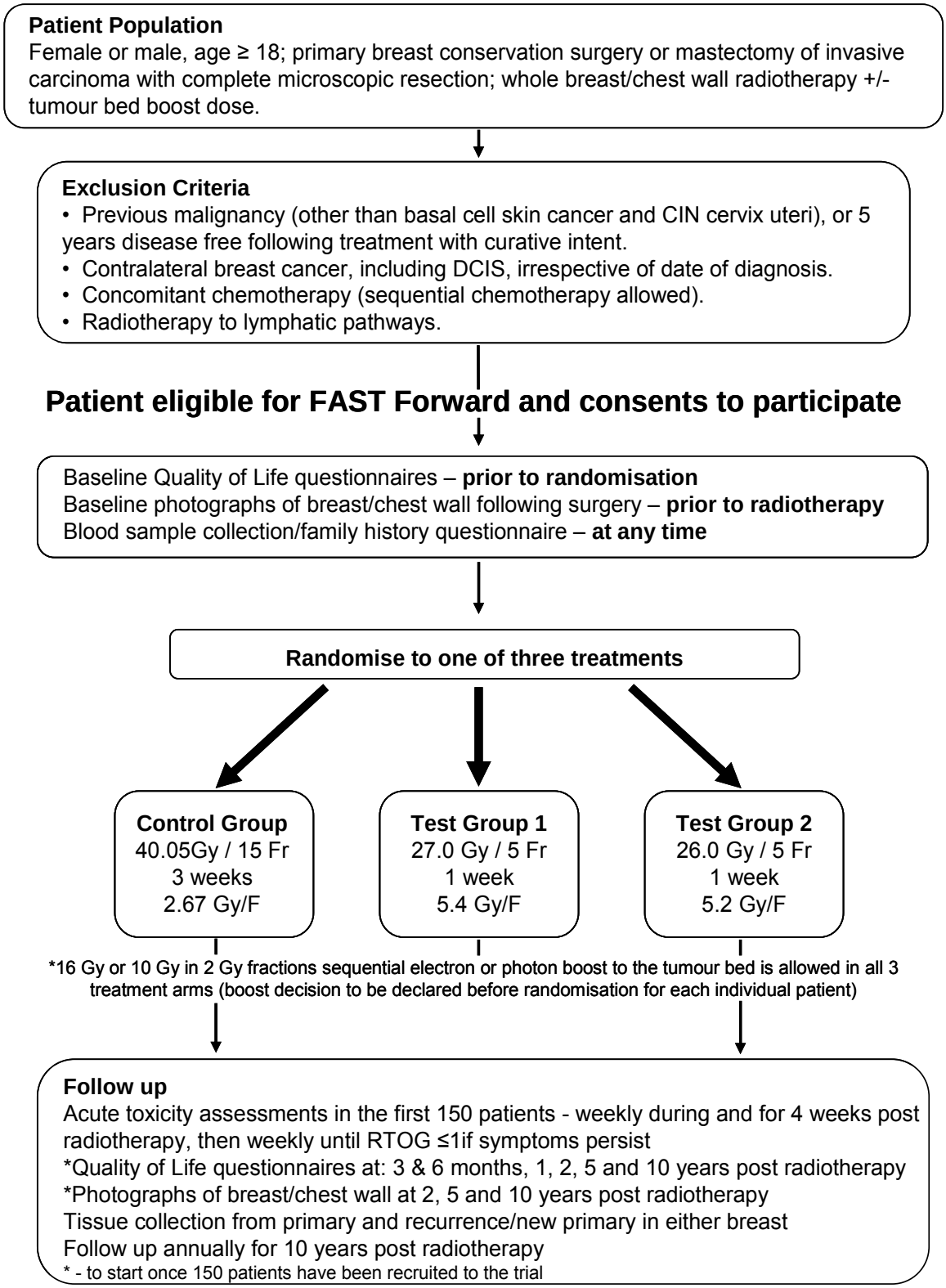
3. AIM

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 and quality of life (QL).

4. TRIAL DESIGN

FAST-Forward is a multicentre phase III randomised controlled trial.

4.1 Trial Schema



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, including quality of life and photographic assessments
- Contralateral primary tumours
- Regional and distant metastases
- Overall survival.

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 unless they have implants).

6.2 Number of Patients

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 $\geq$50 and grades 1 or 2) and high risk (age <50 and/or grade 3).

6.3 Inclusion Criteria

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 allowed, but not with implant. Tissue expanders with distant metal ports are allowed)
- axillary staging &/or dissection
- complete microscopic excision of primary tumour
- pT1-3 pN0-1 M0 disease
- written informed consent

- able to comply with follow up

N.B. concurrent trastuzumab and/or hormone therapy are allowed

6.4 Exclusion Criteria

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

- 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
- contralateral breast cancer, including DCIS, irrespective of date of diagnosis
- breast reconstruction using implant
- concurrent cytotoxic chemotherapy (sequential neoadjuvant or adjuvant cytotoxic therapy allowed)
- radiotherapy to any regional lymph node area (excepting lower axilla included in standard tangential fields to breast/chest wall)

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 treatment side effects study (first 150 patients only)
- whether the patient has consented to photographic assessments (once 150 patients have been recruited to the trial)
- whether the patient has consented to take part in the QL study (once 150 patients have been recruited to the trial)
- whether the patient has consented to blood sample and tissue collection

- whether the patient has consented to the use of information held by the NHS and the General Register Office
- whether a boost is to be given and what dose level

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. Randomisation will be stratified by centre and risk group.

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. Acute reactions (first 150 patients in the trial)

Acute reactions of the skin of the treated breast will be recorded in the first 150 patients recruited into the trial. This will be assessed as described below.

Clinical assessments of acute adverse effects

The acute reactions of the skin of the treated breast will be graded according to the RTOG criteria (Appendix 1) and will be assessed by a healthcare professional at each centre. The assessments will be carried out weekly during treatment and for 4 weeks following the end of radiotherapy. If symptoms persist the assessments will continue weekly until the reaction is RTOG grade 1 or less.

Patient self-assessments of acute adverse effects

The patient will be 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 will be recorded as “none”, “a little”, “quite a bit” or “very much”. If symptoms persist then patients will be asked to continue scoring their adverse effects on a weekly basis until all scores are graded as “none” or “a little”.

8.2.2 Late reactions (all patients)

Late adverse effects will be measured using an annual clinical assessment. Late effects will also be measured in a subset of patients using photographic assessments and patient self-assessments from the quality of life questionnaires. Incidence of ischaemic heart disease and second malignancies will also be recorded.

Clinical assessments of late adverse effects

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 (for all patients).

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

Digital photographs will be taken at baseline (post-surgery but pre-RT) and at years 2, 5 and 10 after radiotherapy. 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. Change in breast/reconstructed breast/chest wall appearance and distortion

compared with the post-surgical baseline will each be scored on a three-point graded scale. Breast size and surgical deficit will each be assessed on a three-point graded scale 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 [15] and assessments for FAST-Forward will build on these existing methods, including validating the method in chest wall patients.

Patient self-assessments of late adverse effects (Quality of Life study)

Patients will be asked to complete self-assessments of quality of life at baseline, 3 and 6 months and 1, 2, 5 and 10 years after treatment. These will include the EORTC QLQ-C30 core questionnaire [16], the EORTC BR-23 Breast Cancer module [17], the Body Image Scale [18] and the Hospital Anxiety and Depression Scale (HADS) [19]. Of particular interest will be patient self-reporting of symptoms and impact on body image and functioning subscales. The aim will be to seek a patient-derived notion of 'radiation tolerance' that can be compared with physician and photographic endpoints, including interpolated estimates of isoeffect.

9. FOLLOW-UP

After treatment clinical follow up should follow local guidelines.

For the purpose of the study, assessment of acute toxicities will be performed in the first 150 patients in the study. These will be undertaken weekly during treatment, for 4 weeks after treatment and weekly until the symptoms have reached RTOG≤1.

Follow up data will be collected annually for 10 years. Assessment of safety (late toxicities) and recurrence will be incorporated into the follow up visits.

Photographs will be taken from consenting patients at baseline and at 2, 5 and 10 years post randomisation.

Quality of Life booklets will be completed by consenting patients at baseline, 3 and 6 months and 1, 2, 5 and 10 years post randomisation.

Both of these studies will commence once 150 patients have been recruited into the trial.

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 QL 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 appropriate CRF form.

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								
Event	Prior to randomisation	Post randomisation pre RT	wk 1	wk 2	wk 3	Weekly to week 8	mth 3	mth 6	yr 1	yr 2	yr 3	yr 4	yr 5	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		**x (first 150 pts)**	**x**	**x**	**x**	**x**								
Clinical assessment		**x (first 150 pts)**	**x**	**x**	**x**	**x (first 150 pts)**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x (Annually to yr 10)**
Quality of life	**x (baseline*)**						**x**	**x**	**x**	**x**			**x**	**x**
Photographic assessment		**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^{o} tumour - recurrence/new 1^{o} tumour		**As requested during the trial**												

***** *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*

10. RADIOTHERAPY

Patients are randomised to 15 or 5 daily fractions (Fr) to the whole breast or post-mastectomy chest wall. 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 Fr) must be declared before randomisation. Each patient will be allocated to one of the following groups:

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

10.1 Dose Prescriptions

10.1.1 Whole breast/chest wall

Trial group	Total dose (Gy)	Dose per fraction (Gy)	Number of fractions	Fractions per week	Treatment time (weeks)
***Control**	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 of each patient, together with the dose to be used. The dose prescription is either 10.0 Gy in 5 fractions or 16.0 Gy in 8 fractions 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.

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 [20]. 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.

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 [21]. 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 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 and tumour bed. A field-based whole breast PTV can be used and this method is illustrated in the planning pack.

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. 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 must not be moved between tangential 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. 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. 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.

Upper and lower dose limits for whole breast PTV

Lower dose limit	Prescription dose	Upper dose limit
>95% of the volume should receive 95% of the prescribed dose	Use START ref 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 PTV

12.1 Dose Constraints for Organs at Risk (OAR)

The dose constraints for 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. 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

12.2 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.

12.3 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.

12.4 Tumour bed radiotherapy

The tumour bed boost treatments can be either delivered by electron or photon beams. Either 10.0 Gy in 5 fractions or 16.0 Gy in 8 fractions 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 and Chest Wall

Verification is carried out using electronic portal imaging of the treatment beam. 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, with imaging to confirm the move. A suitable tolerance for the check of the correction is 5 mm. Verification is then once weekly throughout the remaining whole breast field treatment with a tolerance of 5 mm.

*All systematic errors should be corrected if possible, 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

Test group 1 and 2: Verification imaging and correction are required for each fraction. Set up error is corrected on each fraction prior to treatment, with a further image taken to confirm the correction. A tolerance of 5 mm is suitable for the check of the correction.

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

An off-line verification protocol is recommended. This consists of imaging on the first two fractions. The calculation of any systematic error from this data is then carried out and the correction for the systematic error is applied on fraction three. A check image is recommended prior to treatment on fraction three. A suitable tolerance for the check is 5mm. This protocol is appropriate for a PTV margin of 10 mm.

Where the boost fractionation is 16.0Gy in 8 fractions, centres may wish to image on/around fraction 6 as a further check; again a suitable tolerance is 5 mm.

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 individual centres and should be discussed with the QA team.

15. RADIOTHERAPY QUALITY ASSURANCE

A comprehensive quality assurance 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

N.B. Progressive disease and death due to disease are not considered SAE's but should be reported on the relevant forms.

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 in the section below 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.

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

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. Other endpoints include normal tissue effects and quality of life. 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 QL data will follow algorithms developed for the QL 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 QL 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 QL 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.

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 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. 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

The first 150 or so patients accrued into the study will be assessed by a healthcare professional for acute skin toxicity up to settling of reaction to RTOG grade 1 and at least 4 weeks post radiotherapy. The patients will also be asked to complete the Radiotherapy Breast Symptoms Diary Cards for self-assessment of acute toxicity. This would enable a rate of 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 is 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 will be required (total 150). In each test group, if 3 or more patients develop grade ≥3 acute skin reactions, the IDMC may advise the Trial Steering Committee to consider a change in the test schedule.

17.3.3. QL and photographic sub-studies

For the sub-studies (photographic assessments and quality of life), 732 patients per group (2196 in total) would 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 calculations allow for up to 10% loss to follow-up / unevaluable.

17.4 Interim analyses and Data Monitoring

The Independent Data Monitoring Committee (IDMC) will review the data on early skin reactions (up to 3 months following treatment) after the first evaluable 150 patients. This is based on data from the FAST Trial that has found a proportion of RTOG grade ≥3 acute skin reactions in the test groups (30 Gy and 28.5 Gy) of 2.3% and 10.9% in the control group (50 Gy). For each test group in the FAST-Forward Trial we would like to rule out a proportion of RTOG grade ≥3 acute skin reactions of 10.9% (p_0=89.1%). We expect this rate to be around 2.3% (p_1=97.7%) in the test groups (27 Gy and 26 Gy). 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 will be required (total 150). In each test group, if 3 or more patients develop grade ≥3 acute skin reactions, the IDMC may advise the Trial Steering Committee (TSC) to consider a change in the test schedule.

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 Quality of Life study or in the number of patients having photographic assessments, if it is felt that further information is required to address reliably the hypothesis in question.

18. ASSOCIATED STUDIES

At the time of randomisation all patients will be asked to consent to gift 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 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 Quality of Life Study

The quality of life study will be implemented once the acute toxicity study has finished i.e. after the first 150 patients have been recruited into the trial.

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 of QL such as fatigue. Results from the START trial have highlighted the value of patients' self-reported post–radiotherapy symptoms in discriminating between RT regimens in favour of hypofractionation [22]. Experience of the START trials showed that patient-rated cancer specific QL data, obtained with the EORTC QLQ-C30 [16] provided useful data at baseline (for example concerning the effects of surgery) [23] and also made a small contribution to a comparison of the regimens up to 2 years, fewer changes in parameters were observed from 2-5 years (unpublished data 2010).The FAST-Forward QL sub study is planned to provide subjective views of key breast symptoms and, body image over 10 years of follow-up and 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 QL are hypothesised to be on a range of breast symptoms as reported for the START trial [22] and potentially on body image plus short term general effects such as fatigue. Patient-reported arm and shoulder symptoms associated with RT are expected to be minimal since lymphatic RT is not allowed in the FAST-Forward trial. In the START trials these symptoms largely related to prior surgery [22].

The QL study is detailed in Appendix 4.

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 QL questionnaires returned by post
- logging clinical and QL 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 Quality of Life study will provide their name, address and telephone number and also address and phone number of their GP to ICR-CTSU.

These details will only be used for the purposes of the Quality of Life study. The principal investigator must keep a separate log of patients' trial numbers, names, and hospital numbers. The principal investigator must maintain in strict confidence trial documents, which are to be held in the local centre (e.g. patients' written consent forms). The principal investigator must ensure the patient's confidentiality is maintained.

ICR-CTSU will maintain the confidentiality of all 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 quality assurance 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 are 2 separate PIS for the trial. One is for the first 150 patients in the trial and details the "Short term side effects" study. A second PIS is to be used for all other patients once 150 patients have been recruited into the study. It contains details of the collection of biological samples, Quality of Life and photographic sub-studies. Patients will be encouraged to participate in these 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 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 portfolio and NCRN (or regional equivalent) 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.

25. REFERENCES

1. Bates, T.D., *The 10-year results of a prospective trial of post-operative radiotherapy delivered in 3 fractions per week versus 2 fractions per week in breast carcinoma.* Br J Radiol, 1988. **61**(727): p. 625-30.
2. Whelan, T., et al., *Randomized trial of breast irradiation schedules after lumpectomy for women with lymph node-negative breast cancer.* J Natl Cancer Inst, 2002. **94**(15): p. 1143-50.
3. Yarnold, J., et al., *Fractionation sensitivity and dose response of late adverse effects in the breast after radiotherapy for early breast cancer: long-term results of a randomised trial.* Radiother Oncol, 2005. **75**(1): p. 9-17.
4. Owen, J.R., et al., *Effect of radiotherapy fraction size on tumour control in patients with early-stage breast cancer after local tumour excision: long-term results of a randomised trial.* Lancet Oncol, 2006. **7**(6): p. 467-71.
5. Bentzen, S.M., et al., *The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial.* Lancet Oncol, 2008. **9**(4): p. 331-41.
6. Bentzen, S.M., et al., *The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial.* Lancet, 2008. **371**(9618): p. 1098-107.
7. James, M.L., et al., *Fraction size for radiation treatment for breast conservation in early breast cancer.* Cochrane Database of Systematic Reviews, 2008(3).
8. Courdi, A., et al., *Long-term results of hypofractionated radiotherapy and hormonal therapy without surgery for breast cancer in elderly patients.* Radiother Oncol, 2006. **79**(2): p. 156-61.
9. Kirova, Y.M., et al., *Breast-conserving treatment in the elderly: long-term results of adjuvant hypofractionated and normofractionated radiotherapy.* Int J Radiat Oncol Biol Phys, 2009. **75**(1): p. 76-81.
10. Brunt, A.M., et al., *A 5-fraction regimen of adjuvant radiotherapy for women with early breast cancer: first analysis of the randomised UK FAST trial (ISRCTN62488883, CRUKE/04/015).* EJC Supplements. Presidential sessions late breaking and best of ECCO 15-ESMO 34 Abstracts, 2009. **7**(3): p. 2.
11. Huang, J., et al., *Does delay in starting treatment affect the outcomes of radiotherapy? A systematic review.* J Clin Oncol, 2003. **21**(3): p. 555-63.
12. Hebert-Croteau, N., et al., *Delay in adjuvant radiation treatment and outcomes of breast cancer--a review.* Breast Cancer Res Treat, 2002. **74**(1): p. 77-94.
13. Martin, S., et al., *Acute toxicity and 2-year adverse effects of 30 Gy in five fractions over 15 days to whole breast after local excision of early breast cancer.* Clin Oncol (R Coll Radiol), 2008. **20**(7): p. 502-5.
14. Bartelink, H., et al., *Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC 22881-10882 trial.* J Clin Oncol, 2007. **25**(22): p. 3259-65.
15. Haviland JS et al., Evaluation of a method for grading late photographic change in breast appearance after radiotherapy for early breast cancer. Clin Oncol (R Coll Radiol). 2008 Sep;**20**(7):497-501.
16 Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JC, et al. *The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for*

use in international clinical trials in oncology. J Natl Cancer Inst.1993 Mar 3;85(5):365-76.

17 Sprangers, M.A. and et al, *The European Organisation for Research and Treatment of Cancer Breast Cancer-Specific Quality-of Life Questionnaire Module: First results from a three-country field study.* J Clin Oncol, 2001. **5**(Classic Papers and Current Comments): p. 917-929.

18 Hopwood, P., et al., *A body image scale for use with cancer patients.* Eur J Cancer, 2001. **37**(2): p. 189-97.

19 Zigmond, A.S. and R.P. Snaith, *The hospital anxiety and depression scale.* Acta Psychiatr Scand, 1983. **67**(6): p. 361-70.

20 *START-Standardisation of Breast Radiotherapy, trial protocol*. 1998.

21 *Surgical guidelines for the management of breast cancer.* Eur J Surg Oncol, 2009. **35 Suppl 1**: p. 1-22.

22. Hopwood P, Haviland JS, Sumo G, Mills J, Bliss JM, Yarnold JR; START Trial Management Group. *Comparison of patient-reported breast, arm, and shoulder symptoms and body image after radiotherapy for early breast cancer: 5-year follow-up in the randomised Standardisation of Breast Radiotherapy (START) trials*. Lancet Oncology 2010 Mar;11(3):231-40. Epub 2010 Feb 6.

23. Hopwood P, Haviland J, Mills J, Sumo G, Bliss J on behalf of the START Trial Management Group: The impact of age and clinical factors on quality of life in early breast cancer: An analysis of 2200 women recruited to the UK START (Standardisation of Breast Radiotherapy) Trial. Breast 2007;16: 241-51

APPENDIX 1: Acute skin reactions scoring scale (modified RTOG)

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

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

1. Bentzen, S.M., et al., *The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial.* Lancet, 2008. **371**(9618): p. 1098-107.
2. Martin, S., et al., *Acute toxicity and 2-year adverse effects of 30 Gy in five fractions over 15 days to whole breast after local excision of early breast cancer.* Clin Oncol (R Coll Radiol), 2008. **20**(7): p. 502-5.
3. Turesson, I. and G. Notter, *Accelerated versus conventional fractionation. The degree of incomplete repair in human skin with a four-hour-fraction interval studied after postmastectomy irradiation.* Acta Oncol, 1988. **27**(2): p. 169-79.
4. Bentzen, S.M., M.I. Saunders, and S. Dische, *Repair halftimes estimated from observations of treatment-related morbidity after CHART or conventional radiotherapy in head and neck cancer.* Radiother Oncol, 1999. **53**(3): p. 219-26.

APPENDIX 3: Quality Assurance Programme

1. Background

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

A quality assurance programme is “a mandatory prerequisite when aiming at high dose, high precision radiotherapy” and is an integral component of any radiotherapy trial as defined by the EORTC guidelines for trial protocols in radiotherapy [1, 2].

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

In this way the definition of quality assurance as “all those planned and systematic actions necessary to provide adequate confidence that a produce will satisfy given requirements of quality” [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 quality assurance 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 to around 20 centres over a three and a half to four year period. 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 ideal plans to be produced by each centre, where not already assessed for another trial.

2.2 A visit by the quality assurance 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.

4. Analysis of QA programme

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

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

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

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

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

i) Variations in breast radiotherapy practice in participating centres

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

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

iv) Quantification of dose uniformity during the treatment period

v) Correlation of physical parameters of radiation with trial 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.

Appendix 3 references

1. Horiot, J.C., et al., *The programme of quality assurance of the EORTC radiotherapy group. A historical overview.* Radiother Oncol, 1993. **29**(2): p. 81-4.
2. Bolla, M., et al., *EORTC guidelines for writing protocols for clinical trials of radiotherapy.* Radiother Oncol, 1995. **36**(1): p. 1-8.
3. SMAC, *Quality Assurance in Radiotherapy*. 1991, Standing Committee on Cancer of the Standing Medical Advisory Committee.
4. Aird, E.G., et al., *Quality assurance in the CHART clinical trial.* Radiother Oncol, 1995. **36**(3): p. 235-44.
5. Venables, K., et al., *A survey of radiotherapy quality control practice in the United Kingdom for the START trial.* Radiother Oncol, 2001. **60**(3): p. 311-8.
6. IPEM, *81 Physics aspects of Quality Control in Radiotherapy*. IPEM Report, ed. W.P.M. Mayles, et al. 1999, York: IPEM.

APPENDIX 4: Quality of Life Study

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 of QL such as fatigue. Results from the START trial have highlighted the value of patients' self-reported post–radiotherapy symptoms in discriminating between RT regimens in favour of hypofractionation [1]. Experience of the START trials showed that patient-rated cancer specific QL data, obtained with the EORTC QLQ-C30 [2] provided useful data at baseline (for example concerning the effects of surgery) [3] and also made a small contribution to a comparison of the regimens up to 2 years, fewer changes in parameters were observed from 2-5 years (unpublished data 2010).The FAST-Forward QL sub study is planned to provide subjective views of key breast symptoms and, body image over 10 years of follow-up and 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 QL 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. Patient-reported arm and shoulder symptoms associated with RT are expected to be minimal since lymphatic RT is not allowed in the FAST-Forward trial. In the START trials these symptoms largely related to prior surgery [1].

Rationale for QL 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 six 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 - RT 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.

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 Hospital Anxiety and Depression Scale (HADS) [6], will be used to measure psychological distress. This is the most frequently used scale in clinical trials and provides clinically interpretable outcomes for anxiety and depression [7].

The EORTC 13-item Fatigue module (EORTC QLQ-FA-13 (revised version Phase III) [8, 9] will be used in this trial as detailed data are required to assess the impact of RT in the short and longer term. Relevant permission to use this scale has been obtained.

The QL endpoints 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 QL study is both comparative and descriptive: sample size considerations are addressed where appropriate.

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

The QL 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 QL domain: the aim is to provide information from all QL 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, 1, 2, 5 and 10 years. 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 QL 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 functioning, sexual enjoyment (BR23) and psychological distress (HADS)

Whilst we would not assume that these parameters are influenced primarily by radiotherapy, these domains are interrelated, for example a strong association exists between body image and depression - 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. Anxiety and depression will be assessed using the accepted threshold scores on the Hospital Anxiety and Depression Scale (HADS).

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 QL 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 QL study as part of another trial;
- consent to be part of the QL study and are available for follow up;
- are willing and able to complete the self-report QL questionnaires.

Sample Size

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

Patients will be stratified by centre and due representation geographically will be considered. The IDMC may recommend extending recruitment in the QL study in all or a specific subgroup of patients. 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 QL outcomes.

Baseline Quality of Life: All measures: EORTC QLQ-C30 and BR23, Protocol specific pre-RT items, Body Image Scale, EORTC Fatigue module and HADS.
A designated member of staff, trained in QL administration, will 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.

Quality of Life 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 QL measures (EORTC QLQ-C30 and BR23, Protocol specific post–RT breast symptoms, BIS, HADS and the EORTC Fatigue module) will therefore be mailed to patients from the FAST-Forward Trials Office at 3 and 6 months and 1, 2, 5, and 10 years.

Follow-up - general aspects of QL: 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 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 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. Where necessary, information about the patient's current well-being will be confirmed by email with a named person in the centre before sending a booklet.

Missing data

All reasonable efforts will be made to ensure correct completion of the QL assessments. Full explanation of the QL study will be given by the responsible research nurse/member of breast care team prior to administration of the baseline questionnaires. On collection, the questionnaires will be briefly checked for completeness. The follow-up questionnaires will include instructions for completion. When individual items are missing, procedures, which have been used in similar studies, will be adopted:

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

QL Study Management

Trials Office

The Study Co-ordinator, based in the 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 QL 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 QL protocol. This person will explain the study to the patient, ensure that the patient understands how to complete the QL questionnaire, and forward the first set of completed 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.

QL 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 QL 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 [10]. 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 [11-13]. 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 QL assessment.

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

Appendix 4 references

1. Hopwood P, Haviland JS, Sumo G, Mills J, Bliss JM, Yarnold JR; START Trial Management Group. *Comparison of patient-reported breast, arm, and shoulder symptoms and body image after radiotherapy for early breast cancer: 5-year follow-up in the randomised Standardisation of Breast Radiotherapy (START) trials*. Lancet Oncology 2010 Mar;11(3):231-40. Epub 2010 Feb 6.
2. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JC, et al. *The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology.* J Natl Cancer Inst.1993 Mar 3;85(5):365-76.
3. Hopwood P, Haviland J, Mills J, Sumo G, Bliss J on behalf of the START Trial Management Group: The impact of age and clinical factors on quality of life in early breast cancer: An analysis of 2200 women recruited to the UK START (Standardisation of Breast Radiotherapy) Trial. Breast 2007;16: 241-51
4. Sprangers, M.A. and et al, *The European Organisation for Research and Treatment of Cancer Breast Cancer-Specific Quality-of Life Questionnaire Module: First results from a three-country field study.* J Clin Oncol, 2001. **5**(Classic Papers and Current Comments): p. 917-929.
5. Hopwood, P., et al., *A body image scale for use with cancer patients.* Eur J Cancer, 2001. **37**(2): p. 189-97.
6. Zigmond, A.S. and R.P. Snaith, *The hospital anxiety and depression scale.* Acta Psychiatr Scand, 1983. **67**(6): p. 361-70.
7. Hopwood P, Sumo G, Mills J, Haviland J, Bliss JM; START Trials Management Group. *The course of anxiety and depression over 5 years of follow-up and risk factors in women with early breast cancer: results from the UK Standardisation of Radiotherapy Trials (START).* Breast 2010 Apr;19(2):84-91. Epub 2009 Dec 29.
8. Weis JB, Flechtner H, Bottomley A, Bredart A, Singer S, Holzner B, Larsson G, Jones L *"Development of an EORTC Module for the Assessment of Cancer Related Fatigue (EORTC FA 25; FAR 15)",* Quality of Life Research, (2005) Vol 14, No 9, pp 2035.
9. Weis J, Ya Gao, Conroy T, Singer S, Hammerlid E, Holzner B, Fleissner C, Efficace F, Arraras J, Bottomley A, Flechtner H, Lanceley A, Jones L. *Development of an EORTC module for the assessment of cancer related fatigue (EORTC FAR-15): Phase III results.*

Quality of Life Research, ISOQOL Conference Toronto, Canada, Abstracts Issue October 2007.
10. Agresti, A., *A survey of models for repeated ordered categorical response data.* Stat Med, 1989. **8**(10): p. 1209-24.
11. McCullagh, P. and J.A. Nelder, *Generalised Linear Models*. 1989, London: Chapman & Hall.
12. Liang, K.Y. and S.L. Zeger, *Longitudinal Data Analysis using Generalised Linear Models.* Biometrika, 1986. **73**: p. 13-22.
13 Kimman M et al. *Responsiveness of the EQ-5D in breast cancer patients in their first year after treatment.* Health and Quality of Life Outcomes 2009,7:11