FAST-Forward Boost

A randomised clinical trial testing a 1-week schedule of curative simultaneous integrated boost radiotherapy against a standard 3-week schedule in patients with early breast cancer.

PROTOCOL

Version: 2.1
Dated: 09/12/2025

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Sponsor:	The Institute of Cancer Research
Funder	National Institute for Health and Care Research Health Technology Assessment (NIHR-HTA)
Coordinating Trials Unit:	ICR Clinical Trials and Statistics Unit (ICR-CTSU) The Institute of Cancer Research
REC reference Number:	24/LO/0910
IRAS Reference Number:	341881
ICR-CTSU Protocol Number:	ICR-CTSU/2024/10088
Sponsor Number:	CCR6065
ISRCTN:	ISRCTN13849110
NIHR Reference Number:	NIHR157800

The FAST-Forward Boost study has been approved by National Institute for Health Research and is part of the National Institute for Health Research Clinical Research Network Trial Portfolio

ICR The Institute of Cancer Research

FUNDED BY NIHR | National Institute for Health and Care Research

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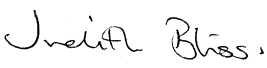
Professor Judith Bliss (ICR-CTSU Scientific Lead)		09/12/2025

This protocol describes the FAST-Forward Boost trial and provides information about procedures for entering participants into this trial. The protocol should not be used as a guide for the treatment of patients outside of this trial.

Every care was taken in the preparation of this protocol, but corrections or amendments may be necessary. Protocol amendments will be circulated to participating sites as they occur, but sites entering patients for the first time are advised to contact ICR-CTSU to confirm they have the most recent version.

HISTORY OF PROTOCOL AMENDMENTS

PROTOCOL VERSION AND DATE	SUMMARY OF CHANGES
2.1, 09.12.2025 (Changes from V2.0)	• Contact details updated • Addition of details regarding international site participation throughout • Clarification of exclusion criterion 7: continued exclusion of proton beam therapy following the closure of the PARABLE trial to recruitment (section 5.4) • PRO participation made non-mandatory after completion of recruitment to the Early Side Effects Substudy (section 8). • Clarification that screening logs include nodal status (section 6.1) • Clarification that Early Side Effects Substudy analysis will include review of dosimetry data (section 9.4)
2.0, 25.06.2025 (Changes from V1.0)	• Team contacts and study reference numbers updated • Trial summary and trial schema updated to reflect protocol changes • **Section 6.2:** clarification on minimum time required for consent; addition of optional Patient Information Leaflet • **Section 7:** clarification on process for database entry at consent/randomisation • **Section 8:** restructured for ease of reading, minor clarifications added on timings of assessments; on-treatment and end-of-treatment sections merged. o **Section 8.4**: Section inserted to clarify timing of assessments o **Section 8.5:** Introduction of 2 additional blood sample collection as part of the early side-effects translational substudy, subject to patient consent o **Section 8.10:** schedule of assessments updated • **Section 9.8:** pregnancy reporting period adapted to come in line with safety reporting period. Fig.1 updated to match non-CTIMP reporting structure. • **Section 10.6:** study progression criteria added • **Section 18.1:** New section added on early side effects translational substudy, including rationale, design and procedures for collecting two blood samples in addition to prior baseline blood sample. • **Section 18.2:** minor clarifications/rewording on other sample collection • Minor wording changes for clarity throughout; references updated

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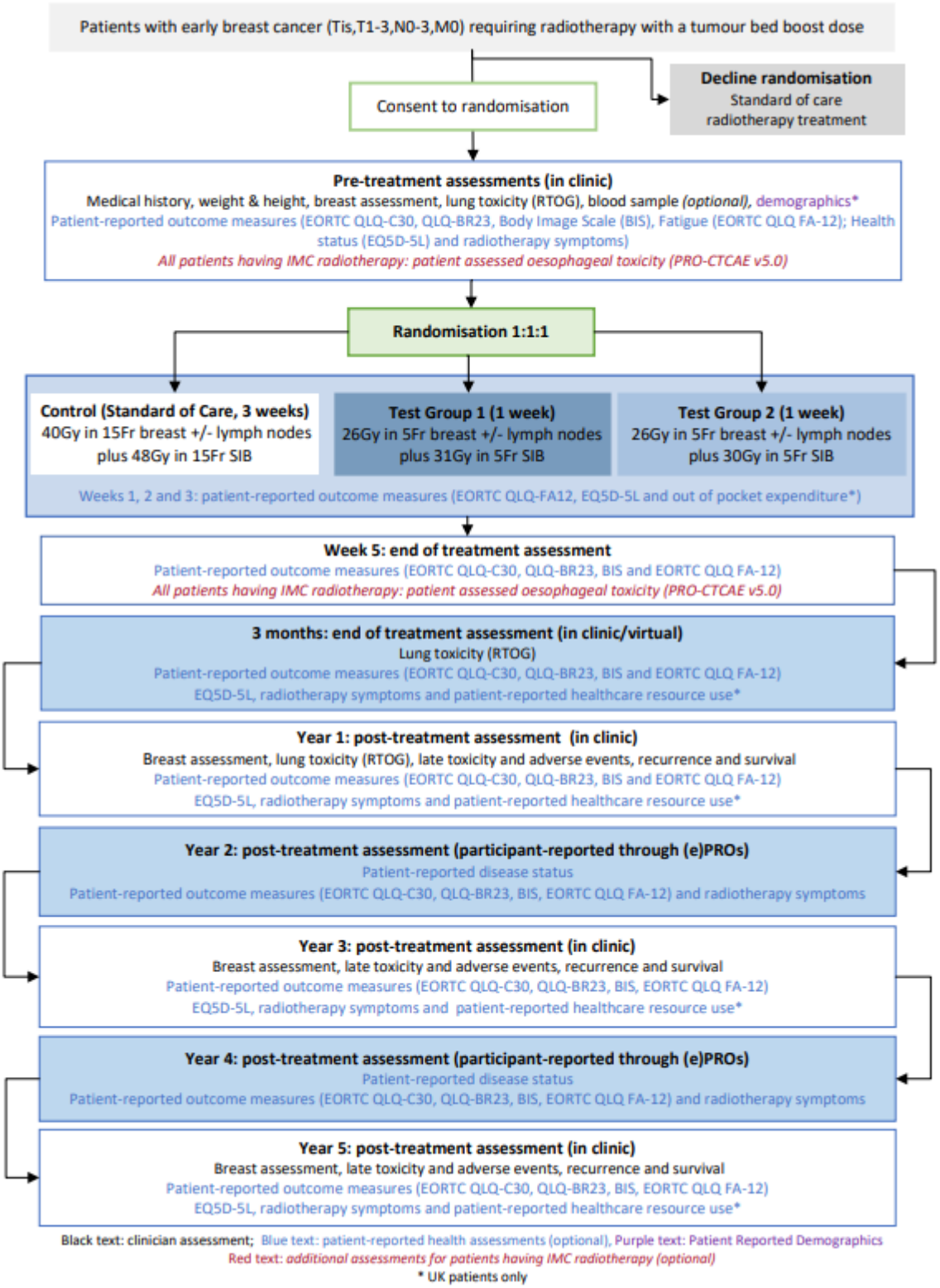
FAST-FORWARD BOOST TRIAL SUMMARY

PROTOCOL TITLE	**FAST-Forward Boost: A randomised clinical trial testing a 1-week schedule of curative simultaneous integrated boost (SIB) radiotherapy against a standard 3-week schedule in patients with early breast cancer.**
TARGET DISEASE	Breast cancer
TRIAL OBJECTIVES	• To establish non-inferiority of 1-week SIB radiotherapy when compared with standard 3-week SIB radiotherapy in terms of local recurrence rates for the treatment of breast cancer requiring radiotherapy with a tumour bed boost. • To describe (long-term) clinical outcomes with 1-week SIB radiotherapy compared with 3-week SIB radiotherapy in this patient group. • To evaluate acute toxicity with 1-week SIB radiotherapy compared with standard 3-week SIB radiotherapy specifically in relation to skin changes and tiredness. • To evaluate late effects of 1-week SIB radiotherapy compared with standard 3-week SIB radiotherapy, specifically breast shrinkage, hardness, tenderness and cosmesis. • To establish rates of acute lung toxicity (pneumonitis) with 1-week SIB radiotherapy compared with standard 3-week SIB radiotherapy in patients receiving internal mammary chain (IMC) radiotherapy. • To establish how early and late side-effects of 1-week versus 3-week SIB radiotherapy impact on patient-reported quality of life and on economic aspects.
TRIAL DESIGN	Phase III multi-centre randomised controlled trial.
TRIAL POPULATION	People with breast cancer (T1-T3, N0-3, M0) requiring a tumour bed boost plus whole breast radiotherapy +/- radiotherapy to nodes (level 1-4 axilla +/- internal mammary chain), or people with DCIS (Tis, N0-3, M0) requiring a tumour bed boost according to local centre policy.
RECRUITMENT TARGET	4830 participants (1:1:1 allocation) provides 90% power to rule out a 2% absolute non-inferiority margin, ensuring 1-week SIB ipsilateral breast recurrence rate is ≤5% at 5 years (assuming a Control Group rate of 3%).
TRIAL TREATMENT	Participants will be randomised in a 1:1:1 ratio to the following: **Control Group:** 3-week SIB radiotherapy of 48Gy in 15Fr (with a whole breast +/- relevant regional lymph nodal dose of 40Gy in 15Fr). **Test Group 1:** 1-week SIB radiotherapy of 31Gy in 5Fr (with a whole breast +/- relevant regional lymph nodal dose of 26Gy in 5Fr). **Test Group 2:** 1-week SIB radiotherapy of 30Gy in 5Fr (with a whole breast +/- relevant regional lymph nodal dose of 26Gy in 5Fr). Treatment allocation will be by computer generated random permuted blocks, stratified by breast surgery type, need for nodal radiotherapy and treating centre.

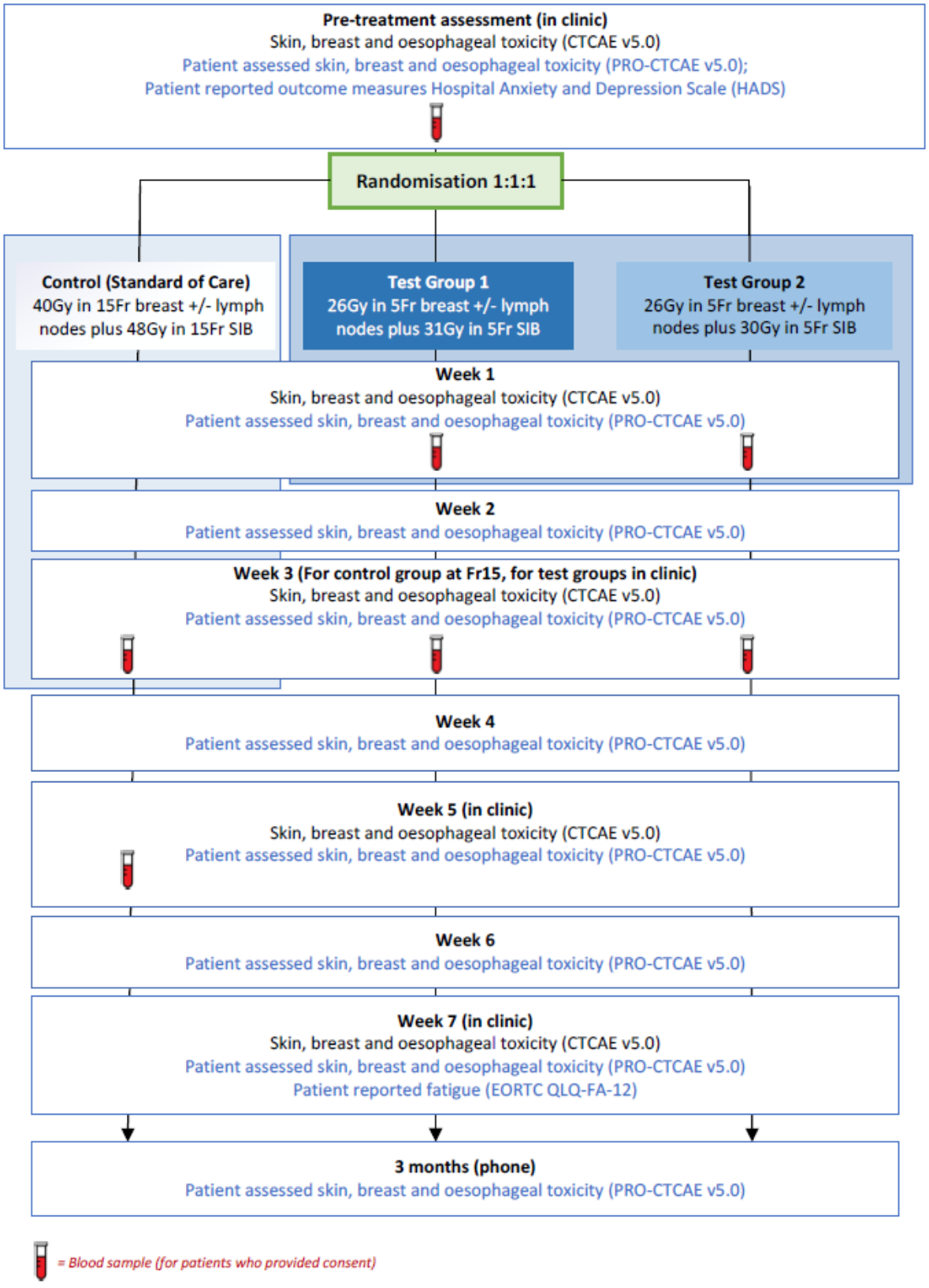
PRIMARY ENDPOINT	The primary endpoint is ipsilateral breast tumour recurrence at 5 years.
SECONDARY ENDPOINTS	Secondary endpoints include: • Patient-reported symptom assessments including radiotherapy adverse effects (acute and late) and quality of life. • Clinician-reported radiotherapy adverse events (acute and late). • Recurrence-free survival. • Breast cancer-related survival. • Overall survival. • Health economics.
PATIENT-REPORTED OUTCOMES (PROs)	All participants in the early side effects sub study will contribute to the evaluation of Patient-Reported Outcomes (PROs). Following completion of recruitment to the early side effects sub study, all participants in the main study will be asked (not mandatory) to contribute to the evaluation of PRO. PROs will be assessed using the EORTC QLQ-C30, EORTC QLQ-BR23, the Body Image Scale (BIS), EORTC QLQ FA12 fatigue and protocol-specific items as used in previous breast radiotherapy trials (radiotherapy symptoms). PRO questionnaires will be completed pre-treatment, week 5, 3 months, years 1-5. Fatigue will also be collected weeks 1-3. Participants in the early side-effects sub-study will also complete Hospital Anxiety Depression Scale (HADS) at the pre-treatment timepoint and skin, breast & oesophageal PRO CTCAEv5.0 and trial specific questions weekly for 7 weeks from the start of radiotherapy.
HEALTH ECONOMICS	All participants will be asked to contribute (not mandatory) to the evaluation of Health Economics (HE). This will be assessed using the EQ-5D-5L questionnaire, out of pocket costs questionnaire* and health care resource use questionnaire*. The EQ-5D-5L will be completed at pre-treatment and weeks 1-3, at 3 months, at years 1, 3 and 5. Out of pocket cost questionnaire will be completed at weeks 1-3. Health care resource use questionnaire will be completed at 3 months, at years 1, 3 and 5. The HE questions will be administered in the PRO booklet. ** UK participants only*
EARLY SIDE-EFFECTS SUB-STUDY (Selected UK sites)	The trial will initially open at selected sites who are able to participate in the early side-effects sub-study; all trial participants recruited at those sites whilst the sub-study is ongoing will contribute to the sub-study. This sub-study, including approximately 345 participants, will facilitate an early review of acute toxicity based on clinician-reported CTCAE v5.0, patient-reported PRO-CTCAE v5.0 and trial-specific questions. The aim is to identify any early safety signal within the test schedules (although not anticipated), with a focus on skin reactions. CTCAE v5.0 grade ≥3 acute skin reactions are expected to be low, about 3% in the Control Group, and the analysis is planned to rule out an increase to ≥10% with either of the 5Fr SIB schedules (Test Group 1 or 2).

TRANSLATIONAL SUB-STUDY (all patients)	All participants will be asked to donate a baseline blood sample (not mandatory, ideally collected prior to first fraction of radiotherapy but can be at any time point) for further translational research associated with the trial and for future research. In addition, consent will be sought from participants to collect tissue samples and other samples collected as part of routine care for the trial and for future research (not mandatory).
EARLY SIDE-EFFECTS TRANSLATIONAL SUBSTUDY (Selected UK sites, as above)	The aim of the early side-effects translational sub-study is to understand the differences in radiation-induced immune-inflammatory changes in blood between a 3-week versus 1-week hypofractionated regimen and correlate these with the incidence and severity of acute toxicity endpoints and treated volume. In addition to the blood sample requested from all trial participants prior to treatment, participants in the early side effects sub-study will be asked to provide blood samples at two further time points (at the end of radiotherapy and 2 weeks after treatment), aligned to acute toxicity assessments. Approximately 240 participants will be included.
RECRUITMENT SUB-STUDY (UK only)	The recruitment sub-study aims to evaluate barriers and facilitators to participation in the trial among under-served populations using an exploratory qualitative research design. Purposive sampling will be used to invite up to 100 patients to participate in interviews (including those who accept or decline randomisation). The work will provide insights into the experiences, interactions, and contexts of participants from under-served groups entering or declining participation in the trial which will facilitate implementation of targeted measures (e.g. additional resource or staff training). This study will be covered by a separate protocol.
CHARACTERISING ACUTE TOXICITY ACROSS SKIN TONES (CATS) (UK only)	An embedded “Study within a Trial” (SWAT) will evaluate a new skin toxicity assessment tool designed to assess acute toxicity in people with a range of skin tones. This SWAT will be covered in a separate protocol.
PATIENT VIEWS ON CARBON TRADE OFF DECISIONS	An embedded “Study within a Trial” (SWAT) will gain insight into the views of patients and healthcare professionals on adaptations made to reduce a trial’s carbon footprint and improve its environmental impact. This SWAT will be covered in a separate protocol.
FOLLOW UP	Clinical follow-up to 5 years will inform the primary analysis. Follow-up via routinely collected healthcare datasets beyond 5 years will inform a later analysis of long-term outcomes.

MAIN TRIAL SCHEMA



EARLY SIDE-EFFECTS SUB-STUDY SCHEMA (showing <u>additional assessments</u> only)



1. INTRODUCTION

1.1. Background/rationale for the trial

Radiotherapy is an important component of breast cancer treatment for many people: Breast cancer is the commonest cancer in the UK and radiotherapy is integral to the curative pathway for 37,000 UK people/year(1). Improvements in treatment, including radiotherapy and systemic therapies, have lowered disease recurrence rates but it remains the case that radiotherapy reduces the risk of local recurrence by up to two-thirds translating into improved breast cancer survival for the majority. Younger patients, and those whose disease expresses more aggressive biology, such as triple negative breast cancer, may have the most to gain from radiotherapy(2, 3) and are the population considered in this trial.

Radiotherapy impacts on the lives of people with breast cancer during treatment and for many years after cancer is cured: Radiotherapy can lead to early and long-term side-effects in breast and adjacent organs with impact on quality of life and wellbeing(2, 4). Acute side-effects include skin changes and fatigue which affect nearly all patients, peaking in the 2-4 weeks after radiotherapy. These tend to be mild for most patients. Symptomatic lung inflammation (pneumonitis) is rare (peaking around 3 months after radiotherapy in up to 2% of patients needing radiotherapy to lymph nodes behind the breastbone) but causes cough, breathlessness and fatigue when it occurs(5). Late breast radiotherapy side-effects include changes in breast appearance, notably breast shrinkage, which increase in incidence over time affecting around 16% people by 5 years(6). Lymphoedema affects 1 in 10 patients but can be lifelong when it occurs(5, 7). Major radiotherapy side-effects, including heart disease and second cancer, are rare (for example the risk of second lung cancer in non-smokers treated with modern radiotherapy techniques including breath-hold is <1 in 1000 at 20-years post-radiotherapy)(8).

Of additional importance to patients and healthcare systems is the impact of the radiotherapy treatment schedule itself. Radiotherapy is a hospital-based treatment requiring daily outpatient attendance for treatments (also known as fractions (Fr)). Not all hospitals have radiotherapy machines, and so patients may need to travel long distances for daily treatment. Historically, patients needed to attend daily for up to 6.5 weeks. Longer treatment schedules increase the burden on patients in terms of fatigue, delayed recovery and impact on working/caring responsibilities, on availability of NHS radiotherapy equipment/staff resource and on all via carbon emissions (predominantly related to patient travel to and from radiotherapy centres). There are also data to suggest that the burden of daily radiotherapy visits precipitates some people choosing mastectomy over breast conservation(9).

UK-led randomised controlled trials have reduced the length of the radiotherapy treatment schedule whilst maintaining cancer control and minimising side-effects for many people with breast cancer but not all: The UK has been world-leading in delivering innovative internationally practice-changing randomised controlled trials (RCTs) aimed at shortening radiotherapy treatment schedule duration. The START-A trial (ISRCTN 59368779) compared the standard of care (SOC) at that time (50Gy in 25Fr of 2Gy delivered over 5 weeks) with test groups in which radiotherapy dose was given in fewer, larger doses per Fr (41.6Gy or 39Gy over 13 alternate days of 3.2Gy or 3Gy)[10]. The trial pioneered the use of two test groups to be able to triangulate the new schedule most effective in preventing local recurrence whilst minimising side-effects. START-A showed that a lower total radiotherapy dose delivered in a smaller number of Fr could offer a similar rate of tumour control and normal tissue damage as the standard 5-week schedule. In 2009, the parallel, pragmatic START-B trial (ISRCTN 59368779) demonstrated that breast radiotherapy could be given as effectively in 15Fr (3 weeks) as in 25Fr (5-weeks) with a lower risk of side-effects such that 3-week (40Gy in 15Fr) radiotherapy became SOC(10-12). These findings have been reproduced in other trials(13-15). In START-B, non-inferiority of local

control at 5-years was maintained at 10 years(12). In 2020, the NIHR HTA-funded FAST-Forward trial (ISRCTN 19906132) showed that breast radiotherapy can as effectively and safely be given in 1-week (26Gy in 5Fr) as in 3-weeks, significantly reducing treatment burden and NHS costs for most patients needing radiotherapy to breast/chest wall only(16). 5-year local control data were practice-changing in the UK(17). Acute skin side-effects were less in the 5Fr groups whilst late effects in breast and other tissues were reported to be similar between 26Gy/5Fr and 40Gy/15Fr(18). It has since been demonstrated that lymphoedema rates are also similar between these schedules(7).

There remain, however, 10,000 people with breast cancer in the UK per year who still require radiotherapy of a duration longer than 1-week due to lack of evidence to confidently reduce their treatment schedule. These are mainly patients needing a tumour bed boost. The European Boost Trial showed that, in younger patients and those with higher grade cancers, adding a boost dose to the site of the original cancer in addition to standard breast radiotherapy reduces local recurrence risk further than radiotherapy to the breast alone(19, 20). Based on older radiotherapy techniques, however, this boost dose increases risks of breast hardening and shrinkage, in turn causing pain and psychological distress particularly when boost volumes were large(21-23). In addition, the boost was delivered sequentially to the breast radiotherapy over an additional 1.5 weeks such that overall treatment durations of up to 4.5 weeks have been the SOC until this year. A 2019 Royal College of Radiologists' (RCR) audit reported that UK practice was heterogeneous with 8 different boost dose schedules and 4 different boost techniques in use across the NHS some of which treat large volumes of breast tissue to higher doses, increasing risk of longer-term breast symptoms(24).

Technical advances in breast radiotherapy have enabled focussed boost doses to be given simultaneously with whole breast radiotherapy reducing treatment duration without compromising treatment efficacy: In parallel with NIHR FAST-Forward, the Cancer Research UK-funded IMPORT HIGH Trial (ISRCTN 47437448) used technical advances in surgical tumour bed clip placement, intensity-modulated radiotherapy and image-guided radiotherapy to more precisely focus radiotherapy on the region of breast tissue at highest risk of local recurrence and to be able to deliver the boost dose *simultaneously* with radiotherapy to the whole breast+/-lymph nodes(25). The NIHR EME-funded IMPORT HIGH Image-Guided radiotherapy Study showed that using tumour bed clips with image guidance led to the smallest boost volumes being irradiated with the potential to reduce boost side-effects(26). IMPORT HIGH randomised 2617 people to receive these *focussed* boosts either *sequentially* over a total of 4.5 weeks (SOC), or *concurrently* with 3-week radiotherapy (as a simultaneous integrated boost known as a SIB). 5-year ipsilateral breast recurrence incidence was 1·9% (95% CI 1·2-3·1) for the sequential boost, 2·0% (1.2-3.2) for 48Gy/15Fr SIB and 3.2% (2.2-4.7) for 53Gy/15Fr SIB(6). 5-year *clinician*-reported moderate/marked breast induration was 10.6% (95% CI 8.6-12.9%) for 48Gy SIB versus 11.5% (9.5-14.0) for the control group. This compared favourably with 19% at 4-years reported using older sequential boost techniques reflecting smaller boost volumes in IMPORT HIGH(27). 5-year *patient*-reported moderate/marked breast firmness was significantly lower for 48Gy SIB (16%) compared with sequential boost (28%) (RR 0·54, 95%CI 0·38-0·78, p=0·001). This reflects the SIB's advantage of combining both breast and boost doses in a single radiotherapy plan minimising dose to normal tissues. Both clinician-reported and patient-reported side-effects were higher in the 53Gy SIB group as expected due to the higher dose. In 2023, the optimal radiotherapy technique and schedule for patients requiring a boost is therefore 48Gy/15 Fr/3-week SIB.

The next step is to unite 1-week breast radiotherapy and optimal boost technique by testing the effectiveness and safety of a 1-week SIB in a randomised controlled trial: Combining what we have learnt from the FAST-Forward and IMPORT HIGH trials, it should now be possible to treat patients requiring a boost

in 1-week using a SIB technique. However, level 1 evidence is required before routine NHS practice can be systematically changed. When reducing SIB duration from 3-weeks to 1-week, adjustment to the total SIB dose (and dose delivered per Fr) is required to ensure that the 1-week SIB radiotherapy is as effective as the 3-week SIB without increasing side-effects; when local recurrence risk is very low the minimisation of side-effects for which all treated patients are at risk becomes paramount. Using radiobiological modelling based on clinical outcome data from FAST-Forward and IMPORT HIGH, it is possible to closely estimate the 1-week SIB dose equivalent to the 3-week IMPORT HIGH 48Gy/15Fr SIB dose. Given that the total boost dose is higher than the whole breast dose used in FAST-Forward (i.e. on a different part of the radiation dose-response curve for tumour and normal tissues), it is critical to obtain robust clinical safety and effectiveness data. The optimal RCT design thus again uses a 3-group trial (as used in START-A and FAST-Forward) whereby 2 test dose-levels estimate the lower and upper bounds of the biologically equivalent dose to that used in the control group. Such modelling hypothesises that a 1-week SIB of 30Gy or 31Gy in 5Fr (with 26Gy in 5Fr to the whole breast) is most likely to be equivalent to the 48Gy/15 Fr/3-week (with 40Gy in 15Fr to the whole breast) SOC; and the proposed trial design provides an efficient way to triangulate between the 1-week (5Fr) SIB doses to identify the 5Fr schedule most closely equivalent to 48Gy/15Fr if required.

Rationale for 30Gy and 31Gy in 5 fractions as choices of SIB dose: Using clinical results from our previous trials, we predict that both 30Gy and 31Gy in 5 treatments delivered over 1 week as a simultaneous integrated boost (SIB) will be similar in terms of cancer control with acceptable late breast tissue toxicity compared with our control of 48Gy SIB delivered in 15 treatments over 3 weeks. We hypothesise that there will be no difference in local control between 30Gy and 31Gy SIB given the shallowness of the dose-response curve, but we need to demonstrate prospectively that one or both schedules are non-inferior to 48Gy SIB in order to be able to change practice. If both test groups are non-inferior in terms of local breast cancer recurrence, we will select the test schedule that gives the least toxicity.

From previous trials we have demonstrated that we are able to discriminate between the test groups in terms of late side-effects even though the total dose only differed by 1Gy. This is because data from our previous clinical trials suggest 30Gy and 31Gy SIB are biologically similar to 60Gy and 64Gy in 2Gy treatments respectively (assuming α/β of 2) for normal breast tissue toxicity, giving a biological dose difference of 4Gy i.e. a numerical difference of 1Gy in total dose translates to a biological difference of 4Gy for normal tissue toxicity given the steepness of the dose-response curve at this dose level, therefore, we expect to be able to show a difference in toxicity reports. The only circumstance under which the higher dose test schedule would be implemented in clinical practice would be if the lower dose test schedule is shown to be inferior to control arm for local tumour control, providing normal tissue toxicities are acceptable. NB The doses to non-breast organs-at-risk will be lower for both one-week test groups such that risks of longer-term side-effects in heart and lungs would be anticipated to be lower.

The table below shows EQuivalent total Doses in 2Gy fractions (EQD2) for the various 5W, 3W and 1W fractionation schedules tested/being tested in various trials for comparison.

Schedule	Alpha/beta (Gy)				
	Late NTE			Breast cancer	
	3.0	*2.5*	*2.0*	*+3.7*	*3.7 + *time*
50Gy/25F (2.0)					
EQD2	50	50	50	50	50
40Gy/15F (2.67)					
EQD2	45	46	47	45	**+8=53
48Gy/15F (3.2)					
EQD2	60	61	62	58	+8=66
26Gy/5F (5.2)					
EQD2	43	44	47	41	+8=49
29Gy/5F (5.8)					
EQD2	51	54	57	48	+8=56
30Gy/5F (6.0)					
EQD2	54	57	60	51	+8=59
31Gy/5F (6.2)					
EQD2	57	60	64	54	+8=62
32Gy/5F (6.4)					
EQD2	60	63	67	57	+8=65

EQuivalent total Doses in 2Gy fractions (EQD2) of 50Gy/25F/5W, START-B 40GY/15F, IMPORT High 48Gy/15F/3W and 5 dose intensities of 5F/1W schedules assuming α/β values of 3.0, 2.5 and 2.0Gy for late NTE. START-P/-A generated α/β=3, FAST α/β=2.5 and FAST-Forward α/β=2 with 95%CI overlapping between all trials and all NTE endpoints. START-P/-A & FAST controlled for time, but FAST-Forward estimates do not attempt to correct for any time-related effects. If real (very slow incomplete repair, no repopulation) and corrected for, time corrections tend to increase α/b very slightly but barely change EQD estimates. The α/β values in the table based on START, FAST and FAST-Forward are estimates of clinical reality in the contexts tested within each trial, whether or not they incorporate a time element representing very slow (>24hr) repair in addition to classical Elkind repair (24hr) or any other process that we are unaware of.

+Based on FAST-Forward estimate of α/β= 3.7Gy for tumour control. START-P/-A trials' estimate of α/β=3.5Gy to tumours controlled for overall time. Clinical literature in H/N cancer suggests accelerated repopulation, the main time-related effect, does not kick in earlier than day 21, but it is conceivable that repopulation in BC starts from day 1 radiotherapy if prior surgery &/or systemic therapy stimulate proliferation.

**Hypothesis-generating analysis of START trials suggests 0.6Gy wasted dose per 2Gy fraction during weeks 4 & 5 in Control group, which would explain why in START-B 40Gy/15F with EQD2=45 has an apparent lower local relapse risk than 50Gy/25F. If this effect operates from day 1 after surgery and/or systemic therapies, a 1-week radiotherapy schedule replacing a 3-week regimen could save an additional EQD2 of 14x0.6=8Gy, partly compensating for the loss of therapeutic ratio associated with large fraction sizes.*

***This value was generated for START-B using α/β value=3.5 estimated by START-P/-A which controlled for time (5w), so it does not take account of the 14 fewer days of wasted dose when 15F are used. In the *footnote above, this effect is postulated to account for the apparent over-performance of 40Gy/15F compared to 50Gy/25F.*

The FAST-Forward Boost Trial (n=4830 patients): In FAST-Forward Boost we plan a definitive RCT whereby people with breast cancer requiring radiotherapy to the breast +/- nodes with a boost will receive either 3-week SIB radiotherapy (SOC) or 1-week SIB radiotherapy (at one of 2 dose levels). Local recurrence of breast cancer within 5 years is the patient-prioritised primary outcome measure. Breast radiotherapy trials report on non-inferiority at 5 years, when the majority of local recurrences have occurred, and this is sufficient to change practice(12). Further local recurrences usually occur by year 10 and confirmatory analysis of the primary local cancer control endpoint will be done using routine dataset linkage(12) (or alternative methods where this is not possible). We will empower patients to tell us directly about both early and longer-term breast changes, and how radiotherapy has affected other aspects of their life, including fatigue, quality of life and financial outlay, using a digital patient-reported outcome (ePRO) system and offering hard-copy questionnaires as an alternative. We will ask clinicians to report on normal tissue effects at given time points to enable comparisons with other international trials. 5-year normal tissue effect data can identify the optimal 1-week SIB as, although the incidence of normal tissue effects increases with time, the 5-year timepoint distinguishes between treatment schedules(12). We will pro-actively increase diversity of the recruited population via educational materials and a qualitative sub-study to investigate barriers to recruitment (UK only). By increasing diversity in the recruited population, we aim to better characterise early radiotherapy side-effects (skin reactions) in people with different skin tones; something currently lacking in the literature. We will quantify the health economic benefits of 1-week SIB radiotherapy for patients and the NHS. We will also collect data to assess carbon emissions aligned with NHS and global prioritisation to reduce climate effects of treatment.

Risks and benefits of 1-week radiotherapy for people with breast cancer who require treatment to the internal mammary chain (IMC): Patients requiring radiotherapy to nodes behind the breastbone (IMC) were not included in the FAST-Forward Nodal Sub-Study since data demonstrating a survival gain of IMC radiotherapy were only published more recently and therefore SOC for this patient group will remain as 3-week radiotherapy even beyond the FAST-Forward Nodal Sub-Study primary analysis(28). The population of patients eligible for FAST-Forward Boost (generally younger women and those with higher grade cancer more likely to have lymph node involvement) will be enriched for patients requiring IMC radiotherapy. This group is currently anticipated to make up 10-15% of the eligible population, with this proportion anticipated to increase following Lancet publication of a meta-analysis supporting the use of IMC radiotherapy in several patient subgroups with lymph node involvement(8). Whilst relative effects on local recurrence would be expected to be comparable to those seen in FAST-Forward and FAST-Forward Nodal Sub-Study, it remains necessary to demonstrate that 1-week IMC radiotherapy is not associated with any increase in lung toxicity (pneumonitis) within the first 3 months from treatment. This is especially pertinent in the modern era of breast cancer management where many patients are receiving increasing adjuvant systemic treatment (e.g. TDM-1, immunotherapy) of which pneumonitis is a recognised side effect. These treatments were not routinely given in the FAST- Forward/IMPORT HIGH recruitment period. FAST-Forward Boost will provide these data and can be extrapolated to those without boost since associated lung doses would be no higher.

A review of existing literature confirms that there are no existing trials capable of changing practice for this patient group: The literature was scoped in April 2023 for information on 1-week SIB radiotherapy looking for published results and ongoing international trials. A PubMed search was undertaken using search terms (English articles only; date unrestricted): *Breast and simultaneous integrated boost and one week* (5 results); *Breast and simultaneous integrated boost and five fractions* (15 results); *Breast and hypofractionated and simultaneous integrated boost* (57 results). There were no published systematic reviews on 1-week SIB radiotherapy in breast cancer. A Cochrane systematic review of breast radiotherapy boost highlights local control benefits but does not address optimal dose/schedule(29). Of 77 total results, 10 were duplicated

across searches. Of 67 remaining, 5 were reviews, 1 commentary, 1 related to brain disease, and 56 articles described radiation dosimetry and/or SIB in ≥15 Fr and were thus not relevant. This left 4 articles describing clinical studies of *5*Fr SIB. A cohort (n=22) treated with a 31Gy/5 Fr SIB showed, at 2 years median follow-up, minimal toxicity (no grade 3-4, 4/22 grade 2 breast firmness) but with Fr delivered *weekly* not daily(30). An RCT (n=200) compared 3-week radiotherapy (40Gy/15Fr & 46.8Gy/15 Fr SIB) *vs 2-week* radiotherapy (28.5Gy/5Fr & *31Gy/5Fr SIB* alternate days)(31). Short-term breast redness, pain, swelling and fatigue were all less frequent and improved health-related QoL, breast symptoms and physical wellbeing with 2-week SIB supporting the hypothesis that shorter radiotherapy schedules are less burdensome**.** A recruiting phase III RCT (HYPORT) in India aims to demonstrate non-inferiority of 5-year locoregional recurrence with 1-week radiotherapy compared with 3-week radiotherapy (n= 2100)(32). Most patients needing boost receive SIB (48Gy/15Fr/3-weeks vs 32Gy/5Fr/1-week) but sequential boosts are also permitted in this RCT. The single 1-week SIB radiotherapy test dose is higher than the 2 test doses proposed in FAST-Forward Boost having been planned prior to the results of IMPORT HIGH being known and with a resulting concern relating to a potential higher incidence of late toxicity than would be deemed acceptable for a UK population. A pre-planned safety analysis (n=271 including 52 treated with 3-week SIB radiotherapy; 53 with 1-week SIB radiotherapy) reported acute grade 3 radiotherapy dermatitis in 1% 3-week vs 1% 1-week SIB patients but data were collected up to 3-months after radiotherapy (i.e. well after most early side-effects resolve)(33). Only 9/271 patients had IMC radiotherapy suggesting that there will be too few IMC radiotherapy cases to draw safety conclusions.

In summary, relevant reports at the time of funding application related to one small case series of 5-fraction SIB radiotherapy delivered over 5 weeks(30), one small RCT of 2-week SIB radiotherapy(31) and an ongoing trial of 1-week SIB in which radiotherapy doses are higher than those likely to be used in the UK(32). Further to the April 2023 literature search, data from a prospective registry of 383 patients, treated with a SIB of 29 to 31Gy/5Fr SIB alongside 26Gy/5Fr/ 1 week to the whole breast +/- nodes have been published. Skin toxicity, breast oedema, breast pain and arm lymphoedema were assessed using CTCAE v5.0 criteria and no G3 events were reported (34). G1 and G2 breast oedema rates were 2% and 0.5% respectively. A small RCT (n=107) compared outcomes in patients treated with 40Gy/15# versus 25Gy/5#/ 1 week. 43% (n=23) of those randomised to the 25Gy group had a SIB of 30Gy/5#. No G3 or higher toxicities were observed. None of these more recent studies are powered to look at local recurrence outcomes(35).

FAST-Forward Boost builds on the UK's established international research reputation for transforming breast radiotherapy delivery by generating robust evidence of clinical and cost-effectiveness of 1-week SIB radiotherapy. Using the UK's experienced collaborative and co-ordinated research infrastructure and networks (both national and international) to collect trial data within a large and diverse population ensures that the research question is answered as quickly and efficiently as possible. Demonstrating non-inferior local control disease and identifying the 1-week SIB radiotherapy dose equivalent to a 3-week SIB radiotherapy will: i) enable >10,000 people per year who require boost radiotherapy and/or IMC radiotherapy to benefit from shorter treatment durations, ii) save NHS resources and iii) reduce the climate impact of radiotherapy for breast cancer.

Importance to patients: Published data and focus group discussions demonstrate that patients find longer radiotherapy schedules burdensome due to short-term side-effects, particularly fatigue(4, 31, 32), alongside the impact on working/caring responsibilities, and delayed return to normal life given that radiotherapy often comes after surgery and chemotherapy(4, 31, 33). The financial toxicity of treatment includes the costs of travelling to and from treatment centres, reduced earnings, and increased childcare/care requirements. Due to the younger age of this group, those needing boost radiotherapy include people with young families and/or

working roles. Given that 1-week radiotherapy delivers a lower total physical dose to breast tissue, it is anticipated to reduce short-term skin side-effects, breast pain and fatigue compared with 3-week radiotherapy(31). Patients highlight that 1-week radiotherapy allows them to transition to "back to normal" sooner. 1-week radiotherapy reduces their travel time/costs and knock-on effects on work/caring responsibilities by up to 2/3, thereby reducing the financial burden on patients. In addition, many younger patients with higher risk disease now go on to receive further systemic therapies after radiotherapy and, as such, reducing the severity and duration of radiotherapy side-effects also reduces the risk of interrupting the treatment pathway.

Importance to NHS: Longer radiotherapy schedules are resource intensive on NHS radiotherapy equipment/staff. Treating patients requiring a boost in 1-week rather than 3-weeks could save 100,000 radiotherapy slots/year, equivalent (at 15 mins/slot and 8 hr working days) to 3125 days of linear accelerator (LINAC) time/year or >50 days' LINAC time *per UK centre*/year. This would significantly increase NHS radiotherapy capacity in an ageing population with increasing radiotherapy need and NHS staff shortages(36), in turn benefitting NHS radiotherapy waiting times. The difference in cost between 1-week SIB radiotherapy versus 3-week SIB radiotherapy is estimated at £1,634/ person(37). Giving all radiotherapy boosts in 1-week rather than 3-weeks would save around (£1,634*10,000 =) **£16.34 million per year.** Based on current estimates of health benefits of NHS expenditure, this cost saving could translate into £16.34million/£15,000=1089 quality adjusted life years(38).

2. TRIAL OBJECTIVES

2.1. Trial Aim and Hypothesis

FAST-Forward Boost aims to establish a 1-week schedule of SIB radiotherapy as standard of care in patients undergoing radiotherapy for breast cancer +/- lymph nodes with a tumour bed boost. It hypothesises that local recurrence rates at 5-years will be no higher with appropriately dosed 1-week SIB radiotherapy than with 3-week SIB radiotherapy and that this can be achieved without an increase in normal tissue side-effects. A secondary aim is to characterise the pneumonitis rates in the subpopulation of patients who require internal mammary chain (IMC) radiotherapy, hypothesising that these are no higher for IMC radiotherapy delivered in 1-week as in 3-weeks.

2.2. Trial Objectives

Specific objectives are:

1. To establish non-inferiority of 1-week SIB radiotherapy when compared with standard 3-week SIB radiotherapy in terms of local recurrence rates for the treatment of breast cancer requiring radiotherapy with a tumour bed boost.
2. To describe (long-term) clinical outcomes with 1-week SIB radiotherapy compared with 3-week SIB radiotherapy in this patient group
3. To evaluate acute toxicity with 1-week SIB radiotherapy compared with standard 3-week SIB radiotherapy specifically in relation to skin changes and tiredness.
4. To evaluate late effects of 1-week SIB radiotherapy compared with standard 3-week SIB radiotherapy, specifically chronic breast shrinkage, hardness, tenderness and cosmesis.
5. To establish rates of acute lung toxicity (pneumonitis) with 1-week SIB radiotherapy compared with standard 3-week SIB radiotherapy in patients receiving IMC radiotherapy.
6. To establish how early and late side-effects of 1-week versus 3-week SIB radiotherapy impact on patient-reported quality of life and on economic aspects.

3. TRIAL DESIGN

FAST-Forward Boost is a phase III, multi-centre, randomised controlled trial. The patient population is people with a diagnosis of breast cancer treated with breast conserving surgery who are recommended radiotherapy which includes a boost dose to the tumour bed. This includes people who need radiotherapy to nodes (level 1-4 axilla, +/- IMC) in addition to radiotherapy to the breast. A total of 4830 patients will be included.

Patients will be treated using standard radiotherapy to the breast +/- nodes with a SIB to the tumour bed and randomised on a 1:1:1 basis to one of the following schedules:

- Standard radiotherapy to the breast +/- nodes using a schedule of 40Gy/15Fr over 3 weeks with a 48Gy/15Fr simultaneous integrated boost (SIB) of the tumour bed (**Control Group**)
- 26Gy/5Fr over 1 week with a 31Gy/5Fr SIB **(Test Group 1)**
- 26Gy/5Fr over 1 week with a 30Gy/5Fr SIB **(Test Group 2)**

Patients requiring nodal boosts will be eligible for inclusion if they also require a tumour bed boost. The nodal boost will be 48Gy/15Fr if randomised to the control group and 30Gy/5Fr if randomised to either of the test groups.

The trial will provide a robust assessment of the test interventions and, in addition to evaluating tumour recurrences rates (primary endpoint with a non-inferiority hypothesis), will assess toxicity in both the short and longer term (considering both patient and clinician perspectives), as well as health economic consequences and long-term disease outcomes.

The trial includes an Early Side-Effects Sub-Study which will provide an early safety review whilst recruitment is ongoing. The trial will initially open at selected sites who can take part in this sub-study which will include the first 345 patients (approximately) recruited at those sites. Both clinician and patient-reported acute toxicity will be assessed, with a focus on acute skin reactions. In particular, the sub-study is powered to exclude a 10% or greater rate of CTCAE v5.0 skin reactions ≥ grade 3 in either of the test arms. Once recruitment to this sub-study is complete then the trial will open to recruitment at further sites.

The trial will also incorporate a recruitment sub-study to assess barriers and facilitators to recruitment in under-served populations (UK only) and two embedded “Studies Within A Trial” (SWATs) considering a new tool for assessing skin toxicity across a range of skin tones, and patient/ healthcare professional views on carbon trade-off decisions in clinical trials. These will be added/activated at a later date.

The trial is 8.5 years in duration including 3.5 years accrual period and 5 years of trial follow-up. Additional follow-up beyond 5 years via routinely collected healthcare datasets (or alternative methods, including ongoing routine data collection at site, where this is not possible) will inform later analyses of long-term outcomes.

This trial has been co-designed with patients and public involvement. Focus groups were held after a national advert (to FAST-Forward trial centres, NIHR People in Research, NIHR BRC Cancer Patient Voice Platform, Independence Cancer Patient Voice, ICR social medial channels and networks linked to co-applicants including Black Women Rising) seeking input from those with lived experience of breast cancer. Over 40 people took part. Patient and Public Involvement (PPI) contributors have been clear that shorter radiotherapy treatment is desirable if it does not compromise the risk of cancer returning. They prioritised local recurrence as the primary endpoint (rather than breast hardness as originally planned) and requested detailed data collection (quantitative & qualitative) about early and late side-effects of SIB, specifically fatigue & QoL, and data that

has not been captured in previous radiotherapy studies (impact on employment/caring, support needed by friends/family during radiotherapy and recovery). The PPI Lead and an additional member will form part of the TMG. Four PPI members reviewed the patient information sheets and informed consent forms.

4. STUDY ENDPOINTS

4.1. Primary Endpoint

The primary endpoint is ipsilateral breast tumour recurrence (IBTR) at 5 years.

4.2. Secondary Endpoints

The secondary endpoints are as follows:

- Patient-reported acute radiotherapy adverse effects, with a focus on skin, breast & oesophageal effects (PRO-CTCAE and trial specific, used in previous trials).
- Patient-reported late effects on quality of life, with a focus on breast symptoms and shoulder/arm functioning, using standard instruments (EORTC QLQ BR-23) and trial specific questionnaires used in previous trials.
- Patient-reported fatigue (EORTC QLQ FA12), health-related quality of life (EORTC QLQ C-30, EQ5D-5L), and body image (Body Image Scale (BIS))
- Clinician-reported acute radiotherapy adverse effects, with a focus on skin, oesophageal (CTCAE v5.0) and lung toxicity (RTOG) and breast oedema (trial specific, used in previous trials).
- Clinician-reported late radiotherapy adverse effects, with a focus on normal tissue effects and cosmesis, assessed with tools developed in previous breast radiotherapy trials and Harvard-Harris scale, and lung toxicity (RTOG).
- Recurrence-free survival, breast cancer-related survival and overall survival using NHS routinely collected data (subject to validation).
- Cost-effectiveness, based on health economic analysis which incorporates data on patient-reported health resource use, out of pocket expenses and health status (EQ5D-5L).

5. PATIENT SELECTION & ELIGIBILITY

5.1. Number of Participants

The aim is to recruit 4830 participants, 1610 into each group of the study.

5.2. Source of Participants

Participants will be recruited from at least 40 participating radiotherapy sites in the UK (initially selected recruiting centres until the early side effects sub-study recruitment is completed) and additional international centre participation from Ireland and France. Sites will be asked to complete an expression of interest initially to assess resources and complete radiotherapy quality assurance prior to opening as a site. Potential participants will be identified in oncology clinics and discussed at Multi-Disciplinary Team (MDT) meetings. ICR-CTSU encourages investigators to consider equality, diversity and inclusion when recruiting participants into its trials. A formal educational package on reducing (sub)conscious biases in trial recruitment will be produced and delivered as part of trial launch and site initiation.

5.3. Inclusion Criteria

1. Age ≥18 years
2. Histologically confirmed breast cancer (T1-T3, N0-3, M0) (multifocal disease is allowed) requiring a tumour bed boost plus whole breast radiotherapy +/- radiotherapy to nodes* (axilla +/- internal mammary chain) or DCIS (Tis, N0-3, M0) requiring a tumour bed boost according to local centre policy.
3. Treated with breast conservation surgery.
4. Complete microscopic resection (invasive cancer and/or DCIS clear of ink on radial margins or, if at margin, surgeon confirms no further breast tissue to excise)
5. Patient can provide informed consent.

*Axilla levels as per MDM recommendation

NB. Patients with synchronous bilateral breast cancer can be included as long as the disease on at least one side fulfils the inclusion criteria above. Where the patient has synchronous bilateral disease and needs a tumour bed boost on both sides, **both** sides will need to fulfil the inclusion criteria for the patient to be eligible for the trial.

5.4. Exclusion Criteria

1. Treated with ipsilateral mastectomy.
2. Previous radiotherapy to ipsilateral chest area that precludes delivery of a radical dose of adjuvant radiotherapy to the breast with tumour bed boost. *NB For any scenarios where there is overlap with previous radiotherapy, approval must be sought from the FAST-Forward Boost trial team prior to randomisation*.
3. Presence of metastatic disease.
4. Unavailable for any trial-related follow-up.
5. History of malignancy *except* non-melanomatous skin cancer, CIS cervix, previously unirradiated precancerous changes in breast (including ductal carcinoma in-situ and lobular carcinoma in-situ), and non-breast malignancy if curative intent and at least 5 years disease free.
6. Pregnant and/or currently breast feeding. *NB pregnancy status to be verified verbally with each patient as part of standard radiotherapy consent undertaken prior to randomisation of an individual into the trial*
7. Being treated with proton beam therapy

6. SCREENING

6.1. Screening Log

All participating sites will be required to keep a log of all patients with breast cancer that are potentially eligible for this study.
The information collected on the log will include:

- Date patient identified as potentially eligible.
- Screening outcome (patient approached/accepted participation/declined participation)
- Nodal status
- Reasons for not approaching / declining participation (patient ineligible / if available)
- Trial ID (if applicable)

This information will be used by the TMG to monitor recruitment activity. No patient identifiable data will be sent to ICR-CTSU at this stage.

6.2. Procedure for Receiving Informed Consent

The Principal Investigator (or designated individual) must ensure that each trial patient is fully informed about the nature and objectives of the trial and possible risks associated with participation. Participants should be given the current ethics approved FAST-Forward Boost patient information sheet for their consideration. Patients should only be asked to consent to the study after they have had sufficient time (usually at least 24 hours but at least overnight) to consider the trial, and the opportunity to ask any further questions. Initially selected sites who will participate in the early side-effects sub-study will open to FAST-Forward Boost trial and should ensure that the FAST-Forward Boost patient information sheet including early side-effects sub-study is given. Whilst the sub-study is ongoing, patients must take part in the early side-effects sub-study in order to participate in FAST-Forward Boost. Once this sub-study is complete, then the FAST-Forward Boost patient information sheet should be given. The patient information sheets are also available in large font for patients who would benefit from this.

Remote consent is permitted provided the following steps are taken:

- A member of the research team should contact the patient to introduce the trial and to organise a telephone appointment with an Investigator in order for the Investigator to discuss the trial with the patient in detail.
- A copy of the ethics approved PIS and ICF should be sent to the patient by email or post ahead of the scheduled appointment so that the patient has sufficient time to review the trial information. (If sending by post, two copies should be sent – one for the patient to retain and one to return to the site).
- During the telephone appointment the Investigator should complete the informed consent process remotely, discussing the study and ensuring that the patient is fully informed.
- If the patient agrees to consent the Investigator should ask the patient to initial the sections of the ICF and sign and date two copies. They should ask the patient to email/post one copy back to the site as soon as possible.
- The Investigator should record the date of verbal consent in the patient's clinical notes and confirm to the patient that this consent has been noted.
- The ICF should be received from the patient within a week of consent. Sites should follow up with patients on any consent forms not received until they have been received, signed and filed.
- On receipt of the signed copy of the ICF from the patient, the consenting Investigator should add their signature and date of signing and place in the patient file.
- A completed copy should be emailed/posted to the patient for their records.

Additionally, an optional short summary information leaflet is available to provide initial information to patients, as part of a layered approach, if suitable. However, all participants will need to be given the full Patient Information Sheet as a basis for written informed consent.

No protocol required assessments should be conducted until the FAST-Forward Boost consent form has been signed and dated by both the patient and the Investigator unless the assessments are performed routinely as part of standard patient care.

Confirmation of the patient's consent and the informed consent process must be documented in the patient's medical notes. A copy of the signed consent form should be provided to the patient and the original retained in the investigator site file, which must be available for verification by ICR-CTSU study staff or for regulatory inspection at any time. GCP-compliant electronic consent forms may be used where available.

6.3. Participation in other clinical trials

Patients who fulfil the eligibility criteria will be given the opportunity to participate in FAST-Forward Boost if they have participated in other clinical trials prior to recruitment assuming there are no fundamental incompatibilities between the trials.

Note that, at this time, concurrent participation in both FAST-Forward Boost and PARABLE (ISRCTN14220944) is not possible. Where a patient is potentially eligible for both trials, PARABLE should be discussed/offered in the first instance at centres recruiting to both trials. FAST-Forward Boost should only be considered once it has been decided that the patient will not enrol in PARABLE.
Patients recruited to ATNEC (ISCRTN36585784) can also be recruited to FAST-Forward Boost if they meet the eligibility criteria.

In case of queries regarding participation in other trials, please contact the trials team for advice.

7. TRIAL ENTRY/RANDOMISATION

Pre-treatment assessments must be completed <u>after consent</u> if not performed as standard of care but <u>before first radiotherapy treatment.</u>

Trial entry and treatment allocation (randomisation) will be done by site staff on the FAST-Forward Boost trial database. Once a patient has provided consent, they can be added to the database, which will generate the patient's unique trial number (Trial ID). Treatment allocation (randomisation) should take place as soon as possible after the patient has given trial consent and been added to the database (but ideally after completion of the baseline PRO booklets).

The following information must be completed on the database before the patient can be randomised:

- Name of randomising and treating hospital, consultant.
- Confirmation that the patient has given written informed consent for trial participation and for any sub-studies.
- Patient preference of whether they would like to receive questionnaires by paper or electronic method (all patients).
- Confirmation that the patient has been provided the pre-treatment PRO booklet (subject to consent).
- Confirmation that the investigator has confirmed in writing that all of the eligibility criteria were met. We recommend (but do not mandate) the paper eligibility checklist is used for this.
- Patient's full name*, hospital number*, date of birth*, address* and postcode*, NHS/CHI number*, and email address (if patient would like to complete PRO electronically, once available).
- Type of surgery.
- Whether radiotherapy to regional lymph nodes is required; if yes: whether this includes IMC.
- Estimated radiotherapy start date.
- In which breast/side disease was diagnosed; if bilateral, which side(s) require(s) a boost.
- Whether patient is taking part in early side-effects sub-study (until sub-study recruitment is complete).

- Whether patient has consented to optional aspects of the study.

* Not required for international participants. For international participants, only initials and partial date of birth will be collected.

Once this information has been entered, the randomisation form will become available, and the patient can be randomised by completing the questions on the form. The system will confirm the patient's treatment allocation. As this is an electronic system sites will have access to this at all times, but the ICR-CTSU FAST-Forward Boost trial team will only be available between 09.00-17:00 (UK time) Monday to Friday excluding bank holidays and closure periods.

8. TRIAL ASSESSMENTS

8.1. Administration of demographics questionnaire

All patients will be asked to complete a demographics booklet at baseline. This booklet is based on the DISTINCT project to monitor inclusivity of clinical research. This will be administered as a separate paper booklet and may become available as an electronic questionnaire at later stage of the study.

8.2. Administration of (e)PRO booklets

All patients who have consented to complete PRO questionnaires will be asked to complete questionnaires at pre-treatment, then from the start of radiotherapy at weeks 1, 2, 3 and 5, 3 months and annually from 1-5 years.
Patients in the early side-effects sub-study will additionally be asked to complete questionnaires at weeks 4, 6 and 7.

It is anticipated that the option of electronic completion (ePRO) will become available whilst the trial is recruiting. Patients will be asked at randomisation whether they prefer electronic or paper questionnaire completion. The FAST-Forward Boost trials office will inform the sites and recruited patients who prefer electronic PRO completion when it is available.

Paper PRO completion
Pre-treatment (baseline) questionnaires will be in a booklet and handed out in the clinical centre by a member of staff. Patients will be asked to complete the questionnaires after a full explanation of the study and after giving informed consent. They should be completed before first radiotherapy treatment and, ideally, before patient is informed of treatment allocation, to avoid the possibility of bias. It is the responsibility of the clinical centre to ensure the completed pre-treatment booklet is sent to the trials office.

Patients will be asked to complete subsequent questionnaires at the timepoints described above. The booklet containing questionnaires for weeks 1, 2, 3 and 5 will be given to the patient at the start of radiotherapy. Sites should remind patients to complete their trial questionnaires on a regular basis. For UK patients all other booklets will be posted to the patient's home from the trials office. Patients will be sent a pre-paid envelope to return each completed booklet to the FAST-Forward Boost trials office (UK only). For international sites all booklets will be administered by the site or national coordinating group.

Early side-effects sub-study
Patients taking part in the early side-effects sub-study will be given a booklet containing questionnaires for weeks 1-7 from the start of radiotherapy and be asked to return the completed booklet to the trials office in

the pre-paid envelope. Sites should regularly remind patients to complete their trial questionnaires on a weekly basis.

Questionnaires for later timepoints will be posted directly to the patient from the trials office.

Electronic PRO completion (ePRO)
When ePRO is available, patients who have indicated a preference for electronic completion will be provided with login details and will receive email notifications and reminders when a questionnaire needs completing following the schedule outlined above.

8.3. PRO responses

The hospital team will not be informed of individual patient responses except where a patient participating in the early side-effects sub-study has a clinically significant score on the HADS, as these patients should be further assessed clinically. The early side-effects sub-study Patient Information Sheet explains that high HADS anxiety/depression scores will be passed on to their doctor. The FAST-Forward Boost trial team will contact the patient's hospital team in these cases.

8.4. Pre-treatment Assessments

The following baseline pre-treatment assessments should be conducted after consent to participate in FAST-Forward Boost, unless they are part of standard of care, and before first treatment of radiotherapy:

- Medical history (including specific risk factors for cardiovascular disease and radiotherapy toxicity).
- Weight and height measurement.
- Breast assessment (trial-specific as used in previous trials and Harvard-Harris scale).
- Lung toxicity assessment (RTOG).
- UK only: Demographic questionnaire completed by patient (including ethnic group, sex and gender, sexual orientation and caring responsibilities)
- Pre-treatment patient-reported outcomes (e)(PRO) health-related quality of life questionnaire booklet*(not mandatory), including:
    - EORTC QLQ-C30 and QLQ-BR23
    - Body Image Scale (BIS)
    - Fatigue (EORTC QLQ FA12)
    - EQ-5D-5L
    - Radiotherapy symptoms (breast & arm/shoulder trial specific, used in previous trials)
    - *For patients receiving treatment to IMC*: oesophageal toxicity (PRO-CTCAE V5.0).
- One blood sample (not mandatory) for those patients providing consent, ideally before radiotherapy starts but can be at any timepoint. If the patient is participating in the early-side effects substudy, see box below.

<u>Additional</u> pre-treatment assessments for EARLY SIDE-EFFECTS SUB-STUDY ONLY

- Health care professional (HCP) assessed skin, breast and oesophageal toxicity assessment (CTCAE V5.0)
- Patients should be given the substudy specific pre-treatment (e)PRO booklet*, containing the following additional questionnaires:

- Patient assessed skin, breast, and oesophageal toxicity assessment (PRO-CTCAE V5.0 and trial specific questions as used in previous trials).
- Patient reported outcome Hospital and Anxiety Depression Scale (HADS)

- For patients who have consented to the translational substudy and early side effects translational substudy, the 1st blood sample **must** be taken **prior to** and as close as possible to the start of radiotherapy treatment.

*NB: Ideally, pre-treatment PRO questionnaires should be completed prior to the patient being aware of treatment allocation. If using ePRO, all questionnaires will be provided electronically by the ICR-CTSU office.

8.5. Timing of on-treatment assessments

Participants in the Control Group will receive radiotherapy over three weeks. Participants in Test Groups 1 and 2 will receive radiotherapy over one week. Assessments should be completed by <u>all</u> participants at the end of each week from the start of radiotherapy:

- Participants in the Control Group will complete these assessments whilst receiving treatment at the end of weeks 1, 2 and 3 (i.e. at fraction 5, at fraction 10 and at final treatment).
- For participants in the Test Groups, the week 1 assessment will be completed at the end of their treatment week (i.e. at fraction 5), and then week 2 and week 3 assessments will take place 7 days and 14 days after their final treatment, respectively.

In the unlikely event of treatment interruptions, the timing of these weekly assessments should remain scheduled in accordance with the originally planned start and end dates.

8.6. On-treatment and end of treatment assessments

At the beginning of their radiotherapy treatment, all participants who have consented to complete PRO questionnaires should be given the **"On-Treatment and End of Treatment Assessments" (e)PRO questionnaire booklet**, containing the following:

At the end of weeks 1, 2 and 3:
- Patient-reported outcome of fatigue (EORTC QLQ FA12).
- Patient-reported outcome of health-related quality of life (EQ-5D-5L).
- Patient-reported out of pocket expenditure questionnaire (UK only).

At the end of week 5:
- Patient-reported health-related quality of life (EORTC QLQ-C30 and QLQ-BR23)
- Patient-reported Body Image Scale (BIS)
- Patient-reported outcome of fatigue (EORTC QLQ FA12)
- *For participants receiving IMC radiotherapy:* Patient reported oesophageal toxicity (PRO-CTCAE V5.0).

Sites should remind patients to complete their trial questionnaires within the booklet at the end of every applicable week.

<u>Additional</u> assessments Week 1 to 7, for EARLY SIDE-EFFECTS SUB-STUDY ONLY
At the beginning of their radiotherapy treatment, patients taking part in the Early Side Effects Sub study should be given the sub study specific "**On-Treatment and End of Treatment Assessments" (e)PRO booklet**, containing the following additional questionnaires:

- **At the end of weeks 1 to 7:** Patient assessed skin, breast, and oesophageal toxicity assessment (PRO-CTCAE V5.0 and trial specific questions as used in previous trials)

- **At the end of week 7 only:** Patient reported outcome of fatigue (EORTC QLQ FA12).

Additionally, the following assessments should be performed **in person:**

At the end of week 1

- HCP assessed skin, breast and oesophageal toxicity assessment (CTCAE V5.0)
- Blood samples (for patients who have given consent):
    - **Test group patients**: 2nd blood sample, taken ideally just after fraction 5.

At the end of week 3

- HCP assessed skin, breast and oesophageal toxicity assessment (CTCAE V5.0)
- Blood samples (for patients who have given consent):
    - **Control group patients**: 2nd blood sample, taken ideally just after fraction 15.
    - **Test group patients**: 3rd blood sample.

At the end of week 5

- HCP assessed skin, breast and oesophageal toxicity assessment (CTCAE V5.0)
- Blood samples (for patients who have given consent):
    - **Control group patients**: 3rd blood sample.

At the end of week 7

- HCP assessed skin, breast and oesophageal toxicity assessment (CTCAE V5.0).

Timing of assessments (assuming no treatment interruptions*):

	Control Group	Test Group
Week 1	At fraction 5	At fraction 5
Week 2	At fraction 10	7 days after final fraction
Week 3	At fraction 15	14 days after final fraction
Week 4	7 days after final fraction	21 days after final fraction
Week 5	14 days after final fraction	28 days after final fraction
Week 6	21 days after final fraction	35 days after final fraction
Week 7	28 days after final fraction	42 days after final fraction

*In the unlikely event of treatment interruptions, the timing of these weekly assessments should remain scheduled in accordance with the originally planned start and end dates.

Month 3

The following assessments should be conducted at 3 months after the start of radiotherapy for <u>all</u> participants:

- Lung toxicity assessment (RTOG) *(can be conducted by remote consultation)*
- Participants who have consented to complete PRO questionnaires will be sent/given a Follow-up (e)PRO booklet, including the following questionnaires *(for UK participants this will be coordinated by ICR-CTSU):*
    - EORTC QLQ-C30 and QLQ-BR23
    - Body Image Scale (BIS)
    - Fatigue (EORTC QLQ FA12)
    - EQ-5D-5L

- Radiotherapy symptoms (breast & arm/shoulder trial specific, used in previous trials).
- Patient reported health care resource use (UK only)

<u>Additional</u> assessments at month 3 for EARLY SIDE-EFFECTS SUB-STUDY ONLY
Patients will be sent the sub study specific "Follow Up Assessments – 3 months" (e)PRO booklet, containing the following additional questionnaires *(this will be coordinated by ICR-CTSU):*

- Patient assessed skin, breast, and oesophageal toxicity assessment (PRO-CTCAE V5.0 and trial specific questions as used in previous trials).

8.7. Post-treatment Follow-up

Year 1

The following post-treatment assessments should be conducted at 1 year after the start of radiotherapy and should be done in clinic:

- Breast assessment (trial-specific, as used in previous trials and Harvard-Harris scale).
- Lung toxicity assessment (RTOG).
- Late toxicity and adverse events (including lymphoedema).
- Assessment for recurrence and survival.
- Participants who have consented to complete PRO questionnaires will be sent/given a Follow-up (e)PRO booklet, including the following questionnaires *(for UK participants this will be coordinated by ICR-CTSU):*
  - EORTC QLQ-C30 and QLQ-BR23
  - Body Image Scale (BIS)
  - Fatigue (EORTC QLQ FA12)
  - EQ-5D-5L
  - Radiotherapy symptoms (breast & arm/shoulder trial specific, used in previous trials).
  - Patient reported health care resource use (UK only).

Year 2

Participants who have consented to complete PRO questionnaires will be sent/given a Follow-up (e)(PRO) booklet, including the following questionnaires *(for UK participants this will be coordinated by ICR-CTSU)*:

- Patient-reported outcomes of health-related quality of life (QoL) including:
  - EORTC QLQ-C30 and QLQ-BR23
  - Body Image Scale (BIS)
  - Fatigue (EORTC QLQ FA12)
  - Radiotherapy symptoms (breast & arm/shoulder trial specific, used in previous trials).
- Patient reported disease status.

Year 3

The following post-treatment assessments should be conducted at 3 years after the start of radiotherapy and should be done in clinic:

- Breast assessment (trial-specific as used in previous trials and Harvard-Harris scale).
- Late toxicity and adverse events.
- Assessment for recurrence and survival.

- Participants who have consented to complete PRO questionnaires will be sent/given a Follow-up (e)(PRO) booklet, including the following questionnaires *(for UK participants this will be coordinated by ICR-CTSU)*:
    - EORTC QLQ-C30 and QLQ-BR23
    - Body Image Scale (BIS)
    - Fatigue (EORTC QLQ FA12)
    - EQ-5D-5L
    - Radiotherapy symptoms (breast & arm/shoulder trial specific, used in previous trials).
    - Patient reported health care resource use (UK only).

Year 4

Participants who have consented to complete PRO questionnaires will be sent/given a Follow-up (e)(PRO) booklet, including the following questionnaires *(for UK participants this will be coordinated by ICR-CTSU):*

- Patient-reported outcomes of health-related quality of life (QoL) including:
    - EORTC QLQ-C30 and QLQ-BR23
    - Body Image Scale (BIS)
    - Fatigue (EORTC QLQ FA12)
    - Radiotherapy symptoms (breast & arm/shoulder trial specific, used in previous trials).
- Patient reported disease status.

Year 5

The following post-treatment assessments should be conducted at 5 years after the start of radiotherapy and should be done in clinic:

- Breast assessment (trial-specific as used in previous trials and Harvard-Harris scale)
- Late toxicity and adverse events
- Assessment for recurrence and survival
- Participants who have consented to complete PRO questionnaires will be sent/given a Follow-up (e)(PRO) booklet, including the following questionnaires *(for UK participants this will be coordinated by ICR-CTSU)*:
    - EORTC QLQ-C30 and QLQ-BR23
    - Body Image Scale (BIS)
    - Fatigue (EORTC QLQ FA12)
    - EQ-5D-5L
    - Radiotherapy symptoms (breast &arm/shoulder trial specific, used in previous trials)
    - Patient reported health care resource use (UK only).

Mammograms should be performed post treatment as per standard of care.

Beyond Year 5

During the trial, the ICR-CTSU team aim to transfer the provision of longer-term follow-up data (including data to determine recurrence outcomes) from research sites to NHS routine data sources (and international equivalent where available), providing the patient has given consent to do so and the required information can be accessed from routine sources. This is intended to relieve the burden of longer-term follow-up on research sites, and as a move towards this, data collection in the eCRF is minimal for patients in whom no disease event has occurred. Where this data is not available from routine data sources, information will continue to be collected from research sites.

8.8. Procedure at Disease Progression/recurrence

If a patient has a local or distant relapse, new primary cancer (including contralateral breast, lung, and oesophagus) the following procedures should be followed:

- Routine clinical, histological and imaging information should be collected on the disease relapse and entered into the relevant FAST-Forward Boost eCRF.
- The patient should be treated according to local protocol for relapse/new primary cancer.

8.9. Discontinuation from Treatment

Participants may discontinue from trial treatment at any time at their own request, or they may be discontinued at the discretion of the Principal Investigator. Reasons for discontinuation may include:

- Disease progression or recurrence
- Unacceptable toxicity
- Pregnancy.

Participants who discontinue treatment should continue to be followed up.

8.10. Change in Participation Status

Participants may choose to change, reduce, or stop their participation after joining the trial. Within FAST-Forward Boost the following changes in participation are possible:

- Stopping trial specific follow up – data will continue to be requested from routine visits.
- Stopping routine clinical follow up – data will continue to be requested from details in the patients' medical record (e.g. date of progression/death).
- Stopping participation in patient reported outcome questionnaires
- Stopping participation in optional sub studies.
- Stopping donated samples being used in FAST-Forward Boost research/analysis
- Stopping future sharing of data/samples.
- Withdrawal of consent for any further data to be submitted – data up to the point of withdrawal will be retained as described in the patient information sheet.

Changes in participation should be led by the participant, and no assumptions should be made on their behalf. If this occurs, a change in participation status form should be submitted to ICR-CTSU to report the details of the reduction in participation. For further guidance on the types of change in participation status and guidance on loss of contact, please refer to trial guidance notes.

8.11. Schedule of Assessments

FAST-Forward Boost Assessments *Additional Early Side-Effects Sub-Study assessments*	Pre-treatment assessments	On-treatment Assessments			End of treatment assessments					Post-treatment assessments				
		Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	3 months	1 year *(in clinic)*	2 years	3 years *(in clinic)*	4 years	5 years *(in clinic)*
Clinician reported														
Medical history	x													
Weight and height measurement	x													
Breast assessment (trial-specific and Harvard-Harris scale)	x									x		x		x
Lung toxicity assessment (RTOG)	x								x	x				
Collection of baseline blood sample *(optional)*	x													
Additional blood samples – control group *(optional)*				x		x								
Additional blood samples – test groups *(optional)*		x		x										
Skin, breast and oesophageal toxicity assessment (CTCAE V5.0)	x	x		x		x		x						
Late toxicity and adverse events										x		x		x
Recurrence and survival										x		x		x
Patient reported demographics														
Demographics booklet (UK only)	x													
Patient reported outcomes *(non-mandatory for main trial)*														
Health related quality of life (EORTC QLQ-C30 and QLQ-BR23)	x					x			x	x	x	x	x	x
Body Image Scale (BIS)	x					x			x	x	x	x	x	x
Hospital Anxiety and Depression Scale (HADS)	x													
Fatigue (EORTC QLQ-FA-12)	x	x	x	x		x		x	x	x	x	x	x	x
Overall quality of life (EQ5D-5L)	x	x	x	x					x	x		x		x
Patient assessed oesophageal toxicity (PRO-CTCAE v5.0) for patients receiving radiotherapy to IMC only	x					x								
Out of pocket expenditure *(UK only)*		x	x	x										
Health care resource use *(UK only)*									x	x		x		x
Early Skin, breast, and oesophageal toxicity assessment (PRO-CTCAE V5.0 and trial specific)	x	x	x	x	x	x	x	x	x					
Longer term Radiotherapy Symptoms (breast & arm/shoulder trial specific)	x								x	x	x	x	x	x
Disease status											x		x	

8.12. Treatment Timelines

Radiotherapy should commence as soon as possible and ideally within 4 weeks of randomisation. It is advised that radiotherapy starts within 8 weeks of surgery and/or last dose of chemotherapy when possible. Timelines from systemic therapy to start of radiotherapy should otherwise be observed as per standard of care.

(please see section 8.15 for advice about timing with systemic therapy).

8.13. Radiotherapy Planning & Treatment

Radiotherapy imaging, positioning, outlining, planning and treatment should be carried out in accordance with the guidelines in the current version of the radiotherapy planning document, available on request from ICR-CTSU (Fastforwardboost-icrctsu@icr.ac.uk).

Radiotherapy prescription doses are as follows:
Control Group: 40Gy/15#/ 3 weeks to breast +/- nodes with 48Gy/15#/ 3 weeks to the boost volume.
Test Group 1: 26Gy/ 5#/ 1 week to breast +/- nodes with 31Gy/5#/ 1 week to the boost volume.
Test Group 2: 26Gy/ 5#/ 1 week to breast +/- nodes with 30Gy/5#/ 1 week to the boost volume.

Where a nodal boost is prescribed this should be 48Gy/15# in the control group and 30Gy/5# in either of the test groups.

8.14. Treatment Scheduling and Gaps

Treatment can start on any day of the week. Patients should not have a break in treatment where possible. Where interruptions are due to breakdown or unavailability of the treatment machine, patients should be transferred to a matched treatment machine in the first instance.

Where this is not possible, the gap should be kept to a minimum in the event of machine service or breakdown. If the treatment machine is unavailable for more than 7 consecutive days (including the weekend days), please contact the RTTQA team and the FAST-Forward Boost Trial team.

8.15. Concomitant Therapy

TDM-1 can be given concomitantly with radiotherapy but, in the test groups, it is recommended that TDM-1 should not be given within 4 days prior to (or after) a fraction of radiotherapy. For the control group, it is accepted that one TDM-1 dose will be given on the same day as a radiotherapy fraction.
Where CDK4/6 inhibitors are recommended, these should ideally be given no earlier than 7 days following completion of radiotherapy. If CDK4/6 inhibitors have been started prior to trial randomisation, they should be stopped at least 7 days prior to the first radiotherapy fraction and can be restarted 7 days after the final fraction.
Immunotherapy can be started before radiotherapy, but doses of immunotherapy should not be given within 7 days prior to the first fraction of radiotherapy or within 7 days of the last fraction of radiotherapy.

Concomitant endocrine therapy, bisphosphonate, denosumab, trastuzumab and pertuzumab *are* permitted.

Other chemotherapy agents (including adjuvant anthracyclines, taxanes and capecitabine) and other biological/targeted therapies (e.g. PARP inhibitors) are not permitted to be delivered concomitantly with radiotherapy. Standard departmental protocols of timing of these agents in relation to radiotherapy should be followed. Contact the ICR-CTSU if any clarification around systemic therapies is required.

It is recommended that radio-sensitising agents such as methotrexate are discontinued for at least one week prior to and after completion of radiotherapy. Otherwise, all medication considered necessary for the patient's welfare, and which is not expected to interfere with the evaluation of the treatment may be given at the discretion of the investigator. All concomitant medications (including start/stop dates, dose frequency, route of administration and indication) must be recorded in the patient's notes.

8.16. Radiotherapy Quality Assurance (QA)

The radiotherapy quality assurance (RT QA) programme for the FAST-Forward Boost Trial has been designed and will be implemented by the UK National Radiotherapy Trials QA (RTTQA) Group. The components of the FAST-Forward Boost QA programme are described in the FAST-Forward Boost Radiotherapy Planning and Delivery guidelines ("Quality Assurance (QA) pack"). There are pre-trial QA components and on trial QA components; please refer to guidelines.

The details of the programme are available on the RTTQA group website https://rttrialsqa.org.uk/. Please contact the RTTQA team for the benchmark cases and radiotherapy guidelines.

9. SAFETY REPORTING

9.1. Definitions

Adverse Event (AE)
An AE is any untoward medical occurrence in a patient administered a study treatment; the event does not necessarily have a causal relationship with the treatment.

Serious Adverse Event (SAE)
An SAE is any untoward medical occurrence that occurs after the first radiotherapy treatment and within 30 days of the last treatment of radiotherapy and

- results in death,
- is life-threatening,
- requires hospitalisation or prolongation of existing inpatients´ hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly or birth defect.

Important adverse events that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, may also be considered serious.

Progression of the indicated disease and death due to progression of the indicated disease are not considered SAEs and do not need to be reported as such but should be reported on the appropriate eCRF as required.

Pregnancy or aid in the conception of a child whilst participating in a trial is not itself considered an SAE but should be followed up for congenital anomalies or birth defects.

Serious Adverse Reaction (SAR)
A serious adverse reaction is an SAE that is suspected as having a causal relationship to the trial treatment, as assessed by the investigator responsible for the care of the patient. A suspected causal relationship is defined as possibly, probably, or definitely related (see definitions of causality table).

Related Unexpected Serious Adverse Event
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 of any of the research procedures, and
"Unexpected" – that is, the type of event is not listed in the protocol as an expected occurrence (see section 9.4))

Definitions of causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship with the trial treatment
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial treatment). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment)
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial treatment). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments)
Probable	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

9.2. Reporting Adverse Events to ICR-CTSU

For the patients in the early side-effects sub-study:
Any toxicity, sign or symptom that occurs after commencement of radiotherapy treatment and up to 7 weeks since the start of radiotherapy, which is not unequivocally due to progression of disease, should be considered an Adverse Event (AE) and reported on the relevant eCRF/(e)PRO booklet and submitted to ICR-CTSU.

All patient's radiotherapy related toxicities will be collected on the eCRF/(e)PRO as per the schedule of assessment.

The severity of AEs should be graded according to the NCIC-CTC criteria v5. For each AE, the highest grade observed since the last visit should be reported.

Whenever one or more toxicity/sign/symptom corresponds to a disease or a well-defined syndrome only the main disease/syndrome should be reported.

9.3. Reporting of Serious Adverse Events to ICR-CTSU

Any SAE that occurs after commencement of radiotherapy treatment and up to 30 days following the last fraction of radiotherapy treatment must be reported. All SAEs should be reported to ICR-CTSU within 24 hours of the Principal Investigator (or designated representative) becoming aware of the event, by completing the FAST-Forward Boost SAE form in the trial database.

As much information as possible, including the Principal Investigator's assessment of causality, must be reported to ICR-CTSU in the first instance. Additional follow up information should be reported as soon as it is available. All SAE forms must be electronically reviewed and approved by the Principal Investigator or designated representative.

9.4. Expected toxicities of radiotherapy

The following are expected toxicities of radiotherapy.

- Fatigue
- Skin changes
- Difficulty swallowing (for those who receive nodal radiotherapy)
- Pneumonitis
- Breast oedema
- Breast tenderness
- Breast shrinkage
- Breast hardening
- Breast lymphoedema
- Arm lymphoedema
- Rib fracture
- Lung fibrosis
- Ischaemia heart disease
- Telangiectasia

Clinical judgement should be exercised when considering the expectedness of events in relation to radiotherapy.

9.5. Review of Serious Adverse Events

The Chief Investigator (or designated representative) will assess all reported SAEs for causality and expectedness (NB. The Chief Investigator cannot down-grade the Principal Investigator's assessment of causality).

SAEs assessed as having a causal relationship to study treatment and as being unexpected will undergo expedited reporting to the relevant authorities and all other interested parties by ICR-CTSU (see 10.6).

Sites should respond as soon as possible to requests from the Chief Investigator or designated representative (via ICR-CTSU) for further information that may be required for final assessment of an SAE.

9.6. Expedited Reporting of Related Unexpected SAEs

If an SAE is identified as being related to radiotherapy and unexpected by the Chief Investigator it will be reported by ICR-CTSU to the main REC, the Sponsor, and all other interested parties within 15 days of being notified of the event.

The Principal Investigators at all actively recruiting sites will be informed of any related unexpected SAEs occurring within the trial at appropriate intervals.

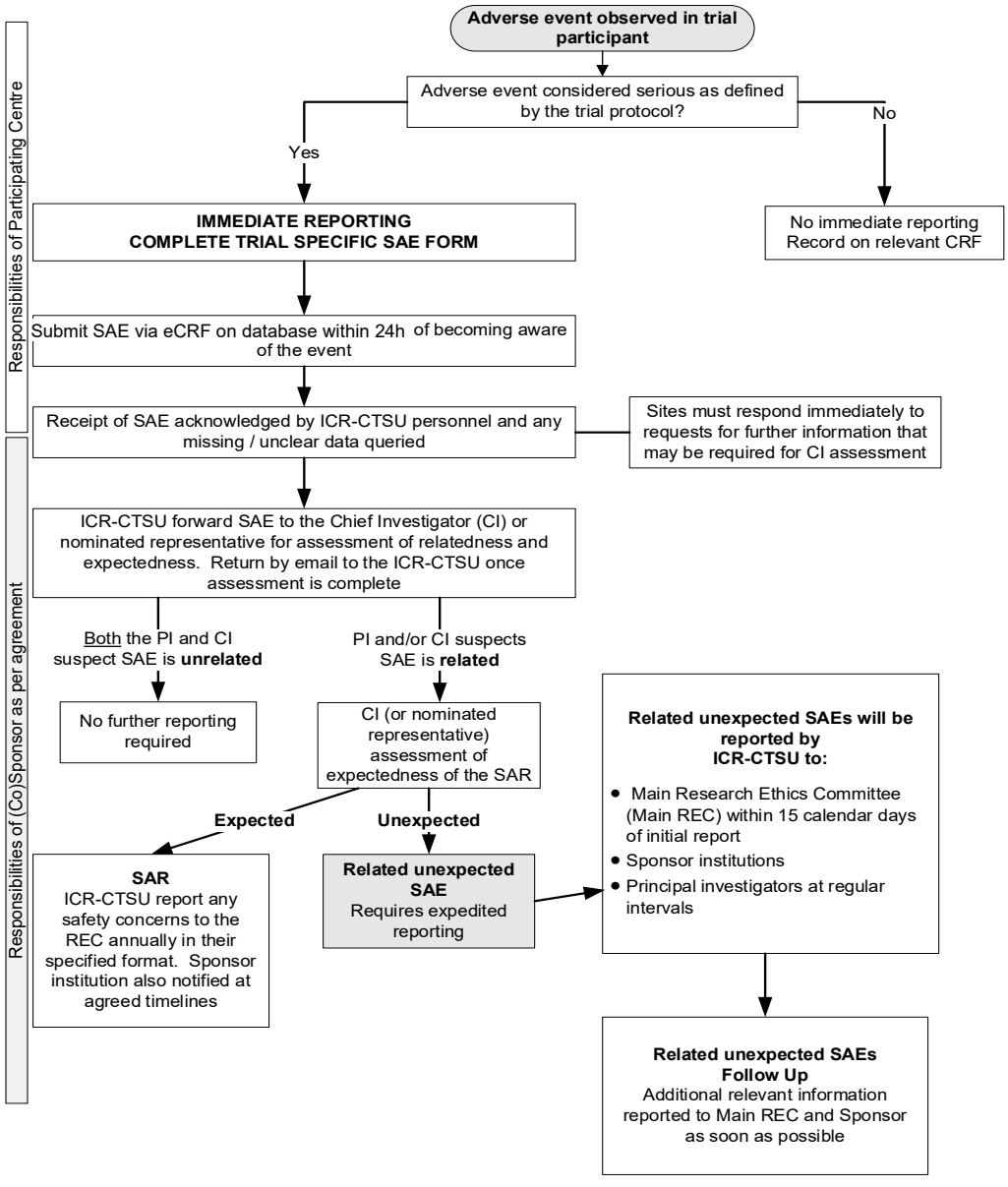
9.7. Follow up of Serious Adverse Events

SAEs should be followed up until clinical recovery is complete or until event has stabilised. SAE outcomes should be reported to ICR-CTSU using the relevant section of the SAE form in the database as soon as the Principal Investigator or designee becomes aware of the outcome.

9.8. Reporting Pregnancies

If any trial participant becomes pregnant while receiving trial treatment or up to 30 days after receiving trial treatment, this should be reported to ICR-CTSU using the pregnancy reporting form. Participants who become pregnant should discuss with their clinical team immediately. Where a clinician agrees appropriate to continue radiotherapy, the patient can remain in the trial. Pregnancies should be followed up until conclusion and all follow-up information should be reported to ICR-CTSU. If the outcome of the pregnancy meets the definition of serious (i.e. congenital abnormality) this should be reported to ICR-CTSU following the serious adverse event reporting procedures described above.

Figure 1: Flow diagram for SAE reporting, and action following report



NB. All SAEs should continue to be followed up as specified above

10. STATISTICAL CONSIDERATIONS

10.1. Statistical Design and Sample Size Justification

This is a multicentre, phase III, randomised trial with the primary aim of demonstrating non-inferiority of the 1-week schedules (test groups 1 and 2) when compared with the standard 3-week schedule (control) in terms of ipsilateral breast tumour recurrence rates at 5 years. Except where indicated, pairwise comparisons will be made between the control group and each of the two test groups.

Sample size for analysis of the primary endpoint.

5-year ipsilateral breast tumour recurrence in the control group is anticipated to be 3%. This has been estimated using information from IMPORT HIGH(6) and the expectation that the FAST-Forward Boost population will likely be a slightly higher risk group with recruitment of more participants with node positive disease. 4830 participants (randomised 1:1:1) provides 90% power to rule out a 2% absolute non-inferiority margin (i.e. ensuring 1-week SIB ipsilateral breast tumour recurrence rate is ≤5% at 5 years). 5-year estimates will be based on Kaplan-Meier estimation with the corresponding critical hazard ratio being 1.68. The calculation allows for 5% loss to follow-up and a 2.5% alpha (1-sided) is used given the two comparisons being made (test group 1 vs control; test group 2 vs control).

Sample size for Early Side-Effects Sub-Study.

An assessment of acute toxicity (clinician- and patient-reported skin, breast and oesophageal symptoms measured using CTCAE v5.0 and PRO-CTCAE v5.0) will be performed with the aim of identifying any early safety signal with either of the test schedules. The primary endpoint for this analysis, on which the sample size is based, is clinician-reported CTCAE v5.0 skin toxicity. Grade ≥3 acute skin reactions are expected to be low, about 3% in the control group. The aim of this analysis will be to rule out ≥10% acute skin reactions CTCAE v5.0 grade ≥3 in either test group. Based on an A'Hern single-stage design with 90% power and 5% one-sided significance level, this would require 103 participants in each of the test groups. The same number of patients will be included from the control group to confirm the design assumptions, but this will be a non-comparative analysis. Allowing for approximately 10% of patients missing the relevant assessment data (or excluded from the per protocol population on which this analysis will be based), approximately 345 patients will be included in this sub-study. If 6/103 or more participants within either test group have CTCAE v5.0 skin reactions ≥ grade 3 then it would not be possible to exclude a 10% rate.

Sample size for subgroup analysis of pneumonitis rates in IMC population.

Acute lung toxicity is a specific consideration relevant to patients receiving radiotherapy to the IMC (expected to be 10-15% of recruited patients). As such, a powered subgroup analysis to evaluate this is planned. Based on RTOG assessment, the rate of ≥G3 pneumonitis occurring up to 3 months post-treatment in patients requiring radiotherapy to the IMC is anticipated to be 2% in the control group and we want to rule out an increase of 3% (to 5%) or more in the test groups. The two test groups will be combined for this analysis since the mean dose to the lung for both schedules is almost identical. Using an A'Hern single stage design with 90% power and a 5% one-sided significance level, 311 participants receiving IMC radiotherapy in either of the experimental arms would allow a rate >5% to be ruled out. Rates of pneumonitis in control arm patients requiring IMC radiotherapy will be considered for the purpose of confirming the design assumptions but this will be a non-comparative analysis. If more than 9/311 cases of ≥G3 pneumonitis were reported in those receiving 5Fr SIB, then it would not be possible to exclude a rate of 5% or more.

Sample size for late normal tissue effects analysis.
Late normal tissue effects, and particularly breast induration, are important secondary endpoints of the trial. An analysis of clinician-assessed breast induration at 3 years is planned with the aim of demonstrating that there is not an unacceptable increase in risk of these symptoms associated with either of the test schedules. Based on IMPORT HIGH(6), we expect 11% of patients to have moderate/marked clinician-assessed breast induration by 3 years in the control group. A sample size of 823 patients per arm will provide 90% power to rule out an increase of 5% (to 16%) or more in either of the test groups (2.5% alpha for each pairwise comparison). This analysis will be based on the per protocol population. Allowing for approximately 20% of patients missing the relevant assessment data (or excluded from the per protocol population), the anticipated timing of this analysis is when 3090 patients have reached 3 years follow-up after randomisation.

10.2. Treatment Allocation

All trial participants will receive radiotherapy.

Participants will be allocated between the three groups – control, test group 1 and test group 2 - on a 1:1:1 basis (open-label). Allocation will be by computer generated random permuted blocks. Randomisation will be stratified by:

- breast surgery type (breast conservation surgery (including mammoplasty) or breast conservation surgery with perforator flap reconstruction)
- need for nodal radiotherapy (none, nodes not including IMC or nodes including IMC)
- treating centre.

10.3. Endpoint Definitions

Primary endpoint
The primary endpoint is ipsilateral breast tumour recurrence at 5 years, defined as either invasive or non-invasive ipsilateral tumour recurrence in the breast, including tumours considered to be new primaries by virtue of biology or location. Kaplan-Meier estimation will be used, with observations censored at death or most recent follow-up assessment for those patients without an event.

Secondary endpoints

- Patient-reported acute radiotherapy adverse effects (up to 3 months post-treatment*), with a focus on skin, breast, and oesophageal toxicity (PRO-CTCAE v5.0 and trial-specific assessments).
- Patient-reported late effects (between 1- and 5-years post-treatment*), with a focus on breast and arm/shoulder symptoms, using both standard instruments (EORTC QLQ BR-23) and trial-specific assessments.
- Patient-reported fatigue and quality of life (EORTC QLQ FA12, QLQ C30, QLQ BR-23, Body Image Scale (BIS), EQ5D-5L), measured throughout follow-up.
- Clinician-reported acute skin and oesophageal toxicity (CTCAE v5.0, up to 7 weeks post-treatment*) and breast oedema (trial specific, used in previous trials).
- Clinician-reported lung toxicity (RTOG, 3- and 12-months post-treatment*).
- Clinician-reported late normal tissue effects and cosmetic outcome (between 1- and 5-years post-treatment*), assessed with tools developed in previous breast radiotherapy trials and the Harvard Harris scale.

- Clinician-reported other late radiotherapy adverse events (between 1- and 5-years post-treatment*), including arm and breast lymphoedema, sensori-motor symptoms, symptomatic rib fracture, symptomatic lung fibrosis and ischaemic heart disease.
- Recurrence-free survival, defined as time to the first of: invasive ipsilateral breast tumour recurrence, invasive loco-regional recurrence, distant recurrence or death from any cause. Observations will be censored at most recent follow-up assessment for those patients without an event.
- Breast cancer-related survival, defined as time to breast cancer death. Observations will be censored at death due to other cause or most recent follow-up in those patients without an event.
- Overall survival, defined as time to death from any cause, with observations censored at most recent follow-up for surviving patients.
- Cost-effectiveness, based on health economic analysis which incorporates data on patient-reported health resource usage and health status (EQ-5D-5L).

**Follow-up times are measured from treatment start date.*

10.4. Statistical Analysis Plan

Statistical analyses will be conducted at the ICR-CTSU. Analysis details are outlined here in brief. Full details will be specified in a Statistical Analysis Plan in accordance with ICR-CTSU Standard Operating Procedures. Health economics analysis will be conducted by the University of York and detailed in a separate analysis plan (Appendix A3 provides further details of the health economic evaluation).

Timing of the analyses

Subject to guidance from the IDMC, the primary analysis is expected to take place when all patients have completed a minimum of 4 years follow-up in the trial (or are known to have been lost to follow-up or withdrawn), with a median follow-up time of approximately 5 years. A later analysis, incorporating routinely collected healthcare data (subject to validation), will focus on long-term cancer outcomes.

Some secondary endpoint data will mature whilst the trial is ongoing and it is intended that results from these analyses will be published ahead of primary endpoint data, to provide reassurance of the safety of the 5Fr approach. These include:

- Early side effects sub-study analysis, including acute toxicity and dosimetry data (103 patients in each test group with relevant CTCAE v5.0 data)
- Subgroup analysis of pneumonitis rates in IMC population (including at least 311 patients receiving IMC radiotherapy in either test group with relevant 3-month RTOG data)
- Late normal tissue effects analysis (including 823 patients in each trial arm with the relevant 3-year data on breast induration)

Analysis sets

Primary efficacy analyses will be based on the intention-to-treat analysis set (including all patients according to allocated trial arm). However, given the non-inferiority hypothesis, sensitivity analysis based on a per protocol analysis set will also be conducted to consider the impact of non-compliance and draw robust conclusions about non-inferiority. Safety analyses will be based on a per protocol analysis set, according to treatment received. Full definitions of the analysis sets will be provided in the analysis plan.

Analysis of the primary endpoint

The primary endpoint will be presented by trial arm using Kaplan-Meier curves; estimated 5-year event rates will be given along with 95% confidence intervals. The treatment effect from each pairwise comparison will be presented as an absolute difference, by applying the hazard ratio (and corresponding 95% confidence interval) to the control group 5-year event-free estimate. This will be the primary assessment of non-inferiority (whether or not the upper limit of the confidence interval exceeds 2%). Additionally, the hazard ratio will be used to present treatment effect on a relative scale, presented with a 95% confidence interval. Hazard ratios will be derived from Cox proportional hazard regression models. The primary analysis will be unadjusted, but estimates will also be presented after adjustment for factors used in the randomisation algorithm and other important prognostic factors (which will be pre-specified in the analysis plan). As noted above, a sensitivity analysis based on a per protocol population will also be reported. The proportional hazards assumption will be checked and, if violated, appropriate alternative methods will be applied.

Analysis of secondary endpoints

PRO questionnaires will be scored using published manuals, including methods for handling missing data. Analyses of both patient-reported and clinician-reported toxicity data will follow methods established in previous breast radiotherapy trials(6, 10, 16, 39, 40) (11) and will account for multiple testing by adjustment of significance levels. Frequencies of early and late toxicities will be summarised at each time point/period and compared between treatment groups using chi-squared test or Fisher's exact test as appropriate. Where appropriate, longitudinal models (e.g. generalised estimating equations) including all assessments over follow-up, and survival analyses of time to first moderate/marked adverse effect will be carried out with comparisons between treatment groups, adjusting for balancing and other factors (for example, pre-treatment HADS score) where relevant. Event rates at key time points will be reported with 95% confidence intervals. For the analysis of late radiation effects on normal tissues the two test groups will be compared to estimate by interpolation the 5Fr schedule equivalent to control in terms of adverse effects.

For the early side effects sub-study analysis, dosimetry data will be summarised descriptively to support interpretation of acute toxicity data.

Recurrence-free survival, breast cancer-related survival and overall survival will be analysed in a similar way to the primary endpoint. However, particularly for breast cancer-related and overall survival, analyses are likely to be largely descriptive due to the rarity of events which may preclude formal statistical comparisons.

Use of routinely collected healthcare datasets

Data on cancer events and deaths reported via routinely collected healthcare datasets, where available, will be obtained over a 10-year follow-up period. An initial snapshot of this data will cover the primary analysis period (when all patients have been followed up for 5 years) and the aim of this complementary analysis will be to explore ascertainment of the primary endpoint events (ipsilateral breast tumour recurrence) within these datasets when compared with trial-specific reporting. Depending on the results of this analysis, a 10-year analysis based on routinely collected data is planned which would provide updated data on the primary endpoint and other cancer outcomes.

10.5. Interim Analyses and Stopping Rules

An Independent Data Monitoring Committee (IDMC) will be formed and will confidentially review accumulating safety and efficacy data from the trial at regular intervals (at least annually). Given the non-inferiority hypothesis, and that primary endpoint events will accrue slowly relative to recruitment timescales, early stopping on the basis of efficacy is not expected to be relevant and so no formal interim analysis or

stopping rules are in place. However, at each review, the IDMC will consider the balance of risks and benefits in the accumulating data, as well as any emerging external evidence, in making recommendations to the TSC regarding continuation of the trial.

At the time of analysis for the Early Side-Effects Sub-Study, if 6 or more participants (out of 103) within either test group have skin reactions ≥ grade 3 (on CTCAE v5.0) then it would not be possible to exclude a 10% rate and this will provide stopping guidelines on which the IDMC will base their recommendations. PRO-CTCAE v5.0 data will also be considered. Similarly, for the subgroup analysis of IMC patients, 9 or more cases of RTOG ≥ grade 3 pneumonitis in the first 311 IMC patients receiving 5Fr SIB (either test group) would mean a 5% rate could not be excluded and provides stopping guidelines on which the IDMC will base their recommendations. In both cases, consideration will also be given to the observed control arm rates for these toxicities and whether these align with design assumptions. Unless the IDMC advise otherwise, recruitment will continue whilst these analyses are undertaken.

10.6. Internal pilot

The internal pilot will assess centre set-up and overall recruitment at end of month 15 (expected to be 9 months after opening to recruitment). This will be assessed by:

Progression criteria	Red	Amber	Green
Recruitment rate (participants/site/month)	1	2-3	4
Number of sites opened	<12	13-17	>18
Total number of participants recruited	<100	101-350	>350

The internal pilot will be considered successful, and the trial will continue as planned, if all sets of criteria are "green". Where progression criteria are falling into the amber or red categories, this will be discussed within the trial management group in the first instance, considering data from screening logs and feedback from recruiting site teams, to identify any issues and the appropriate measures to address these. If significant changes to the trial are warranted, this will be discussed and agreed with the TSC and funders.

11. TRIAL MANAGEMENT

11.1. Trial Management Group (TMG)

A Trial Management Group (TMG) will be set up and will include the Chief Investigator, ICR-CTSU Scientific Lead, Co-investigators and identified collaborators, the Trial Statistician and Clinical Trial Manager. Principal Investigators and key study personnel will be invited to join the TMG as appropriate to ensure representation from a range of sites and professional groups. Membership will include at least two patient advocate representatives. The TMG will meet at regular intervals, and at least annually. Notwithstanding the legal obligations of the Sponsor and Chief Investigator, the TMG have operational responsibility for the conduct of the trial. The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSU.

11.2. Trial Steering Committee (TSC)

A Trial Steering Committee (TSC) will be set up and will comprise an independent Chairman and at least two further independent members with clinical or statistical expertise (at least one member must be a statistician). The TSC will meet at regular intervals, and at least annually. The TSC will provide expert independent oversight

of the trial on behalf of the Sponsor and funder(s). The Committee's terms of reference, roles and responsibilities will be defined in charter issued by ICR-CTSU.

11.3. Independent Data Monitoring Committee (IDMC)

An Independent Data Monitoring Committee (IDMC) will be set up to monitor the progress of the trial and will comprise a chairperson and at least two further members with clinical or statistical expertise (at least one member must be a statistician). Membership of the IDMC will be proposed by the TMG and approved by the TSC.

The IDMC will meet in confidence at regular intervals, and at least annually. A summary of findings and any recommendations will be produced following each meeting. This summary will be submitted to the TMG and TSC, and if required, the main REC.

The IDMC will reserve the right to release any data on outcomes 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.

The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSU.

12. RESEARCH GOVERNANCE

12.1. Sponsor Responsibilities

The Sponsor of this clinical trial is the Institute of Cancer Research (ICR).

12.2. Participating Site Responsibilities

Responsibilities delegated to participating sites are defined in an agreement between the Sponsor and the individual site. The Principal Investigator is responsible for the trial team and trial conduct at the participating site.

13. TRIAL ADMINISTRATION & LOGISTICS

13.1. Site Activation

Before activating the trial, participating sites are required to sign an agreement accepting responsibility for all trial activity which takes place within their site.

Sites may commence recruitment once the site agreement has been signed by all required signatories, the required trial documentation is in place (as specified by ICR-CTSU) and a site initiation (visit or teleconference) has taken place. Site initiation visits will be conducted at sites where the Principal Investigator has requested one or where ICR-CTSU deems it is appropriate.

13.2. Investigator Training

Each centre should complete the comprehensive pre-trial section of the radiotherapy quality assurance programme prior to commencing recruitment, as detailed in the FAST-Forward Boost Radiotherapy Planning and Delivery guidelines ("Radiotherapy Quality Assurance (RTTQA) Pack"). In addition to this, again prior to commencing recruitment, centres will need to complete QA training in contouring and planning according to the schedule described in the RTTQA pack.

13.3. Data Acquisition

Electronic (e) Case Report Forms (CRF) will be used for the collection of trial data. ICR-CTSU will provide specific guidance to sites via trial guidance notes on how data will be collected including details on how to complete the eCRFs. The Trial Management Group reserves the right to amend or add to the eCRF template as appropriate. Such changes do not constitute a protocol amendment, and revised or additional forms should be used by sites in accordance with the guidelines provided by ICR-CTSU. Clinical data should be reported on the FAST-Forward Boost eCRFs to ICR-CTSU in a timely manner. On receipt at ICR-CTSU, CRFs will be recorded as received and any missing data will be reported to the originating site.

Patient Reported Outcomes will be collected using paper questionnaires, or electronic data collection systems if and when available, following current Standard Operating Procedures within ICR-CTSU. However, it may be possible to utilise electronic data collection systems in future when available. An embedded Study Within a Trial will explore options for collecting acute toxicity assessments from patients.

Radiotherapy treatment DICOM data will also be collected. Guidelines on DICOM data submission will be given in the FAST-Forward Boost RTTQA pack.

13.4. Central Data Monitoring

Once data has been entered on the eCRF by the site personnel, ICR-CTSU will review it for compliance with the protocol, and for inconsistent or missing data. Should any missing data or data anomalies be found, queries will be raised for resolution by the site. Any systematic inconsistencies identified through central data monitoring may trigger an on-site monitoring visit.

Any major deviations from the trial protocol, whether identified by the site team or via monitoring activities, will be documented on the eCRFs. Deviations will be reviewed by the Trial Management Group periodically, as part of trial oversight.

The statistical analysis plan will detail how protocol deviations will be managed in the analyses.

13.5. On-Site and Remote Monitoring

On-site monitoring visits or remote monitoring sessions may be conducted by ICR-CTSU for UK (or by each national coordinating group for other participating countries) to review essential documentation and carry out source data verification to confirm compliance with the protocol, in accordance with the study monitoring plan. If an on-site monitoring visit/remote monitoring session is required, ICR-CTSU (or the relevant national coordinating group) will contact the site to make the necessary arrangements. Once a date has been confirmed, the site should ensure that full patient notes of participants, including electronic notes, selected for source data verification are available for monitoring. If any problems are detected during the schedule of monitoring activities, ICR-CTSU (or the relevant national coordinating group) will work with the Principal Investigator or delegated individual to resolve issues and determine appropriate action.

The investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

13.6. Completion of the Study and Definition of Study End Date

The study end date is deemed to be the date of last data capture.

13.7. Archiving

Essential trial documents should be retained according to local policy and for a sufficient period for possible inspection by the regulatory authorities (at least 5 years after the date of last data capture). Documents should be securely stored, and access restricted to authorised personnel.

14. PATIENT PROTECTION AND ETHICAL CONSIDERATIONS

14.1. Risk Assessment and Approval

This trial has been formally assessed for risk and approved by the Sponsor's Committee for Clinical Research.

14.2. Public and Patient Involvement

As described in section 3, the FAST-Forward Boost Trial has been co-designed with patient advocates from the outset with ongoing involvement of PPI colleagues in the development of the trial written materials including the protocol, patient information sheet and consent form. PPI will continue to be central to the delivery of the trial via representation on the TMG.

14.3. Ethics Approvals

The trial will not commence at any participating site until the required approvals are in place. In the UK, ICR-CTSU, on behalf of the Sponsor, will ensure that the trial has received ethics approval from a research ethics committee (REC) for multi-centre trials, HRA approval and relevant NHS Permissions. Before recruiting patients, the Principal Investigator at each site is responsible for obtaining local approvals.

Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the trial with the exception of urgent safety measures.

All sponsor correspondence with the REC will be retained in the Trial Master File. The Chief Investigator will notify the REC of the end of the trial.

If the trial is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination. Within one year after the end of the trial, the Chief Investigator will submit a final report to the REC.

For non-UK sites it will be the responsibility of each national coordinating group to ensure that appropriate approvals are in place as per local requirements.

14.4. Trial Conduct

This trial will be conducted according to the approved protocol and its amendments, supplementary guidance and manuals supplied by the Sponsor and in accordance with the UK Policy Framework for Health and Social Care and the principles of GCP.

14.5. Informed Consent

The Principal Investigator retains overall responsibility for the conduct of research at their site; this includes the taking of informed consent of participants. They must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to do so in accordance with the ethically approved protocol, principles of Good Clinical Practice and Declaration of Helsinki.

Patients should be asked to sign the current ethics approved FAST-Forward Boost consent form at trial entry after receiving both verbal and written information about the trial, having been given sufficient time (usually

at least 24 hours but at least overnight) to consider this information. All consent forms must be countersigned by the Principal Investigator or a designated individual. GCP-compliant electronic consent forms may be used where available. A signature log of delegated responsibilities, listing the designated individuals and the circumstances under which they may countersign consent forms, must be maintained at the participating site. This log, together with original copies of all signed patient consent forms, should be retained in the Site Investigator File and must be available for inspection. The current ethics approved FAST-Forward Boost patient information sheets should be provided in addition to any standard patient information sheets that are provided by the site and used in routine practice.

14.6. Patient Confidentiality

UK patients will be asked to consent to their full name being collected at trial entry in addition to their date of birth, hospital number, email address, address and postcode, and NHS number or equivalent to allow linkage with routinely collected NHS data, ensure accuracy in handling biological samples, and facilitate questionnaire collection. Where permitted, international participants will be asked to consent to their initials and partial date of birth being collected at trial entry to ensure accuracy of data collection.

Each investigator should keep a separate log of all participants' Trial IDs, names, addresses and hospital numbers. The investigator must retain trial documents (e.g. participants' written consent forms) in strict confidence. The investigator must ensure the participants' confidentiality is always maintained.

Representatives of ICR-CTSU (or national coordinating group) will require access to participants' hospital notes for quality assurance purposes. ICR-CTSU will always maintain the confidentiality of participants and will not reproduce or disclose any information by which participants could be identified.

14.7. Data Protection

All investigators and trials staff must comply with applicable data protection laws at all times including Data Protection 2018.

14.8. Liability

Indemnity to meet the potential legal liability of investigators participating in this trial is provided in the UK by the usual NHS indemnity arrangements.

For non-UK sites, the national coordinating group will ensure appropriate arrangements are in place.

15. FINANCIAL MATTERS

This trial is investigator designed and led, has been endorsed by the Joint Royal Marsden & Institute of Cancer Research Committee for Clinical Research (CCR). ICR has received funding from National Institute of Health Research (NIHR) for the central coordination of the trial. The trial 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 is part of the National Institute for Health Research Clinical Research Network (NIHR CRN) portfolio by virtue of its funding by the NIHR. NIHR CRN resources should therefore be made available for the trial to cover UK specific research costs.

16. PUBLICATION POLICY

The main trial results will be published in a peer-reviewed journal, on behalf of all collaborators. The manuscript will be prepared by a writing group, consisting of members of the TMG. Participating clinicians

may be selected to join the writing group on the basis of intellectual and time input. All participating clinicians will be acknowledged in the publication.
Any presentations and publications relating to the trial must be authorised by the TMG. Authorship of any secondary publications e.g. those relating to sub-studies, will reflect intellectual and time input into these studies. Authorship of all publication will usually be in accordance with ICMJE guidance.

No investigator may present or attempt to publish data relating to the FAST-Forward Boost trial without prior permission from the TMG.

It is an expectation that all publications relating to the trial are published as "open-access". Trial updates and reports on published results will also be on the FAST-Forward Boost trial website for participants and everyone to access.

17. TRIAL IMPACT AND ASSOCIATED STUDIES

17.1. Importance to the environment:

The NHS Green Plan highlights the importance of reducing the impact of the NHS on the climate[41]. In radiotherapy, reducing the number of treatments substantially reduces carbon emissions. Indeed 1-week radiotherapy is likely to halve carbon emissions compared with 3-week radiotherapy[41-43]. Via an NIHR-funded project, ICR-CTSU has developed a method to quantify clinical trials' carbon footprint which, whilst still in validation phase, has been used to estimate the impact of FAST-Forward Boost(44). Per patient emissions attributed to 15Fr radiotherapy are 94kgCO2e (7kgCO2e from radiotherapy delivery and 87kgCO2e from patient travel associated with 15 hospital visits)(43). In comparison, 5Fr radiotherapy produces 32kgCO2e (3kgCO2e from radiotherapy and 29kgCO2e from travel). 1-week radiotherapy therefore saves 62kgCO2e/patient equating to a total saving of 198,000kgCO2e resulting from patient participation in FAST-Forward Boost. Recent work highlights the importance of both undertaking trials to provide the evidence base for shorter treatment durations and prospectively collecting data including travel distances to measure the true impact of shorter radiotherapy schedules (45). In light of this work, an **embedded "Study within a Trial" (SWAT) on carbon footprint** will gain insight into the views of patients and healthcare professionals on adaptations made to reduce a trial's carbon footprint and improve its environmental impact. This SWAT will be covered in a separate protocol.

17.2. Global impact:

In low/middle income countries (LMICs) with less radiotherapy resource, longer radiotherapy schedules may be unavailable or unfeasible leading to decisions not to treat and, thereby, increasing breast cancer mortality. Many patients in LMICs are diagnosed with more advanced disease requiring boost and/or IMC radiotherapy. Demonstrating efficacy and safety of 1-week SIB radiotherapy would support the NIHR Global Health strategic priority to develop health systems that respond to population needs and local context. In higher income countries, long travel distances to radiotherapy can precipitate patients choosing mastectomy over breast conservation(9). 1-week SIB radiotherapy would be welcomed in such geographies both in the UK and internationally.

17.3. Relevance of trial findings in the longer term:

Breast cancer remains the commonest worldwide cancer and radiotherapy will remain central to curative breast cancer treatment. There are likely to be around 70,000 new cases in the UK alone per year by 2038-40(46) and the proportion requiring radiotherapy boost is likely to remain similar such that the findings of this

trial will be of relevance to up to 13,000 patients per year by the time they are published. Therefore, benefits to patients, the NHS, global radiotherapy provision and the environment from shorter schedules will be durable.

17.4. Reducing inequities in care:

FAST-Forward Boost will provide evidence to underpin use of 1-week radiotherapy in all patients with breast cancer who need radiotherapy reducing disparities in radiotherapy provision whilst maintaining a tailored, risk-adapted approach for those who need it. Some families with lower incomes are put in the very real difficult position of having to choose between attending daily cancer treatments and losing financially from income and childcare costs; a 1-week schedule of radiotherapy will help to reduce this burden. FAST-Forward Boost sub-studies will further explore reducing inequities along two themes:

17.4.1. Increasing the diversity of recruitment to clinical trials:

The NHS Long Term Plan for earlier diagnosis and longer survival from cancer explicitly states that these should be delivered in a way that reduces inequities in care(47). People from deprived backgrounds report poorer experiences and inequities in treatment options leading to worse outcomes(48, 49), including lower recruitment into research trials(50). Recruitment data from FAST-Forward and IMPORT-HIGH trials demonstrate the broad geographical spread of participants across the UK. Ninety-five percent of IMPORT HIGH and 97% of FAST-Forward participants were of white ethnicity and 20% percent of those living in England lived in the most economically deprived postcodes (lowest 3 deciles of the Index of Multiple Deprivation (IMD)). These figures fall short of the proportions expected given the characteristics of the eligible population and should therefore be increased(51, 52). Complementing other national projects on diversity in trial recruitment, we will achieve this in FAST-Forward Boost by working with collaborators to provide training for healthcare professionals in facilitating recruitment from underserved populations. We will learn from demographic data collected during the pilot phase from as broad a group as possible who are eligible for the trial with a view to undertaking targeted in-depth qualitative work to identify and address site and patient level barriers and facilitators to recruitment.

Region		FAST-Forward recruitment %	IMPORT HIGH recruitment %
England	North East	3	10
	North West	5	11
	Midlands	24	9
	London	7	12
	East	12	25
	South West	20	17
	South East	17	14
Scotland		4	2
Wales		7	<1
Northern Ireland		<1	0
Total		100	100

IMD decile	FAST-Forward %	IMPORT HIGH %
1	4	5
2	7	6
3	8	7
4	11	9
5	12	11
6	12	12
7	13	13
8	11	11
9	11	14
10	11	12
Total	100	100

A formal FAST-Forward Boost recruitment sub-study will evaluate barriers and facilitators to participation in the trial among under-served populations using an exploratory qualitative research design. This sub-study will be covered in a separate protocol (UK only).

Throughout this protocol and the forthcoming sub-study, the term “underserved populations” will be used and is the term agreed by the NIHR-INCLUDE(53) project patient and public stakeholder consensus workshop. While they acknowledge there is no single definition, they identify the following characteristics that are common to several underserved groups:

1. Lower inclusion in research than one would expect from population estimates.
2. High healthcare burden that is not matched by the volume of research designed for the group.
3. Important differences in how a group responds to or engages with healthcare interventions compared to other groups, with research neglecting to address these factors.

As these characteristics depend on the context, the population, disease under study and the questions being asked, they will be used as a guide when considering the underserved nature of the population within the FAST-Forward Boost Trial. In this trial the focus is people with a diagnosis of breast cancer receiving radiotherapy in designated radiotherapy units across different geographical places in England as part of their treatment plan. It is therefore anticipated that a range of demographic (age, sex, gender, ethnicity, education), social and economic, and health status factors will contribute to the characteristics of an underserved population in this study.

Purposive sampling will be used to invite up to 100 patients (UK only) to participate in interviews (including those who decline and accept randomisation). The work will provide insights into the experiences, interactions, and contexts of participants from under-served groups entering or declining participation in the trial which will facilitate implementation of targeted measures (e.g. additional resource or staff training). This study will be covered by a separate protocol.

17.4.2. Gaining a better understanding of acute toxicity across different skin tones:

Radiotherapy skin reactions cause discomfort and fatigue and, where inadequately described or managed, can significantly impact on patients' daily lives as well as delaying return to normal activities. The characterisation, information-giving and management of radiation-induced skin reactions across different skin tones is poorly described in the literature and in clinical practice, not least because clinical trials of breast radiotherapy have historically included high proportions of patients with white skin tones. Additionally, tools for assessing radiation-induced skin reactions in clinical trials use terminology that is more applicable to white skin than to brown or black skin tones (e.g. degree of redness). Increasing the diversity of the recruited population in FAST-Forward Boost provides a unique opportunity to improve the characterisation, recording and management of radiation-induced skin toxicity across different skin tones[52, 54, 55].

The "Characterising Acute Toxicity across Skin tones" (CATS) SWAT will be described in a separate protocol depending on the findings of the ESSS (UK only).

18. TRANSLATIONAL STUDIES

18.1. Early side effects translational sub-study

Patients included in the early side effects sub-study will be asked if they are willing to donate blood samples for the following associated translational study. Participation will be optional and subject to patients' written informed consent.

Rationale: Radiotherapy can have immunomodulatory effects on tumour and surrounding normal tissues(56). Studies have shown that, in normal tissues exposed to radiotherapy, acute immune cell changes and release of pro-inflammatory cytokines can ultimately lead to chronic inflammation and radiotherapy-induced toxicity (e.g. pneumonitis and fatigue), which limits quality of life(56).

Radiation-induced lymphopenia (RIL) has been described in several solid tumours, with severe lymphopenia linked to poorer prognosis(57, 58). A study comparing 50Gy/25#/5 weeks versus 43.5Gy/15#/3 weeks of radiotherapy in breast cancer patients found that the risk of RIL was lower with the 3-week regimen in which total dose is lower(59). In addition, a lower ratio of nadir peripheral lymphocyte count during radiation to peripheral lymphocyte count before radiation predicted poorer prognosis in patients with breast cancer(59). Field size and irradiated volume are also known to influence radiation-induced immune effects(57, 60).

The FAST-Forward Boost early side effects study provides a unique opportunity to study the systemic immune consequences of different radiotherapy fractionation regimens and treatment volumes and to explore the association with radiotherapy-induced side effects.

Objectives: The primary objective is to assess differences in radiation-induced immune-inflammatory changes in blood for patients in the Control Group (3-week schedule) compared with Test Groups (1-week schedule). Secondary objectives will explore differences in these changes according to treated volume, and consider associations with the incidence and severity of acute toxicity endpoints.

Endpoints: The primary endpoint is the incidence of CTCAE grade ≥2 lymphopenia (based on central assessment of blood samples at both follow-up time points during the sub-study). Secondary endpoints include: ratio of nadir lymphocyte count to pre-treatment lymphocyte count, and clinician-reported and patient-reported acute toxicity endpoints (e.g. pneumonitis, skin toxicity, fatigue) as assessed in the trial.

Design and sample analysis: Blood will be collected at 3 time points, aligned with clinician assessment of acute toxicity in the early side effects sub-study: baseline (prior to start of radiotherapy); on the final day of radiotherapy; and 2 weeks following completion of radiotherapy. 2X10ml EDTA tubes will be collected at each timepoint for immediate processing into component parts. Whole blood flow cytometry analysis will be conducted using bespoke panel/s to capture the wider immune cell repertoire. An initial pilot assessment in 40-50 patients (120-150 samples) will assess technical feasibility of the approach.

Statistical considerations: With the 3-week (Control) radiotherapy schedule, 25% of patients are expected to have grade ≥2 lymphopenia(59). We hypothesize that this will be approximately halved with the 1-week schedule (to 12%, a 13% reduction). In order to have 80% power to detect this difference with a one-sided alpha=0.05 requires 240 patients (80 Control Group, 160 Test Groups). Since participants in this translational sub-study will also need to be participating in the early side effects sub-study, recruitment to these studies will run in parallel and the final sample size for the translational work will be determined by the recruitment period remaining for the early side effects sub-study at the time of implementation. The power calculation is indicative of what we might expect to achieve but it is acknowledged that a smaller sample size is possible. Furthermore, smaller difference between groups could be important and may not be detectable within this study. As such, the analysis is seen as exploratory and will inform future work in this area.

Incidence of grade ≥2 lymphopenia (based on highest grade observed during/post-treatment) will be compared between the Control and Test Groups using a chi-squared test. The ratio of nadir lymphocyte count to pre-treatment lymphocyte count will be compared using t-test or non-parametric equivalent. The two Test Groups will be combined since no difference is expected. Other analyses will be largely descriptive. Incidence of lymphopenia and ratio of nadir to pre-treatment lymphocyte count will be considered according to treatment volume, and will also be cross-tabulated with acute toxicity endpoints.

Data from the pilot assessment will be reviewed by the IDMC as part of their routine trial monitoring. Final statistical analysis will be conducted when all sample collection and analysis is complete. Full details of statistical analysis will be specified in a Statistical Analysis Plan.

18.2. Sample collection for further translational studies

All trial participants will be asked if they are willing to donate a baseline blood sample to be collected and stored for use in further translational sub-studies within the FAST-Forward Boost trial. The objectives of these studies will be defined separately. Participation in this aspect of the trial will be optional and subject to patients' written informed consent. For patients who are also participating in the early side effects translational sub-study, the baseline blood sample will count as the first of the three blood samples described in section 18.1 above.

The blood samples will be sent by the site to the ICR laboratory, where they will be stored until the end of the trial. Consent will also be sought to allow these samples to be used for future research projects, subject to ethical approval.

Subject to patients' written informed consent, archival tissue samples (FFPE blocks) of primary tumour at the time of diagnosis or any other applicable surgical procedures (including subsequent disease relapses or new primary cancers) and associated information, including imaging scans obtained as part of standard care, may be requested for translational sub-studies as part of FAST-Forward Boost, which will be defined separately. Consent will also be sought to allow these samples to be used for future research projects, ethics approval permitting.

Subject to patients' written informed consent, other samples taken as part of previous or future routine care (such as but not limited to blood, scans, urine) may be requested for translational studies as part of FAST-Forward Boost which will be defined separately. Consent will also be sought to allow these samples to be used for future research projects, ethics approval permitting.

All tissue/other samples will remain at site of collection until relevant translational projects are approved and funded. The TMG will review and approve any sample data access request.

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A1. GLOSSARY

AE	Adverse Event
BIS	Body Image Scale
CCR	Committee for Clinical Research
CI	Chief Investigator
CIS	Carcinoma In Situ
CRF	Case Report Form
DCF	Data Capture Form
DCIS	Ductal Carcinoma in Situ
DFS	Disease Free Survival
eCRF	electronic Case Report Form
EORTC	European Organisation for Research and Treatment of Cancer
Gy	Gray, unit of radiation dose
HADS	Hospital Anxiety Depression Scale
HE	Health Economics
HR	Hazard Ratio
ICR	The Institute of Cancer Research
ICR-CTSU	The Institute of Cancer Research Clinical Trials Statistics Unit
IMC	Internal mammary chain
IDMC	Independent Data Monitoring Committee
ISRCTN	International Standard Randomised Controlled Trial Number
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHS	National Health Service
NIHR-HTA	National Institute for Health and Care Research Health Technology Assessment
PI	Principal Investigator
PIS	Patient Information Sheet
PPI	Patient and Public Involvement
PRO	Patient Reported Outcomes
QoL	Quality of Life
R&D	Research and Development
RCT	Randomised controlled Trial
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
RTTQA	National Radiotherapy Trials Quality Assurance
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SIB	Simultaneous Integrated Boost
SUSAR	Suspected Unexpected Serious Adverse Reaction
SWAT	Study within a Trial
TMG	Trial Management Group
TSC	Trial Steering Committee

A2. PATIENT REPORTED OUTCOMES

Rationale for PRO measurement

Patient reported outcomes (PROs) have become an important measure in breast cancer research. This is an umbrella term coined for any subjective report from the patients on outcomes such as quality of life, functional well-being and satisfaction of treatment received. There is evidence that radiotherapy causes long-term effects on quality of life in terms of altered breast appearance, breast, arm, and shoulder symptoms, as well as a possible impact on some general aspects of health, such as fatigue. In evaluating radiotherapy interventions, it is important that these effects are understood from the patients' perspective. All participants must be asked to consent to complete PRO assessments, but this will be non-mandatory for participants in the main study.

FAST-Forward Boost aims to evaluate acute and late effects of 1-week SIB radiotherapy compared with the standard 3-week SIB. PRO evaluations in FAST-Forward Boost are based on standard instruments used in previous studies in this setting that will provide interpretable data and allow comparison with other relevant trials. The scales selected include specific measures for evaluating breast cancer therapies, body image, post-radiotherapy symptoms, fatigue and psychological distress together with a general cancer health-related quality of life scale and a generic quality of life scale widely used in health economic evaluations. These measures have been used in the START, IMPORT, FAST-Forward and PARABLE breast radiotherapy trials. Assessments will be carried out over at least 5 years of follow-up. Timings of assessments are in line or similar to those used in these previous breast radiotherapy trials.

Measures used for all participants

- EORTC QLQ-C30 is a 30-item cancer quality of life-specific instrument, which comprises 5 functional sub-scales, 2 symptom subscales and additional symptom items and questions about global health and global quality of life.(61)

- EORTC QLQ-BR23 breast cancer module is a 23-item scale designed for use in breast cancer patients. It incorporates five multi-item scales to assess systemic therapy side effects, breast symptoms, arm symptoms, body image and sexual functioning. In addition, single items assess sexual enjoyment, hair loss and future perspective.(62)

- 10-item Body Image Scale (BIS) (of which 4 items are already incorporated in the BR23) was designed for use with cancer patients and has been widely used in national breast cancer treatment trials. (63)

- EORTC QLQ FA12 is a 12-item scale on fatigue which will be used in this trial to provide detailed data to assess the short- and longer-term impact of radiotherapy.(64)

- Protocol-specific items to assess radiotherapy symptoms as used in previous breast radiotherapy trials: 13 items specific to post-radiotherapy breast symptoms and shoulder/arm functioning. These include change in skin appearance, change in overall appearance of the breast, breast shrinkage and hardening, position of the nipple, difficulty getting a bra to fit, shoulder stiffness, experience of pins and needles in arm, numbness on fingers, weakness on arms or hands.

Please refer to appendix A3 for details of additional questionnaires that will be used to inform health economics analysis.

Measures used in the early side effects sub-study

In addition, the first 115 patients recruited into each arm of the trial will take part in the early side-effects sub-study and will complete the following questionnaires:

- PRO-CTCAE v5.0 items relating to acute toxicities in skin, breast, and oesophagus
- Trial specific questions: 4-items specific to any acute symptoms in the treated breast: skin reddening, skin blistering, breast swelling and breast pain or tenderness during and immediately after radiotherapy.
- Hospital Anxiety and Depression Scale (HADS)(65) will measure psychological distress. HADS has been widely used in clinical trials to date and provides clinically interpretable outcomes. This is not a trial endpoint itself but will be assessed pre-treatment and used to support interpretation of the other patient-reported outcome data.

PRO-CTCAE and trial specific questions on acute symptom data will be collected pre-treatment and at weeks 1-7 and 12 from the start of radiotherapy. Patients in the sub-study will also complete the QLQ FA12 at an additional time point.

There are separate versions of the paper PRO booklets until the 3 month timepoint, ones which contain the early side-effects sub-study additional questionnaires and those that do not.

Electronic PRO booklets will be automatically sent to the patient at the relevant timepoints.

A3. HEALTH ECONOMICS

Rationale for HE measurement

The primary outcome measure for the health economic (HE) evaluation will be the cost per quality-adjusted life year (QALY) gained. This will be estimated from health resource usage and duration of time spent in different health states, with health status measured by EQ-5D-5L. The objective of the health economic evaluation is to establish whether a 5-fraction radiotherapy boost to the breast (test groups 1 and 2) is cost effective relative to current UK practice (15-fraction radiotherapy boost, control) and in comparison, to other NHS activity. The analysis will also have broader implications for cost-effectiveness of the approach when delivered in other countries.

The health economic analysis will make use of a generic, preference-based measure of HRQoL (health-related quality of life). The objective is to have an index measure of HRQoL where quality of life and absence of morbidity are valued on the same scale as quantity or length of life. This enables the calculation of quality adjusted survival where duration of time spent experiencing certain health states (e.g. receiving radiotherapy, experiencing a local recurrence) is weighted according to the HRQoL value associated with that health state.(66, 67)

Health care resource use data (UK only)

The aim of this part of the HE evaluation is to compare the treatment groups in terms of Health care resource use. This primarily relates to the cost of resources used to provide each radiotherapy regimen and the cost of treating adverse events (short and long term) and further breast cancer events. For example, the trial will collect any information on hospitalisations associated with adverse events and/or further breast cancer events. Questions relating to resource use, such as the use of specialist nurses, GP visits, and outpatient visits for treating adverse events from treatment will be incorporated in the PRO questionnaires, as was done successfully in the FAST-Forward and IMPORT LOW trials. Information on the resource use associated with recurrent breast cancer events will be obtained from literature review and published NHS costs.

Quality of life measure

The **EQ-5D-5L** is a standardised instrument designed for self-completion in an adult population.(68) questionnaire asks patients to describe their current health status by specifying one of five levels of severity (no problems, slight problems, moderate problems, severe problems and unable to/extreme problems) across five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). We will follow National Institute for Health and Clinical Excellence(NICE) recommendations to estimate QALYs from EQ-5D-5L so that our results are comparable with other appraisals undertaken to inform NHS treatment decisions.(69, 70)

The resultant quality of life scores will be compared across time and between 5-fraction radiotherapy boost (test groups 1 and 2) and 15-fraction radiotherapy boost (control). This analysis will inform the health economic analysis in calculating quality adjusted survival for patients receiving each regimen. To extrapolate beyond the trial these data will be supplemented by a literature search of previous studies of the health-related quality of life impact of treatment and events in patients with breast cancer.

The EQ-5D-5L will enable the calculation of quality adjusted life years that would be consistent and comparable with those routinely used in the economic evaluation of health care technologies by the NICE in the UK.(71)

Out of pocket costs (UK only)

Radiotherapy treatment can have important impacts on personal income through lost earnings and costs associated with travelling to receive therapy. These will be captured using a questionnaire administered during periods patients are on treatment. This information will be used to supplement the analysis based from the NHS and personal social services (PSS) perspective.

Timing of assessments

Where participants have consented to PRO participation, EQ-5D-5L will be collected at: pre-treatment, week 1, week 2, week 3, month 3, year 1, year 3 and year 5 from treatment start date. The “Health care resource use questionnaire” (UK only) will be collected at: month 3, year 1, year 3 and year 5 post treatment start date. The “out of pocket costs” questionnaire (UK only) will be collected during the on treatment period i.e. week 1, week 2 and week 3.

Methods

A decision analytic model describing a series of health states and health events experienced by patients with early breast cancer will be developed.(72). This will be based on the model developed to undertake cost-effectiveness analysis of radiotherapy regimens studied in the FAST-Forward and IMPORT LOW trials .(37) This model will be used to synthesise information from the trial and other published studies in order to estimate costs and quality adjusted survival over an appropriate time horizon from the perspective of the UK NHS and PSS. Uncertainty around the values used in the decision analytic model will be characterised using probabilistic sensitivity analysis. The trial regimens will be evaluated using standard cost-effectiveness analysis. Data from the two test groups will be combined and compared with the control group consistent with previous HE analyses in FAST-Forward. If one strategy is not found to be dominant (i.e. less costly and more effective) in comparison to the other, then an incremental cost-effectiveness ratio (ICER) will be determined. (73) The ICER will be based on the mean costs and mean QALYs estimated within the probabilistic sensitivity analysis of the decision model. Uncertainty around cost-effectiveness will be described using cost-effectiveness acceptability curves which describe the probability that an intervention is cost-effective.