SIF section

1.2

Post-operative avoidance of radiotherapy: biomarker selection of women categorised to be in a very low risk group by IHC4+C

PROTOCOL

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The PRIMETIME study has been approved
by Cancer Research UK's Population Research Committee (PRC)
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The Trial Management Group (TMG) will be constituted from members of the Protocol Development Group and will include the Chief Investigator, ICR-CTSU Scientific Lead, Co-investigators and identified collaborators, the Trial Statistician and 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 a lay/consumer representative. A copy of the current membership of the TMG can be obtained from the PRIMETIME Trial Manager at ICR-CTSU.

Protocol Authorised by:

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This protocol describes the PRIMETIME study and provides information about procedures for entering participants into this study. The protocol should not be used as a guide for the treatment of patients outside of this study.

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.

CONTENTS

1.1. Background 1
1.2. Description of Population 5
1.3. Study Rationale 5

2. STUDY OBJECTIVES 5

2.1. Primary Objective 5
2.2. Secondary Objectives 6
2.3. Exploratory Objectives 6

3. STUDY DESIGN 6
4. STUDY ENDPOINTS 7

4.1. Primary Endpoint 7
4.2. Secondary Endpoints 7
4.3. Exploratory Endpoints 8

5. PATIENT SELECTION 8

5.1. Number of Participants 8
5.2. Source of Participants 8

6. PRE-SCREENING – Ki67 RESEARCH TESTING 8

6.1. Procedure for Obtaining Informed Consent for pre-screening 9
6.2. Pre-screening procedures 9
6.3. Pre-Screening Log 10
6.4. Follow-up of Patients Pre-screened 10

7. SCREENING FOR PRIMETIME STUDY 10

7.1. Eligibility criteria 10

7.1.1. Inclusion Criteria 10
7.1.2. Exclusion Criteria 11

7.2. Procedure for Obtaining Informed Consent 12
7.3. Participation in other Clinical Studies 12

8. STUDY ASSESSMENTS 12

8.1. Screening 12
8.2. Registration 14
8.3. Baseline 15
8.4. IHC4+C directed treatment 15
8.5. Follow-up 15

8.5.1. Patients who do not receive radiotherapy 15
8.5.2. Patients who receive radiotherapy 16
8.5.3. Follow up from routine data sources 16

8.6. Procedure at disease recurrence/relapse or diagnosis of new primary cancer 16
8.7. Discontinuation from Follow-up 16
8.8. Schedule of Events/Assessments 18

9. RADIOTHERAPY 20

9.1. Radiotherapy Treatment Timelines 20
9.2. Radiotherapy Planning and Delivery 20
9.3. Supportive Care Guidelines 20

9.4 Radiotherapy Quality Assurance (QA) 20

10. CONCOMITANT ANTI-CANCER THERAPY 21
11. SAFETY REPORTING 21

11.1. Definitions 21
11.2. Reporting of Serious Adverse Events to ICR-CTSU 22
11.3. Review of Serious Adverse Events 23
11.4. Expedited Reporting of Related Unexpected SAEs 23
11.5. Follow up of Serious Adverse Events 23
11.6. Annual Safety Reporting 23

12. STATISTICAL CONSIDERATIONS 25

12.1. Statistical Design and Sample Size Justification 25
12.2. Treatment Allocation 25
12.3. Endpoint Definitions 25

12.3.1. Primary endpoint 25
12.3.2. Secondary endpoints 25
12.3.3. Exploratory endpoints 26

12.4. Statistical Analysis Plan 26
12.5. Interim Analyses and Stopping Rules 26
12.6. Planned meta-analysis 27

13. TRIAL MANAGEMENT 27

13.1. Trial Management Group (TMG) 27
13.2. Trial Steering Committee (TSC) 27
13.3. Independent Data Monitoring Committee (IDMC) 27

14. RESEARCH GOVERNANCE 28

14.1. Sponsor Responsibilities 28
14.2. Chief Investigator's Responsibilities 28
14.3. Participating Site Responsibilities 28

15. STUDY ADMINISTRATION & LOGISTICS 28

15.1. Site activation 28
15.2. Data Acquisition 28
15.3. Central Data Monitoring 29
15.4. On-Site Monitoring 29
15.5. Completion of the Study and Definition of Study End Date 29
15.6. Archiving 29

16. PATIENT PROTECTION AND ETHICAL CONSIDERATIONS 29

16.1. Study Approvals 29
16.2. Study Conduct 29
16.3. Informed Consent 30
16.4. Patient Confidentiality 30
16.5. Data Protection 30
16.6. Liability 30

17. FINANCIAL MATTERS 31
18. PUBLICATION POLICY 31
19. ASSOCIATED STUDIES 31

19.1. Translational study 31

19.2. Information Giving Study....31

20. REFERENCES.... 33
A1. GLOSSARY.... 35
A2. QUALITY ASSURANCE PROGRAMME.... 36
A3. Why is this the preferred design of PRIMETIME?.... 38
A4. IHC4+C CALCULATOR – EXAMPLE.... 40
A5. PRIMETIME Information Giving Study (IGS) Protocol.... 41

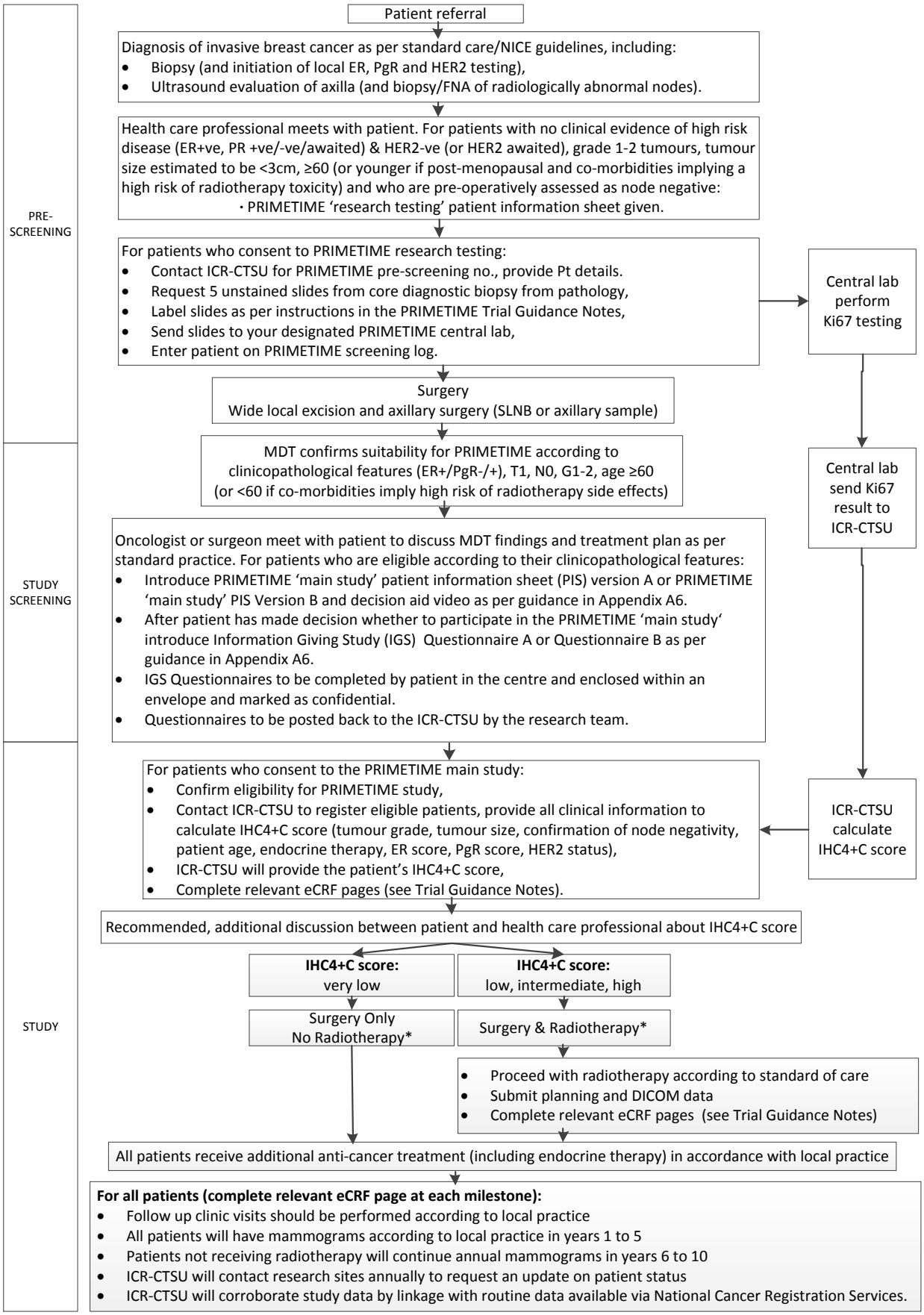
PRIMETIME STUDY SUMMARY

PROTOCOL TITLE	PRIMETIME - Post-operative avoidance of radiotherapy: biomarker selection of women categorised to be in a very low risk group by IHC4+C.
TARGET DISEASE	Breast cancer
STUDY OBJECTIVES	• To assess the risk of any ipsilateral invasive and DCIS breast disease by 5 years following omission of postoperative breast radiotherapy (given according to local practice) • To use immunohistochemical biomarkers with clinical information (IHC4+C) to direct selective avoidance of breast radiotherapy • To assess the long term disease outcomes following omission of postoperative breast radiotherapy, including: o the risk of any ipsilateral invasive and DCIS breast disease by 10 years following omission of postoperative breast radiotherapy o the risk of regional and distant relapse by 5 and 10 years following omission of postoperative breast radiotherapy o The risk of any ipsilateral breast disease (including non-invasive (DCIS) and invasive ipsilateral disease) by 5 and 10 years following omission of postoperative breast radiotherapy. o The risk of contralateral breast second primary cancer by 5 and 10 years following omission of postoperative breast radiotherapy o The risk of any contralateral breast disease (including non-invasive (DCIS) and invasive disease) by 5 and 10 years following omission of postoperative breast radiotherapy. o The risk of ipsilateral invasive breast local relapse by 5 and 10 years following omission of postoperative breast radiotherapy (subject to availability of tumour profiling data) o The risk of ipsilateral invasive breast second primary cancer by 5 and 10 years following omission of postoperative breast radiotherapy (subject to availability of tumour profiling data) o overall invasive disease free survival following omission of postoperative breast radiotherapy o breast cancer specific survival following omission of postoperative breast radiotherapy o overall survival following omission of postoperative breast radiotherapy

	• To confirm viability of collecting cancer outcomes via record linkage with data collected routinely through the NCRAS's Cancer Analysis System and other informative UK cancer registries. • To assess disease-related outcomes using routinely collected data for both patients who enter the main trial and patients who enter pre-screening for Ki67 in the trial but who subsequently do not enter the main trial.
STUDY DESIGN	PRIMETIME is a prospective study of biomarker directed treatment.
STUDY POPULATION	Women treated by breast conserving surgery and prescribed endocrine therapy for whom the residual risk of ipsilateral breast disease is predicted to be <1% per year.
RECRUITMENT TARGET	Approximately 2400 patients registered to recruit 1550 patients in the no radiotherapy cohort.
STUDY TREATMENT	The IHC4+C algorithm will be used to risk stratify patients into a very low risk group (recommended avoidance of radiotherapy) or not (standard radiotherapy).
PRIMARY ENDPOINT	Any ipsilateral breast disease rate (non-invasive (DCIS) and invasive breast cancer)
SECONDARY ENDPOINTS	• Regional relapse rate • Distant relapse rate • Ipsilateral invasive breast disease rate • Contralateral breast second primary cancer rate • Any contralateral breast disease rate (non-invasive (DCIS) and invasive breast cancer) • Ipsilateral invasive breast local relapse rate (subject to availability of tumour profiling data) • Ipsilateral invasive breast second primary cancer rate (subject to availability of tumour profiling data) • Overall invasive disease free survival • Breast cancer specific survival • Overall survival
EXPLORATORY ENDPOINTS	• Completeness and accuracy of routinely collected record linked (event) data compared with data collected directly from participating hospitals • Estimation of disease-related endpoints as stated above using routinely collected data for both patients who enter the main trial and separately for patients who enter pre-screening for Ki67 in the trial but who subsequently do not enter the main trial
SUB-STUDY	Translational sub-study Written informed consent will be sought from patients to collect and analyse primary and relapsed tumour samples (and any new primary cancer diagnosed) for use in future translational research studies. Information Giving Study

	The Information Giving Study will identify if the introduction of a patient decision aid video in addition to written patient information reduces decisional conflict (patient uncertainty) regarding whether to participate in the PRIMETIME main study.
FOLLOW UP	<u>Patients who do not receive radiotherapy (Surgery Only):</u> o Patients should have annual mammography for 10 years. o Patients should attend follow up clinics according to local practice o ICR-CTSU will contact research sites annually to request an update on patient status. o Information on disease relapse will be collected at follow up clinics, by telephone call and by annual mammography and recorded in the PRIMETIME eCRF. <u>Patients who receive radiotherapy:</u> o Patients will have annual mammography according to local practice. o Patients will attend follow up clinics according to local practice. o ICR-CTSU will contact research sites annually to request an update on patient status. o Information on disease relapse will be collected at follow up clinics, by telephone call and by annual mammography and recorded in the PRIMETIME eCRF. <u>Routine data linkage:</u> In addition to the above, the study will establish mechanisms for collecting data (including local, distant relapse, new primary cancers, death, cause of death) directly from routinely collected health data. Routine data collection will be compared to the gold-standard centre-based follow-up, including identification of ipsilateral breast local relapse versus new ipsilateral breast second primary cancer. The relevant data sources proposed include the Cancer Services and Outcomes Dataset (COSD), the National Radiotherapy Dataset (RTDS), the Systemic Anti-Cancer Therapy Dataset (SACT), the Hospital Episodes Statistics (HES), the ONS mortality file, the equivalent databases in the devolved nations and any other UK informative registries. Routine data linkage will performed for all patients (pre-screened for Ki67 and registered for the main study i.e. IHC4+C directed treatment)

STUDY SCHEMA



* Patients deviating from biomarker-directed treatment allocation will continue to be followed up. The rate of deviation from allocated treatment, as a result of patient choice, will be monitored by the IDMC.

INTRODUCTION

1.1. Background

Radiotherapy is currently part of standard treatment for the many thousands of UK women with early breast cancer who receive breast conserving surgery. The beneficial and adverse effects of radiotherapy are well documented by the EBCTCG analysis of >10,000 patients randomised into trials of breast conserving surgery ±radiotherapy over 30 years Early Breast Cancer Trialists' Collaborative, Darby [1]. Radiotherapy to the conserved breast has been shown to halve the rate at which any disease recurs and reduce breast cancer death rate by about a sixth. These proportional benefits vary little between different subgroups. By contrast, the absolute benefits from radiotherapy vary substantially according to patient and tumour characteristics and predicted risk of relapse.

Earlier cancer detection and improvements in the quality of surgery and systemic therapy have dramatically improved breast cancer outcomes resulting in much lower local relapse rates than reported in trials on which the EBCTCG meta-analysis was based [2]. The absolute long-term risk of local relapse following breast conserving surgery and radiotherapy is now low enough to consider avoiding radiotherapy for selected patient groups. The PRIME II trial (recruitment 2003-2009) recruited patients aged over 65 with unilateral invasive breast cancer of tumour size ≤3cm and no nodal involvement following breast conserving surgery. Patients had ER or PR positive cancers and were treated with endocrine therapy. PRIME II showed a 5-year local relapse rate of only 1.3% following breast conserving surgery and radiotherapy [3, 4]. If the radiotherapy effects are as predicted from EBCTCG analysis described above, the estimated rate of local relapse in the absence of radiotherapy would still be <3% by 5 years for such patients [5].

Although the technological delivery of modern radiotherapy is vastly improved as compared with traditional techniques, consideration of potential side effects following breast radiotherapy is still relevant. The 10-year analysis of the NCRI START Trials testing radiotherapy fractionation in women with early breast cancer reported moderate/severe chronic adverse effects (breast shrinkage, pain, tenderness or hardness) in up to one-third of patients [6]. These side-effects also impair quality of life and can cause psychological distress [7]. Even using intensity-modulated radiotherapy, 12% of patients had poor cosmesis at 5 years in a randomised trial of 815 patients [8].

Despite routine adoption of advanced radiotherapy planning, some rare but life threatening risks remain. A case-control study in 2168 women who underwent radiotherapy for breast cancer (from 1958 to 2001) showed that rates of major coronary events increased by 7.4% per Gy mean heart dose (95% confidence interval, 2.9 to 14.5; P<0.001) with no threshold below which the additional risk is zero [9]. This suggests that even using modern heart-sparing techniques such as deep-inspiratory breath-hold to reduce mean heart doses to less than 1Gy may confer risk [10]. Furthermore, estimates of a patient's individual risk of radiation induced cardiac toxicity increases substantially in patients with pre-existing cardiac risk factors including a history of circulatory disease, diabetes, chronic obstructive pulmonary disease and smoking [9]. Many of these risk factors are in turn more common in older women who will form the majority of the women recruited into this study. In summary, omitting radiotherapy in older women at very low risk of relapse will reduce the risk of radiation-induced heart disease in this population.

In a meta-analysis, including over 700,000 women treated for early breast cancer, breast radiotherapy is significantly associated with an excess risk of second cancers in organs with close proximity to the radiation treatment fields [11]. The risk of second cancer increased over time, up to 15 or more years after treatment with the highest being second lung relative risk (RR) 1.66 (95% CI 1.36–2.01) and second oesophageal cancer RR 2.17 (95% CI 1.11–4.25) [11]. Although the risk of second malignancy is likely to be lower with modern radiotherapy techniques, the dose response to tumour induction in both lung and oesophagus has shown to be linear. So although the absolute risk is very low, it is relatively higher in those already at risk of these cancers and therefore any reduction in radiation dose is likely to reduce this risk of a second cancer.

Currently, breast radiotherapy is recommended for all women after breast conserving surgery, even those at lowest risk of local relapse and, whilst there is no consensus as to which subgroup of patients can safely avoid breast radiotherapy [12], there is an increasing view amongst clinicians that this subgroup exists – the challenge is to identify which group it comprises and to provide robust evidence of the safe omission of radiotherapy in that group.

Randomised trials of omission of breast radiotherapy for patients with good prognosis disease show no detriment in survival, but patient selection needs further refinement

By the 1990s, 5-year local relapse rates reported in randomised trials were already falling from 20-30% to <10% without radiotherapy for some patient groups [13, 14]. The Cancer and Leukaemia Group (CALGB) 9943 trial randomised 636 women with T1, NO, ER positive tumours with clear margins to breast conserving surgery and tamoxifen or breast conserving surgery, tamoxifen and the addition of whole breast irradiation. In a subsequent analysis of Medicare patients meeting the eligibility criteria of the CALGB trial, the 3% reduction in local recurrence at 5 years (4% vs 1%) was shown to have reduced the use of radiotherapy only slightly in subsequent non-trial patients, i.e. the trial results were not practice changing [15]. The 10 year local recurrence rates of the CALGB trial showed some widening between irradiated and non irradiated patients (2%, 95%CI:1-4% vs 9%, 95%CI:6-13%). Whilst the authors proposed that radiotherapy could be omitted in such low risk patients, others disagree [13, 16, 17]. It is important to add that despite these differences in local control, there was no difference in overall survival (OS) or breast cancer specific death (10 year OS TamRT; 67%, 95%CI:62-72% vs Tam; 66%, 95%CI61-71%).

More recently, PRIME II randomised 1326 women aged ≥65 years with ER+, tumour size ≤3cm pN0 tumours to radiotherapy or not, with both groups receiving endocrine therapy. At 5-year median follow-up (IQR: 3.84-6.05) it showed a 1.3% (95%CI: 0.2-2.3) local relapse rate after radiotherapy (n=5) and 4.1% (95%CI: 2.4-5.7) after no radiotherapy (n=26, p=0.002). Consistent with previous studies [15, 16], there was no reported excess of distant relapse, second cancers or deaths illustrating that local relapses can be salvaged with surgery (± radiotherapy) without increasing the risk of breast cancer death (5 year OS 93.9%, CI:91.8-96% in both groups). In an unplanned subgroup analysis, ER-rich patients receiving radiotherapy had only a 2.4% absolute gain in local relapse over non-irradiated patients (local relapse with radiotherapy 0.8% (95%CI: 0.3-1.9) vs 3.2% (95%CI: 2.1-5.2) without radiotherapy). A multivariable analysis for local relapse suggested only use of radiotherapy and oestrogen receptor as independent risk factors (grade non-significant in model). HER2 and Ki67 status was unavailable and there was limited PR data. A larger study is required to confirm the existence and definition of a subgroup with a very low local relapse risk without radiotherapy.

Immunohistochemical markers may optimise selection of patients at very low risk of recurrence

The randomised controlled trials cited above illustrate that basic clinicopathological parameters, (e.g. T1/N0/ER+, grade 1/2 and older patient age) broadly identify a group of patients with an expected low 5-year local relapse rate without radiotherapy. Better selection of patients at very low risk of relapse is needed before widespread change in routine practice can be advocated. The discovery of breast cancer intrinsic molecular subtypes shows that tumours can be sub-classified into distinct prognostic groups using expression based genotyping. However, these techniques are expensive and are not used routinely worldwide. As a result, much work has been done to validate the use of combinations of relatively inexpensive immunohistochemical biomarkers as alternatives to expression -based genotyping.

Much of the research investigating immunohistochemical biomarkers as surrogates for molecular subtype has focused on quantifying risk from distant metastasis and death from breast cancer. This approach can identify a group of patients expected to remain alive and disease-free from a breast cancer perspective – thus at risk of the adverse effects of radiotherapy, but with the expectation for little gain given the corresponding low risk of local relapse. There is, however, some direct evidence to show that immunohistochemical biomarkers can give prognostic information regarding local relapse following radiotherapy [18]. This study approximated intrinsic subtype classification retrospectively, using validated

immunohistochemical biomarkers, to a subgroup of tumour blocks from the Hypofractionation Whole Breast Irradiation (HWBI) Trial [19]. Central pathology review of tumour blocks from 989 of 1234 trial patients was carried out [18]. Tumours were classified by molecular subtype using a six-biomarker panel; ER, PR, HER2, Ki67, CK5/6 and EGFR. The primary endpoint was local relapse. In the multivariable Cox model, molecular subtype was the only factor predictive of local relapse, the 10-year cumulative incidence was 4.5% for luminal A and basal-like, 7.9% for luminal B and 16.9% for HER-2 enriched tumours ($P < 0.01$).

IHC4+C has added value over dichotomous evaluation of Ki67 & PR

The use of Ki67 (≤13%) and PR (≥20%) assessed by immunohistochemistry within ER+HER2- subgroup was originally developed to distinguish luminal A and luminal B [20, 21]. The cut-offs of Ki67 and PR were selected to distinguish the highly proliferative luminal B tumours from luminal A. In general, luminal A tumours are predominantly lower grade, and have better prognosis than luminal B tumours. Patients with the latter generally benefit from adjuvant chemotherapy in addition to endocrine therapy. Based on a retrospective study with 2376 hormone receptor+/HER2- tumours, 73% of grade 1 tumours (n=1275) were classified as luminal A and 27% as luminal B. A subsequent study using the same cohort of patients showed that the 10-year local relapse rate of luminal A tumours was 8% [22] after breast-conserving surgery followed by adjuvant radiotherapy. There is still a spectrum of risk of recurrence (mainly low and intermediate risks of recurrence across the luminal A group) and therefore, it may be difficult to identify those patients at *very low* risk of recurrence without incorporating independent clinical risk factors.

Exploratory analyses from relevant trials have been conducted specifically to better understand the characterisation of the population eligible for PRIMETIME in terms of their intrinsic subtype (HWBI trial) and estimation of risk by IHC4+C (TransATAC) (examples 1 and 2). These estimates show there is a small but significant group of patients with favourable clinicopathological features, including grade 1, for whom the additional biomarker classification indicates the presence of higher risk disease, as manifested by high proliferation (18.2% HWBI trial, 8% TransATAC). Such patients would, therefore, not be considered suitable for selective avoidance of radiotherapy as their risk of recurrence is above the threshold endorsed by the Trial Management Group (which includes patient advocates) as being relevant for the implementation of a cost-effective biomarker test (3-5% cumulative risk of local relapse by 5 years). For patients with otherwise good prognosis disease, but with grade 2 tumours, the relevant proportion is considerably higher. On this basis biomarker analysis available from IHC4+C is needed in optimally defining risk-stratification in relation to selective avoidance of radiotherapy.

Example 1 – characterizing the eligible PRIMETIME population using HWBI trial data

For patients ≥60, T1N0 (ER is defined with an Allred score ≥2) then:

- There were 22 patients who were ER+ (score of ≥2), PR+ (score of >4), Her2- (score of 0) and grade=1.
    - Of these, 4 of 22 (18.2%) had a Ki-67 of ≥14%.

- There were 89 patients who were ER+ (score of ≥2), PR+ (score of >4), Her2- (score of 0) and grade=2.
    - Of these, 44 of 89 (49.4%) had a Ki-67 of ≥14%.

Hypofractionation Whole Breast Irradiation (HWBI) Trial (Bane et al 2014) supplementary analysis via personal communication: Tim Whelan & Greg Pond

Example 2 – estimation of very-low, low and intermediate risk by IHC4+C using TransATAC data

For patients ≥60, T1N0 then:

- There were 125 patients who were ER+ (score of ≥2), PR+ (score of >4), Her2- (score of 0) and grade=1. Of these 10 (8%) were classified as low risk by IHC4+C.
- There were 210 patients who were ER+ (score of ≥2), PR+ (score of >4), Her2- (score of 0) and grade=2. Of these 93 (44%) were classified as low risk and 11 (5%) as intermediate risk by IHC4+C.
    - Very-low risk: <5% probability of distant recurrence at 10 years.
    - Low risk: ≥5% and <10% probability of distant recurrence at 10 years.
    - Intermediate risk: ≥ 10% and < 20% probability of distant recurrence at 10 years

Arimidex, Tamoxifen Alone or Combined (ATAC) Trial (Dowsett et al. 2013) supplementary analysis via personal communication: Mitch Dowsett

The IHC4+clinical (IHC4+C) score combines assessment of protein expression levels as revealed by immunohistochemistry (IHC) of ER, PR, HER2 and Ki67 with clinic-pathological parameters to identify breast cancer patients at low, intermediate or high risk of distant disease recurrence so aiding treatment decision-making [23].

% distant recurrence probability score at 10 years	Assigned risk category
<5%	Very low
≥5 - <10%	Low
≥10 - <20%	Intermediate
≥20	High

In particular it aims to identify those patients at such low risk of distant recurrence that the use of adjuvant chemotherapy would provide no appreciable additional benefit [24]. PRIMETIME presupposes that the risk categorization acquired by IHC4+C can be used similarly to direct selective avoidance of radiotherapy given the close association between risk of local and distant relapse when characterized by tumour subtype [Bane, 2014 #342;Voduc, 2010 #374]. The relative risk of local relapse is assumed to follow a similar prognostic pattern to the relative risk of distant relapse and therefore the use of IHC4+C to predict a group of patients at very low risk of local relapse is deemed appropriate. Furthermore, the recent translational study using ATAC trial data and samples (Arimidex, Tamoxifen Alone or Combined), referred to as TransATAC, has shown that IHC4+C provided comparable prognostic information as the Oncotype DX Recurrence Score and was better than OncotypeDX for postmenopausal women treated with endocrine therapy [25].

IHC4+C offers a pragmatic and cost-effective approach to risk stratification. At the time of trial initiation uncertainties remain regarding the validity of using locally assessed Ki67 immunohistochemistry as no internationally validated method is available, if however during the study recruitment period, a validated Ki67 assessment becomes available at sites the protocol will be amended to incorporate local Ki67 testing into the IHC4-C algorithm.

Long term follow up can now be cost effective

The implementation of Cancer Outcomes and Services Dataset (COSD), the new national standard for reporting cancer in the NHS in England and active since January 2013, incorporates revised generic cancer registration and additional clinical and pathology site specific items relevant to all new diagnoses of cancer and all diagnoses of secondary or metastatic breast cancer from that date. These data and other available datasets, e.g. the National Radiotherapy Dataset (RTDS), Systemic Anti-Cancer Therapy Dataset (SACT) and Hospital Episode Statistics (HES), can be linked, allowing a patient's individual cancer treatment pathway to be mapped from diagnosis to cure or death.

PRIMETIME will explore the possibility of obtaining local and distant recurrence information from routinely available data in addition to the gold standard of hospital collected relapse data. In the long term it is anticipated that hospitals could avoid having to send in routine follow-up data, in the short term, collecting data using both methods will allow verification of completeness of reporting and avoid hospital reporting of follow up data in patients without relapse, thus reducing the burden of data collection by staff at local centres. The trial will also use routine data to follow-up patients who enter the pre-screening phase of the trial but do not subsequently enter the main trial for baseline and treatment characteristics and disease-related outcomes to fully define this cohort.

Successful avoidance of breast radiotherapy would save the NHS money

The number of incident female breast cancers in the UK in 2012 was 50,800, with >10,000 of these patients having very good prognosis disease. The rising incidence of breast cancer, particularly among the elderly which represent over half of patients presenting with early breast cancer, places an increasing burden on radiotherapy resources. Avoiding radiotherapy in just 5,000 patients/year at today's rate would save >£12 million/year, at the expense of adding a relatively inexpensive biomarker test.

1.2. Description of Population

The study population will be women treated by breast conserving surgery and prescribed endocrine therapy for whom the residual risk of ipsilateral breast disease is estimated to be no more than 1% per year without radiotherapy.

The patients approached to take part in the study will have oestrogen receptor positive (ER +ve) small tumours (T1) of low grade (G1-2). Patients will in most cases be older than 60 years of age however patients younger than 60 years of age may participate if they are post-menopausal and have co-morbidities which imply a high risk of radiotherapy side effects.

1.3. Study Rationale

The study rationale is to obtain high quality, practice changing, clinical evidence supporting the safe avoidance of radiotherapy for a highly selected subgroup of breast cancer patients treated with breast conserving surgery and with planned endocrine therapy who are deemed to be at such low risk of further ipsilateral breast disease that the potential benefits associated with radiotherapy do not outweigh the known risks. Immunohistochemical biomarkers will be used to supplement clinicopathological factors (IHC4+C) and will inform patient selection for avoidance of radiotherapy.

The effect of radiotherapy in reducing ipsilateral breast disease risk after breast conserving surgery for early breast cancer has been fully quantified by randomised controlled trials involving thousands of women [3]. The design of PRIMETIME tests whether radiotherapy can be safely avoided in a patient population considered to have such a low risk of local recurrence that the potential absolute gain from radiotherapy is so small as to not outweigh the established risks associated with breast radiotherapy. Rates of ipsilateral breast disease in patients allocated to avoid radiotherapy and those who are allocated to radiotherapy will not be formally compared. A full justification of the design is described in appendix A4.

2. STUDY OBJECTIVES

2.1. Primary Objective

- To assess the risk of any ipsilateral invasive and DCIS breast disease by 5 years following omission of postoperative breast radiotherapy (given according to local practice)

2.2. Secondary Objectives

- To use immunohistochemical biomarkers with clinical information (IHC4+C) to direct selective avoidance of breast radiotherapy
- To assess the long term disease outcomes following omission of postoperative breast radiotherapy, including:
    - the risk of any ipsilateral invasive and DCIS breast disease by 10 years following omission of postoperative breast radiotherapy
    - the risk of regional and distant relapse by 5 and 10 years following omission of postoperative breast radiotherapy
    - The risk of any ipsilateral breast disease (including non-invasive (DCIS) and invasive ipsilateral disease) by 5 and 10 years following omission of postoperative breast radiotherapy.
    - The risk of contralateral breast second primary cancer by 5 and 10 years following omission of postoperative breast radiotherapy
    - The risk of any contralateral breast disease (including non-invasive (DCIS) and invasive disease) by 5 and 10 years following omission of postoperative breast radiotherapy.
    - The risk of ipsilateral invasive breast local relapse by 5 and 10 years following omission of postoperative breast radiotherapy (subject to availability of tumour profiling data)
    - The risk of ipsilateral invasive breast second primary cancer by 5 and 10 years following omission of postoperative breast radiotherapy (subject to availability of tumour profiling data)
    - overall invasive disease free survival following omission of postoperative breast radiotherapy
    - breast cancer specific survival following omission of postoperative breast radiotherapy
    - overall survival following omission of postoperative breast radiotherapy

2.3. Exploratory Objectives

- To confirm viability of collecting cancer outcomes via record linkage with data collected routinely through the NCRAS's Cancer Analysis System and other informative UK cancer registries.
- To assess disease-related outcomes using routinely collected data for both patients who enter the main trial and patients who enter pre-screening for Ki67 in the trial but who subsequently do not enter the main trial.

3. STUDY DESIGN

PRIMETIME is a prospective study with biomarker-directed treatment recommendations.

Patients will be approached for pre-screening once their diagnostic biopsy has been taken. The eligible population is described in Section 6. At this stage patients will receive a patient information sheet for research testing and be asked to donate tissue taken at the time of their diagnostic biopsy. Once a pre-screening number has been assigned by ICR-CTSU, samples will be tested for Ki67 levels at a central laboratory.

Breast conserving surgery will proceed according to standard practice. Possible candidates who have been pre-screened and meet the eligibility for registration into the PRIMETIME study will be identified following surgery, based on clinicopathological features. The eligible population is described in Section 7. Potential participants will be approached to participate in PRIMETIME and the study patient information sheet will be provided. Once a patient has provided written informed consent any study-specific screening assessments required to confirm eligibility may be conducted.

Once eligibility has been confirmed, patients will be registered into PRIMETIME (See Section 8). At the time of registration, ICR-CTSU will calculate the IHC4+C score using clinicopathological information provided by the site and the centrally tested Ki67 result. The IHC4+C score will be provided to the site on confirmation of study registration.

The IHC4+C score will be used by the centre, to inform the patient whether the recommendation is for them to selectively avoid radiotherapy (because they are classed as 'very low' risk) or whether they are advised to continue with standard of care radiotherapy.

Research centres are encouraged to discuss the risk categorisation with the patient to ensure any questions relating to this result are fully answered before proceeding with biomarker-directed treatment.

The risk categories predicted by the IHC4+C calculator and the resultant recommended treatment options are as follows:

Assigned risk category	Directed treatment
Very low	Avoidance of radiotherapy (Surgery only)
Low	Radiotherapy
Intermediate	Radiotherapy
High	Radiotherapy

Patients at a 'very low' risk of recurrence still have the option to have radiotherapy and likewise those at slightly higher risk still have the option not to have radiotherapy. PRIMETIME will record all registered patients irrespective of their treatment choice, but their final treatment decisions must be recorded and follow up must be according to the treatment the patient receives.

All patients registered into the study, regardless of their risk category or whether or not they receive radiotherapy will be prescribed at least 5 years adjuvant endocrine therapy and any additional anti-cancer treatment in accordance with local practice. Patients will attend follow up clinic visits in accordance with local practice.

Patients receiving radiotherapy will have annual mammography according to local practice. Patients not receiving radiotherapy will require annual mammography for 10 years therefore mammograms performed according to local practice should be supplemented with additional scans to ensure annual mammography for 10 years. For all patients registered in PRIMETIME, centres should inform ICR-CTSU of disease relapse, new primary disease or death until the end of study. Centres will be prompted to provide a patient status update on an annual basis.

Study data will be corroborated by linkage with routine data available for example via the National Cancer Registration Service and Hospital Episode Statistics.

4. STUDY ENDPOINTS

4.1. Primary Endpoint

Any ipsilateral breast disease rate (non-invasive (DCIS) and invasive breast cancer)

4.2. Secondary Endpoints

- Regional relapse rate
- Distant relapse rate

- Ipsilateral invasive breast disease rate
- Contralateral breast second primary cancer rate
- Any contralateral breast disease rate (non-invasive (DCIS) and invasive breast cancer)
- Ipsilateral invasive breast local relapse rate (subject to availability of tumour profiling data)
- Ipsilateral invasive breast second primary cancer rate (subject to availability of tumour profiling data)
- Overall invasive disease free survival
- Breast cancer specific survival
- Overall survival

4.3. Exploratory Endpoints

- Completeness and accuracy of routinely collected record linked (event) data compared with data collected directly from participating hospitals
- Estimation of disease-related endpoints as stated above using routinely collected data for both patients who enter the main trial and separately for patients who enter pre-screening for Ki67 in the trial but who subsequently do not enter the main trial

5. PATIENT SELECTION

5.1. Number of Participants

The aim is to register approximately 2400 participants into the PRIMETIME study in order for 1550 patients to be recruited into the no radiotherapy cohort.

5.2. Source of Participants

Participants will be recruited from approximately 80 participating sites in the UK. Potential participants will be identified in pre-operative breast surgery clinics, oncology clinics and discussed at Multi-Disciplinary Team (MDT) meetings.

6. PRE-SCREENING – Ki67 RESEARCH TESTING

Pre-operative identification of patients likely to meet PRIMETIME eligibility criteria, allows sufficient time for pre-screening Ki67 testing prior to post-operative study registration. Patients meeting the pre-screening criteria and who provide written informed consent to PRIMETIME pre-screening will be asked to donate five slides taken from their diagnostic biopsy for central testing of Ki67.

The patients who should be approached for pre-screening are those who appear likely to be eligible for PRIMETIME based on the information known prior to surgery. Such patients will be those:

- who are over 60 (or younger than 60 if they are post-menopausal and have co-morbidities that imply a high risk of radiotherapy toxicity (e.g. significant cardiovascular disease with left sided breast cancer)).
- with no clinical evidence of high risk disease,
- who are ER positive,
- who are tested for PR
- who are HER2 negative (or whose HER2 result is awaited),
- with grade 1 or 2 tumours,
- who are pre-operatively assessed as node negative,
- With a tumour estimated to be ≤2cm in size

Patients should be approached as early as possible in their treatment pathway to allow ample time for Ki67 testing before post-operative registration into the study. A minimum of 2 weeks should be allowed to complete Ki67 testing.

The patient's Ki67 result will be provided by the testing laboratory to ICR-CTSU and used to calculate the IHC4+C score for patients who subsequently register for the PRIMETIME study. For patients registering into the PRIMETIME study, their IHC4+C score (and Ki67 result) will be provided to centres at the time of registration (post surgery). For patients who provide tissue samples for Ki67 testing but who do not go on to register into the main PRIMETIME study, ICR-CTSU will provide the IHC4+C score to centres. Centres will need to provide the additional clinicopathological data required for IHC4+C calculation for the score to be calculated (see study guidance notes for more information on requesting this). Please note, we strongly advise that the IHC4+C is used in its entirety rather than the Ki67 score in isolation.

There will be a dynamic process throughout the study whereby centres may be able to transfer to local Ki67 testing subject to protocol amendment and once the relevant quality control checks have been carried out.

6.1. Procedure for Obtaining Informed Consent for pre-screening

Participants should be given the current ethics approved patient information sheet for research testing for their consideration. The Principal Investigator (or designated individual) must ensure that patients are fully informed about the nature and objectives of the research testing. Patients should only be asked to consent to the research testing after they have had sufficient time to consider participation, within the constraints of the patient pathway, and the opportunity to ask any further questions.

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.

6.2. Pre-screening procedures

Once a patient has provided written informed consent for PRIMETIME pre-screening the research team should:

Register the patient for PRIMETIME pre-screening by calling ICR-CTSU on:
+44 (0)208 643 7150

The following information will be required for pre-screening registration:

- Provide ICR-CTSU with patient's full name, hospital number, date of birth, postcode and NHS/CHI number (or equivalent for international participants).
- ICR-CTSU will provide a patient-specific pre-screening number
- Request 5 unstained slides cut from the patient's diagnostic biopsy from their pathology department. The slides should be labelled with the pre-screening number provided by ICR-CTSU and in accordance with the instructions in the PRIMETIME Trial Guidance Notes and sent to the site's designated PRIMETIME central laboratory.
- Enter the patient's details on the PRIMETIME pre-screening log.

There are 3 laboratories performing Ki67 testing in the PRIMETIME study. Each site will have a designated central laboratory confirmed at the time of site initiation. Upon receipt of the slides, the site's designated central laboratory will undertake Ki67 testing. The Ki67 result will be provided to ICR-CTSU in order to calculate the IHC4+C score for patients subsequently registered into PRIMETIME. Further details are provided in the study guidance notes.

The patient should proceed to breast conserving surgery (wide local excision) and axillary surgery (sentinel lymph node biopsy or axillary sample according to local policy).

6.3. Pre-Screening Log

Details of all patients who consent to the pre-screening research testing stage of PRIMETIME should be added to the pre-screening log. The information collected on the log will include:

Date patient identified
Pre-screening number and date of birth
Main study screening outcome (patient accepted/declined participation in study; patient was eligible/ineligible for main study)
Reasons for not approaching / declining participation in main study (if available)
Reasons patient was ineligible for main study (if applicable)
Study ID (where patient accepted participation and was eligible)

This information will be used by the Trial Management Group (TMG) to monitor recruitment activity.

6.4. Follow-up of Patients Pre-screened

Written informed consent should be sought from patients for the ICR-CTSU team to access data in their national medical records, currently held by Public Health England and the Health and Social Care Information Centre on their health status. The relevant data sources include the Cancer Services and Outcomes Dataset (COSD), the National Radiotherapy Dataset (RTDS), the Systemic Anti-Cancer Therapy Dataset (SACT), the Hospital Episodes Statistics (HES), the ONS mortality file, equivalent databases in the devolved nations and any other informative UK registries. It is likely that some level of data mining will be required to examine hospital episodic activity as a proxy indicator.

Prospective collection of routine data will be requested from these sources at regular intervals for patients who are pre-screened for PRIMETIME but who do not enter the main PRIMETIME study following Ki67 research testing.

7. SCREENING FOR PRIMETIME STUDY

Please refer to the study flow diagram on p.X for a summary of the required procedures at each applicable timepoint.

After surgery and discussion at the multi-disciplinary team meeting, it will be possible to identify suitable candidates for PRIMETIME.

7.1. Eligibility criteria

7.1.1. Inclusion Criteria

1. Provision of written informed consent to participate in the PRIMETIME study
2. Provision of slides for research testing and availability of Ki67 result (contact ICR-CTSU to confirm Ki67 result is available)
3. Women aged ≥60 years at the time of histopathological diagnosis of primary invasive breast cancer (younger patients are eligible if they are post-menopausal and have co-morbidities that imply a high risk of radiotherapy toxicity (e.g. significant cardiovascular disease with left sided breast cancer);

4. Women having had breast conserving surgery with complete resection of tumour tissue (≥1 mm microscopic, circumferential margins of normal tissue from invasive cancer and DCIS). Note: Patient considered eligible if a margin of <1mm is reported, but the operating surgeon reports that it is not possible to take any further breast tissue (E.g.: posterior margin, with wide local excision performed down to pectoral major muscle, or medial margin at very medial aspect of breast). Patient is not eligible where the pathology report described tumour as transected or where margin is involved. All instances where margin is <1mm must be discussed with the PRIMETIME Trial Manager prior to patient registration.
5. pT1/pN0/M0, tumours should be unifocal (DCIS is allowed in combination with invasive breast cancer, providing whole tumour size (in-situ and invasive ≤2cm); isolated tumour cells in axillary nodes are allowed);
6. Histological confirmation of grade 1 or 2 invasive breast cancer;
7. Oestrogen receptor (ER) positive according to local practice. The H score must be available;
8. Progesterone receptor (PR) status tested. The percentage positivity result must be available at the time of IHC4+C calculation;
9. Human epidermal growth factor receptor (HER2) negative according to local practice;
10. Patients must be recommended for ≥5 years adjuvant endocrine therapy according to local policy, they must also be willing to start endocrine therapy and in the investigator's opinion, deemed able to comply with the duration of treatment.

7.1.2. Exclusion Criteria

1. Patients with known or suspected lymphovascular space invasion and/or axillary nodal micrometastases or macrometastases.
2. Synchronous bilateral breast cancer
3. Patients with a past history of malignancy except
   (i) basal cell skin cancer and CIN cervix uteri or
   (ii) treated, localised squamous cell carcinoma of the skin or
   (iii) malignancies treated with curative intent (including contralateral breast cancer and DCIS) and the patient has been disease free ≥5 years;
4. Patients who have had an ipsilateral mastectomy;
5. Patients who have received neoadjuvant therapy (endocrine or cytotoxic chemotherapy with therapeutic intent) or who are deemed by the MDT to require adjuvant cytotoxic chemotherapy. Note 1: In most instances treatment within a window of opportunity study is not considered of therapeutic intent and will therefore be allowed: please check with the PRIMETIME trial manager if a patient has participated in a window of opportunity study. Note 2: It is recognised that breast surgery may occasionally be delayed for non-clinical reasons. These situations should be discussed with the PRIMETIME Trial Manager prior to patient registration. Consideration will be given to endocrine therapy not exceeding 28 days and the final pathological tumour size not exceeding 15mm (as tumour shrinkage during pre-operative endocrine therapy is possible).
6. Patients with mammographically occult breast cancers, ie. present with lump, but not visible on mammogram.
7. Patients who are currently receiving endocrine therapy for previous breast cancer.

7.2. Procedure for Obtaining Informed Consent

The Principal Investigator (or designated individual) must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation. Patients should be given the current ethics approved patient information sheets for their consideration.

As per guidance in Appendix 6, patients should be given either:

- PRIMETIME main study information sheet Version A or
- PRIMETIME main study information sheet Version B and decision aid video.

Patients should only be asked to consent to PRIMETIME after they have had sufficient time to review the information, consider the study and have the opportunity to ask any further questions. No protocol required assessments should be conducted until the PRIMETIME consent form has been signed and dated by both the patient and the Investigator unless they are performed routinely as part of standard patient care.

After the patient has decided whether or not to consent to PRIMETIME they should be given either Questionnaire A or Questionnaire B as part of the Information Giving Study as per guidance in Appendix A6. Patients should be given Questionnaire A or Questionnaire B regardless of whether or not they have consented to the PRIMETIME main study.

Patients should be made aware that return of the questionnaire indicates consent to the PRIMETIME Information Giving Study; that completion of the questionnaire is voluntary and independent of participation in the PRIMETIME main study.

Patients who consent to PRIMETIME will be asked to consent to donate archival tissue for future translational studies. Patients should be made aware that participation in this aspect of the study is entirely voluntary. Refusal to participate in the PRIMETIME sub- study will not result in ineligibility to participate in the main study and will not impact on the medical care received.

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.

7.3. Participation in other Clinical Studies

Patients who fulfil the eligibility criteria will be given the opportunity to participate in PRIMETIME if they have participated in other clinical trials prior to recruitment.

Participation in window of opportunity studies is not an exclusion criterion, but should be discussed with the PRIMETIME study team prior to patient registration. Please contact the PRIMETIME trial manager, primetime-icrctsu@icr.ac.uk, in the first instance.

8. STUDY ASSESSMENTS

8.1. Screening

The following activities should be conducted prior to contacting ICR-CTSU to register a patient for the main study:

Provision of written informed consent for the main study by the patient,

Completion of study eligibility checklist by research team,

Confirmation that the patient's Ki67 result is available. Contact ICR-CTSU prior to registration to ensure the Ki67 testing conducted by the central laboratories during pre-screening is complete and results are available.

NB. Research teams can request the IHC4+C score for patients who consented to PRIMETIME pre-screening but who later decided not to participate in the main study or who were found to be ineligible. ICR-CTSU can provide the IHC4+C score on request and following provision of the supporting clinicopathological data.

8.2. Registration

Participants must be registered centrally with the ICR-CTSU once written informed consent has been provided and study eligibility has been confirmed.

The eligibility and registration checklists should be completed, and sites should then call ICR-CTSU:

Patients should be registered by calling ICR-CTSU on:
+44 (0)208 643 7150

The following information will be required for registration:

Name of hospital, consultant and person registering patient
Confirmation that patient has given written informed consent for study participation (and whether there are any aspects of the study the patient has not consented to eg. optional sub-studies)
Confirmation that patient is eligible for the study by completion of the eligibility checklist
Patient's full name, date of birth,
Patient's PRIMETIME pre-screening number
Clinicopathological data required for IHC4+C calculation:

- tumour grade,
- tumour size (mm),
- confirmation that the patient is node negative (as per the definitions in eligibility criteria),
- patient age,
- planned endocrine therapy type,
- ER score (H score), PR score (% positivity), HER2 status.

Using the above information, ICR-CTSU will calculate the patient's IHC4+C score and provide this score to the participating site.

ICR-CTSU will return confirmation of registration, within 24 hours. Confirmation will include:

- a summary of the information provided by the centre used to perform the IHC4+C calculation
- confirmation of the patient's IHC4+C score
- recommended directed treatment informed by IHC4+C score. Patients who are categorised to be in a 'very low' risk group will be directed to avoid radiotherapy. All other patients will be directed to receive radiotherapy according to standard practice (see Study Treatment section below for a summary of risk categories and their directed treatment recommendation).
- Confirmation of the patient's unique Study ID

Research centres are encouraged to discuss the risk categorisation with the patient to ensure any questions relating to this result are fully answered before proceeding with biomarker-directed treatment.

Patients categorised to be in the 'very low' risk group still have the option to have radiotherapy and likewise those in the higher risk groups still have the option not to have radiotherapy. PRIMETIME will record all registered patients irrespective of whether they deviate from the protocol-directed treatment recommendation, but their final treatment decisions must be recorded and follow up must be according to the treatment the patient receives.

8.3. Baseline

For all registered patients:

- Baseline characteristics and medical history should be recorded on the relevant PRIMETIME eCRFs.
- An archival tissue sample should be identified and requested from the local pathology department. This sample should be an FFPE block of primary tumour collected at surgery.

8.4. IHC4+C directed treatment

The recommended need for radiotherapy will be directed by the biomarker read out from IHC4+C calculation.

Patients categorised to be in the 'very low' risk group, as confirmed at study registration, will be recommended for avoidance of radiotherapy.

Patients categorised to be in the 'Low', 'Intermediate' or 'High' risk groups, as confirmed at study registration, will be directed to receive radiotherapy according to the PRIMETIME radiotherapy planning pack.

The risk categories are defined in the table below:

Assigned risk category	**Directed treatment**
Very low	Avoidance of radiotherapy (Surgery only)
Low	Radiotherapy
Intermediate	Radiotherapy
High	Radiotherapy

For all patients, regardless of risk category, all other anti-cancer treatments (for example endocrine therapy) should be administered and managed according to local practice.

For patients receiving radiotherapy, data on radiotherapy planning and delivery (including DICOM data) should be recorded in the relevant PRIMETIME eCRF.

8.5. Follow-up

Follow up of patients will vary according to whether or not the patient receives radiotherapy. If treatment deviates from that directed at registration the follow up schedule should proceed according to the treatment the patient ultimately *receives*.

8.5.1. Patients who do not receive radiotherapy

- Patients should have an annual mammogram for 10 years. (i.e. mammograms in line with local practice for the first 5 years, patients have annual mammogram for 5 additional years)
- Patients should attend clinic visits according to local practice.
- ICR-CTSU will contact research sites annually to request an update on patient status. Reasonable efforts should be made to contact patients annually for ten years.
- Information collected at follow up visits and the annual mammogram should be recorded in the PRIMETIME eCRF.

8.5.2. Patients who receive radiotherapy

- Patients should have annual mammograms according to local practice.
- Patients should attend clinic visits according to local practice.
- ICR-CTSU will contact research sites annually to request an update on patient status. Reasonable efforts should be made to contact patients annually for ten years.
- Information collected at follow up visits and the annual mammogram should be recorded in the PRIMETIME eCRF.

As described above, it is intended that research sites will follow up all patients annually for ten years. Over the course of the study, the study team aim to transfer the provision of long term follow up data from research sites to routine data sources where the patient has provided consent to do so and where the required data point is available. This is intended to relieve the burden of long term follow up on research sites, and as a move towards this, data collection in the eCRF for patients where no disease event has occurred is minimal.

8.5.3. Follow up from routine data sources

Written informed consent should be sought from patients for the ICR-CTSU team to access data in their national medical records, currently held by Public Health England and the Health and Social Care Information Centre on their health status. The relevant data sources include the Cancer Services and Outcomes Dataset (COSD), the National Radiotherapy Dataset (RTDS), the Systemic Anti-Cancer Therapy Dataset (SACT), the Hospital Episodes Statistics (HES), the ONS mortality file, equivalent databases in the devolved nations and any other informative UK registries. It is likely that some level of data mining will be required to examine hospital episodic activity as a proxy indicator.

Prospective collection of routine data will be requested from these sources at regular intervals for patients who enter the main study and those who are pre-screened, but do not subsequently enter the main study (ie. who consent for Ki67 research testing).

8.6. Procedure at disease recurrence/relapse or diagnosis of new primary cancer

If a patient has a local or distant relapse, new breast primary cancer the following procedures should be followed:

- Routine clinical, histological and imaging information should be collected on the disease relapse and entered into the PRIMETIME eCRF.
- Tumour tissue collected from the diagnostic biopsy and/or any applicable surgical procedures should be provided to the study central laboratory.
- The patient should be treated accordingly to local protocol for relapse / new primary cancer. For those not receiving radiotherapy at initial diagnosis, further breast conserving surgery and radiotherapy could be considered.

8.7. Discontinuation from Follow-up

If a patient no longer wishes to attend follow up visits:
If a patient chooses to withdraw from further follow-up, centre personnel should confirm whether they simply no longer wish to attend study follow up visits, but are happy for the information to be collected from other sources or whether the patient has withdrawn consent for further information to be sent to the ICR-CTSU. ICR-CTSU should be informed via completion of the relevant forms in the eCRF.

If a patient no longer wants their data to be sent to ICR-CTSU:
In the very rare event that a patient requests that the ICR-CTSU can no longer collect information on them from routine data sources, the implications of this should be discussed with the patient first to ensure that this is their intent and, if confirmed, ICR-CTSU should be notified in writing.

8.8. Schedule of Events/Assessments

Visit/Assessment	Pre-Screening	Screening (post surgery)	Registration	Baseline (prior to commencing radiotherapy)	Radiotherapy delivery	Data collection from routine follow up clinics	Annually – years 1-10	Disease Relapse
Informed consent (research testing)	X							
Pre-screening request submitted to ICR-CTSU	X							
5 slides from diagnostic biopsy sent to central lab	X							
Central lab perform Ki67 testing, feedback result to ICR-CTSU	X							
Informed consent (main study)		X						
Completion of IGS Questionnaire (either A or B, see Appendix A5)[6]		X						
Study eligibility checklist completed		X						
Study registration form submitted to ICR-CTSU			X					
ICR-CTSU confirms IHC4+C score and directed treatment			X					
Discuss IHC4+C score and directed treatment with patient				X				
Baseline characteristics / medical history				X				
FFPE block from primary tumour identified				X				
Radiotherapy planning and DICOM data collection[1]								
Radiotherapy according to standard care					X[2]			
Radiotherapy delivery data collection						X[3]		
Concomitant anti-cancer treatment data collection							X	
Mammogram						X	X[4]	
Access to information from routine follow up						X		
Disease status						X	X	
Routine clinical, histological and imaging information[5]						X		X
FFPE block from site of disease relapse identified								X

Footnotes

1. Radiotherapy plans may be collected electronically by the QA team if requested by the PRIMETIME study team, TMG or IDMC based on the recurrence rates seen in the study.
2. For patients categorised to be in the 'low', 'intermediate' or 'high' risk groups according to the IHC4+C score calculated in the PRIMETIME study. Or for patients categorised to be in the 'very low' risk group directed to avoid radiotherapy, but who decide not to follow the study recommendations, such patients would also receive radiotherapy according to standard care.
3. At the first follow up following completion of radiotherapy
4. Patients not receiving radiotherapy should have an annual mammogram for 10 years. Patients receiving radiotherapy should have annual mammograms according to local practice.
5. At any time during the study
6. The questionnaire needs to be given to the patient immediately AFTER they have decided whether or not to participate in PRIMETIME main study.

9. RADIOTHERAPY

For patients directed to receive radiotherapy, standard of care radiotherapy should be delivered.

9.1. Radiotherapy Treatment Timelines

Radiotherapy should commence within 8 weeks following breast conserving surgery and ideally within 31 days following breast conserving surgery as recommended by NICE. Occasionally, this will need to be delayed to allow treatment for breast infection or persistent seroma.

Radiotherapy is not thought to be effective if there is a long delay between surgery and radiotherapy. The PRIMETIME patient information sheet states "If you agreed not to have radiotherapy at the start of the study, you can change your mind up to 8 weeks after your surgery. Radiotherapy is not thought to be as effective if there is too long a delay between surgery and radiotherapy, so after this time you may not be able to receive radiotherapy".

The patient's treatment in this scenario is at the investigator's discretion.

9.2. Radiotherapy Planning and Delivery

Radiotherapy planning and delivery should be carried out in accordance with the best current routine practice, as exemplified in the Fast Forward planning and delivery guidelines.

9.3. Supportive Care Guidelines

All required supportive care should be delivered according to local practice.

9.4 Radiotherapy Quality Assurance (QA)

A quality assurance program will be instigated to ensure the safety and consistency of radiotherapy delivery at participating sites. For further information please see Appendix A2.

10. CONCOMITANT ANTI-CANCER THERAPY

For all patients, regardless of whether they receive radiotherapy or not, all other anti-cancer therapy should be delivered according to standard care. As per the inclusion criteria, patients must have been recommended 5 or more years of endocrine therapy. At the time of registration into the study investigators must deem the patient to be able to comply with the duration of the endocrine therapy and any other required anti-cancer therapies prescribed.

Compliance with endocrine therapy (ie. continuation with prescribed treatment) should be followed up by the research team at the time of annual follow up and recorded in the PRIMETIME eCRF.

Details of other anti-cancer therapies should be recorded in the PRIMETIME eCRF.

11. SAFETY REPORTING

11.1. Definitions

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

The recording of AEs not meeting the definition of serious is not required in PRIMETIME.

Serious Adverse Event (SAE)
An SAE is any untoward medical occurrence that:

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

For patients receiving radiotherapy, the SAE reporting period should commence at study registration and end 30 days after radiotherapy is complete.

For patients not receiving radiotherapy the equivalent SAE reporting period is considered to commence at study registration and cease after 17 weeks. This is considered equivalent to the reporting period for those receiving radiotherapy, as radiotherapy must commence within 8 weeks of breast conserving surgery, will last a maximum of 5 weeks and the SAE reporting period continues for 30 days after the end of radiotherapy.

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.

Recurrence of the indicated disease, new primary cancers, death due to progression of the indicated disease and planned/elective hospital admissions are not considered SAEs.

Serious Adverse Reaction (SAR)
A serious adverse reaction is an SAE that is suspected as having a causal relationship to the study intervention, 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).

In PRIMETIME, the study intervention is considered to be the omission of radiotherapy.

Definitions of causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship with the study intervention
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time of the study intervention). 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 of the study intervention). 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.

Related **Unexpected Serious Adverse** Event
An adverse event that meets the definition of serious and is assessed by the Chief Investigator or nominative representative as:

"Related" – that is, it resulted from the research intervention, and

"Unexpected" – that is, the type of event judged as being related to the omission of radiotherapy that is not considered to be an expected occurrence by the Chief Investigator.

11.2. Reporting of Serious Adverse Events to ICR-CTSU

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 PRIMETIME SAE form and faxing to:

The ICR-CTSU safety desk
Fax no: **+44 (0)208 722 4368**
For the attention of the PRIMETIME Study team

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 completed, signed and dated by the Principal Investigator or designated representative.

11.3. 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 the study intervention and as being unexpected will undergo expedited reporting to the relevant authorities and all other interested parties by ICR-CTSU.

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.

11.4. Expedited Reporting of Related Unexpected SAEs

If an SAE is identified as being related 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 study at appropriate intervals.

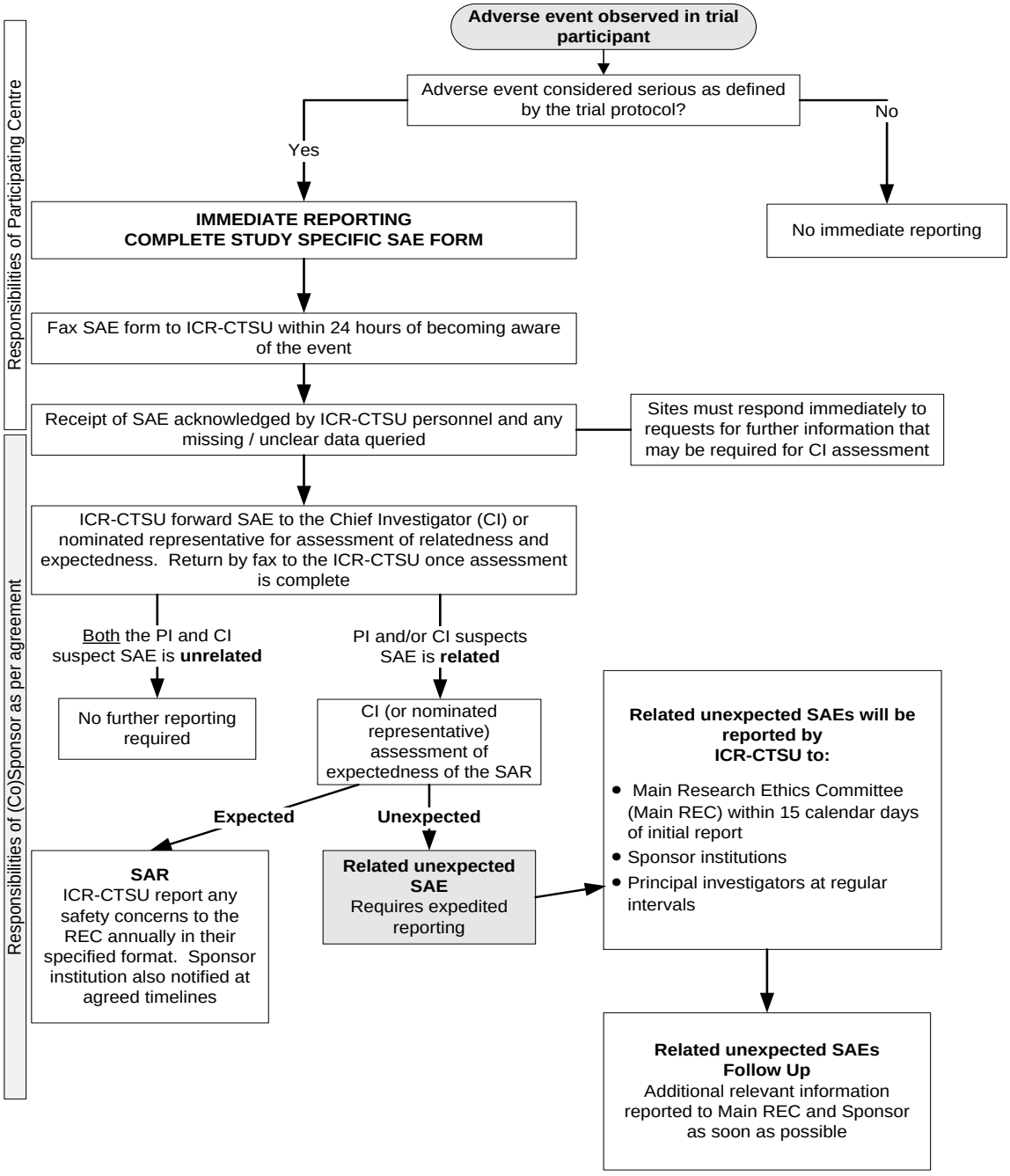
11.5. Follow up of Serious Adverse Events

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

11.6. Annual Safety Reporting

An annual progress report will be provided to the main REC by ICR-CTSU and copied to the Sponsor at the end of the reporting year. This will include data about related unexpected SAEs and whether any safety concerns have arisen during the reporting period.

Figure 3: Flow diagram for SAE reporting, and action following report



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

12. STATISTICAL CONSIDERATIONS

12.1. Statistical Design and Sample Size Justification

The primary objective is to assess the safety of avoiding radiotherapy in terms of risk of ipsilateral breast disease. In the cohort of patients for whom selective avoidance of radiotherapy is advocated, the ipsilateral breast disease rate is expected to be ≤4% at 5 years. The sample size has been calculated based on excluding at most a 5% ipsilateral breast disease rate at 5 years within this group using a one-sided 97.5% confidence interval. Allowing for 5% of patients to be non-evaluable at the time of primary endpoint analysis (due to patients progressing with metastatic BC or dying from unrelated causes) gives a total of 1550 patients required in the no radiotherapy cohort.

It is expected approximately 70% of patients screened for PRIMETIME will be defined as very low risk using the IHC4+C score, and assuming a 7.5% non-compliance with the screening stage, 2400 patients will need to be screened to ensure sufficient numbers enter the no radiotherapy cohort. Therefore, it is estimated that approximately 660 patients who are screened for PRIMETIME will be advised to receive radiotherapy according to standard practice. These patients will provide an estimate (and 95%CI) of ipsilateral breast disease rates following radiotherapy in a largely low risk patient group (as opposed to a very low risk group) however they will not form a direct comparator group due to the inherent differences in their risk profile. For example, with 660 patients and 16 ipsilateral breast disease events, a 2.4% ipsilateral breast disease rate with 95% CI 1.4-3.9% can be estimated.

12.2. Treatment Allocation

There is no randomised treatment allocation, all registered patients will be directed to receive radiotherapy or not depending on their IHC4+C assigned risk category. Patients with a <5% probability of local relapse at 10 years (very low risk) will be directed not to receive radiotherapy.

12.3. Endpoint Definitions

12.3.1. Primary endpoint

Any ipsilateral breast disease rate (defined as invasive and/or non-invasive disease (DCIS) in the ipsilateral breast).

12.3.2. Secondary endpoints

- Regional relapse rate (regional relapse is defined as invasive relapse within the axilla, supraclavicular fossa and internal mammary chain)
- Distant relapse rate
- Ipsilateral invasive breast disease rate (defined as invasive disease in the ipsilateral breast)
- Contralateral invasive breast second primary cancer rate
- Any contralateral breast disease rate (defined as invasive and/or non-invasive disease (DCIS) in the contralateral breast).
- Ipsilateral invasive breast local relapse rate (subject to availability of tumour profiling data)
- Ipsilateral invasive breast second primary cancer rate (subject to availability of tumour profiling data)
- Invasive disease free survival defined as time from registration to first event where event can be any invasive local recurrence, regional recurrence, distant recurrence, second primary cancer or death from any cause.

- Breast cancer specific survival defined as time from registration to first event where event can be local recurrence, regional recurrence, distant recurrence, breast second primary or breast cancer death. Death from unknown cause would be classed conservatively as breast cancer death.
- Overall survival defined as time from registration to death from any cause

12.3.3. Exploratory endpoints

- Completeness and accuracy of routinely collected record linked data compared with data collected directly from participating hospitals.
- Estimation of disease-related outcomes as defined above using routine data for patients entered into the main trial. For patients pre-screened but who do not subsequently enter the trial the starting point for these endpoints would be the date of pre-screening.

12.4. Statistical Analysis Plan

Time from registration to ipsilateral breast disease will be analysed using survival analyses methods (e.g. Kaplan Meier graphs) and will include all patients registered to the study (i. by protocol directed treatment recommendation and ii. By treatment received). Patients who have a regional or distant relapse, second cancer or death event prior to an ipsilateral breast disease event will be censored at the date of this event. Ipsilateral breast disease rate estimates at 5 years will be reported with 95%CIs. Rates in patients allocated to avoid radiotherapy and those who are allocated to radiotherapy will not be formally compared. The probability of the true rate of local relapse not being greater than 5% by 5 years will also be presented.

Secondary disease related endpoints will be analysed using the same methodology as for the primary endpoint. Estimates at 5 and 10 years will be reported with 95%CIs. Rates in patients allocated to avoid radiotherapy and those who are allocated to radiotherapy will not be formally compared. Patients who have had a previous contralateral breast cancer are eligible for the study but will not be included in the analysis of contralateral breast second primary cancer rates. In addition to the ITT analysis of the other secondary endpoints, a sensitivity analysis will exclude patients who have had a previous contralateral breast cancer.

Routinely collected record-linked, baseline, treatment and disease-outcome data will be compared with local centre data completion via eCRFs. Concordance between data sources will be presented by reporting the proportion of patients with matching data between the CRF and relevant routine data items. The definition of what is classed as matching will vary for each data item (e.g. some dates could have acceptable time-windows) and will be specified in the Statistical Analysis Plan. In addition, routinely collected baseline and treatment data will be tabulated for patients who enter pre-screening but not the main trial. Disease related outcomes will also be analysed using survival analysis methods and the proportion event-free at 5 and 10 years will be reported by type of follow-up (CRF or routine data). The absolute differences and corresponding 95%CIs between methods will then be calculated for patients entering the main trial.

Further details of analysis methods will be specified in a Statistical Analysis Plan in accordance with ICR-CTSU Standard Operating Procedures.

12.5. Interim Analyses and Stopping Rules

Whilst the primary endpoint includes non-invasive ipsilateral disease, the IDMC will be guided by stopping rules that include invasive disease only. The IDMC will review the emerging ipsilateral

invasive breast disease rates in all cohorts and monitor ipsilateral invasive breast disease rates in the no radiotherapy cohort in particular to ensure that observed interim rates within this cohort are consistent with an overall ipsilateral invasive breast disease rate of ≤1% per year. At each relevant interim analysis, the conditional power of the "final" ipsilateral invasive breast disease rate being ≤1% given the "current" interim analysis ipsilateral invasive breast disease rate will be calculated to help inform the IDMC. This interim monitoring will permit early stopping of the study if evidence emerges that observed incidence of ipsilateral invasive breast disease is higher than expected. The timing of interim analyses will take into account the number of patient-years of follow-up accrued. Whilst it is expected that absolute rates will be the determining measure of ipsilateral invasive breast disease, consideration will also be given to the comparison of the rates of contralateral new breast cancer versus ipsilateral invasive breast disease.

The first interim analysis is anticipated after two years of recruitment and then annually until the primary endpoint analysis. In addition to monitoring ipsilateral invasive breast disease rates, the IDMC will monitor the proportion of patients calculated as "very low" risk according to IHC4+C and rates of non-compliance.

12.6. Planned meta-analysis

A meta-analysis has been agreed in principle with the Canadian LUMINA trial http://clinicaltrials.gov/show/NCT01791829, which has a similar biomarker directed cohort design.

13. TRIAL MANAGEMENT

13.1. 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 (Senior) 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 a lay/consumer representative. 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 PRIMETIME study. The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSU.

13.2. Trial Steering Committee (TSC)

The study will be overseen by the generic ICR-CTSU Breast Radiotherapy Trial Steering Committee (TSC) which comprises 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 study on behalf of the Sponsor and funder. The Committee's terms of reference, roles and responsibilities will be defined in charter issued by ICR-CTSU.

13.3. 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 Chairman 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 data 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.

14. RESEARCH GOVERNANCE

14.1. Sponsor Responsibilities

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

As per the definition in the Research Governance Framework the ICR is responsible for confirming the proper arrangements to initiate, manage, monitor and finance the study.

14.2. Chief Investigator's Responsibilities

Responsibilities delegated to the Chief Investigator are defined in an agreement between the Sponsor and the Chief Investigator's host institution.

14.3. Participating Site Responsibilities

Responsibilities delegated to participating sites are defined in an agreement between the Sponsor and the individual site.

15. STUDY ADMINISTRATION & LOGISTICS

15.1. Site activation

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

Sites may commence recruitment once the site agreement has been signed by all required signatories, the required study 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.

15.2. Data Acquisition

Electronic (e)Case Report Forms (CRF) and routine datasets will be used for the collection of study data. ICR-CTSU will provide guidance to sites to aid the completion of 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.

The clinical data should be reported on the PRIMETIME eCRFs in a timely manner. Specific guidance on how data will be collected will be detailed in trial guidance notes. On review at ICR-CTSU missing data will be reported to the originating site.

15.3. 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.

15.4. On-Site Monitoring

If a monitoring visit is required, ICR-CTSU will contact the site to arrange the visit. Once a date has been confirmed, the site should ensure that full patient notes of participants selected for source data verification are available for monitoring.

ICR-CTSU staff conducting on-site monitoring will review essential documentation and carry out source data verification to confirm compliance with the protocol. If any problems are detected during the course of the monitoring visit, ICR-CTSU will work with the Principal Investigator or delegated individual to resolve issues and determine appropriate action.

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

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

15.6. Archiving

Essential study documents should be retained according to local policy. Documents should be securely stored and access restricted to authorised personnel.

16. PATIENT PROTECTION AND ETHICAL CONSIDERATIONS

16.1. Study Approvals

This study has been formally assessed for risk by ICR-CTSU.

ICR-CTSU, on behalf of the Sponsor, will ensure that the study has received ethics approval from a research ethics committee for multi-centre studies and applicable NHS Permissions. Before entering patients, the Principal Investigator at each site is responsible for submitting site specific information and gaining local Research and Development approval of this protocol.

16.2. Study Conduct

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

16.3. Informed Consent

There are two stages of informed consent involved in the PRIMETIME study.

1. **PRIMETIME PRE-SCREENING**

Patients are first approached following initial diagnosis of invasive breast cancer. At this stage patients are asked to provide written informed consent to donate tissue samples for research testing and for linkage to routine data sources.

2. **PRIMETIME MAIN STUDY**

Following a patient's definitive surgery, potential candidates are approached to provide written informed consent to participate in the PRIMETIME study. In both instances, patients should be asked to sign the current REC approved consent form after receiving both verbal and written information, having been given sufficient time to consider this information. All consent forms must be countersigned by the Principal Investigator or a designated individual. 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 PRIMETIME main study patient information sheets Version A or Version B and decision aid video should be provided in addition to any standard patient information sheets that are provided by the site and used in routine practice.

16.4. Patient Confidentiality

Patients will be asked to consent to their full name, date of birth, hospital number, postcode and NHS number or equivalent being collected at pre-screening registration to allow linkage with routinely collected NHS data and to ensure accuracy in handling biological samples..

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

Representatives of ICR-CTSU, the participating hospital trust, the MREC, and other applicable regulatory authorities will require access to participants' hospital notes for quality assurance purposes. ICR-CTSU will maintain the confidentiality of participants at all times and will not reproduce or disclose any information by which participants could be identified, other than in the ways defined in the patient information sheet and consent form.

16.5. Data Protection

ICR-CTSU will comply with all applicable data protection laws.

16.6. Liability

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

17. FINANCIAL MATTERS

This study is investigator designed and led and has been approved by the Population Research Committee (PRC) of Cancer Research UK.

ICR has received funding from Cancer Research UK for the central coordination of the study. The study 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 study is part of the National Institute for Health Research Clinical Research Network (NIHR CRN) portfolio. NIHR CRN resources should therefore be made available for the study to cover UK specific service support and research costs, where appropriate.

18. PUBLICATION POLICY

The main study 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 study 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.

No investigator may present or attempt to publish data relating to the PRIMETIME study without prior permission from the TMG. It is not envisaged that individual sites would attempt to publish their own results separately from the main study.

As per ICR-CTSU standard practice a statement thanking study participants for their participation will be included in the study publication.

19. ASSOCIATED STUDIES

19.1. Translational study

Subject to patients' written informed consent, archival tissue samples (FFPE blocks) of primary tumour collected at the time of a patients' surgery will be collected for patients registered into the PRIMETIME study. Available samples from subsequent disease relapses or new primary cancers will also be requested, where applicable.

Tissue samples are prospectively collected for use in future translational sub-studies which will be defined separately.

19.2. Information Giving Study

The Information Giving Study involves the introduction of a patient decision aid, in the form of a patient information video which is watched by the patient in addition to the written patient information sheets. The patient will be asked to complete a single questionnaire once they have decided whether or not to participate in the PRIMETIME study.

The Information Giving Study investigates whether the decision aid video will reduce patients' decisional conflict (patient uncertainty) regarding whether or not to participate in the PRIMETIME study. All centres recruiting to PRIMETIME will participate in the PRIMETIME Information Giving Study.

The Information Giving Study will utilise a 'cluster stepped-wedge trial design'. Details of how sites are allocated to a cluster and more detail on the design of the Information Giving Study are included in Appendix A6.

All clusters will begin in Group A. In Group A, all patients receive the PRIMETIME main study patient information sheet, Version A. Patients will be asked to complete Questionnaire A after they have decided whether or not to participate in PRIMETIME.

All clusters will subsequently switch to Group B. The timing of the switch from Group A to Group B is allocated by the ICR-CTSU, as described in Appendix A6. Clusters will therefore be informed by ICR-CTSU when to switch from Group A to Group B.

Please Note – sites should not make patients aware of the availability of the video before the switch over date.

Once a cluster has switched to Group B they will use the PRIMETIME main study patient information sheet Version B in conjunction with the decision aid video, as described in Appendix A6. Patients will be asked to complete Questionnaire B after they have decided whether or not to participate in PRIMETIME.

20. REFERENCES

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APPENDICES

A1. GLOSSARY

AE	Adverse Event
CI	Chief Investigator
CIS	Carcinoma In Situ
eCRF	Electronic Case Report Form
DCF	Data Capture Form
DFS	Disease Free Survival
EORTC	European Organisation for Research and Treatment of Cancer
HR	Hazard Ratio
ICR	The Institute Of Cancer Research
IDMC	Independent Data Monitoring Committee
MDT	Multi-disciplinary team
PI	Principal Investigator
PIS	Patient Information Sheet
R&D	Research and Development
RCT	Randomised controlled trial
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
WHO	World Health Organisation

A2. QUALITY ASSURANCE PROGRAMME

A radiotherapy quality assurance programme is an integral component of any radiotherapy trial. The NCRI Radiotherapy Trials Quality Assurance (RTTQA) group will be responsible for implementing and coordinating the PRIMETIME Radiotherapy Quality Assurance (RTQA) programme.

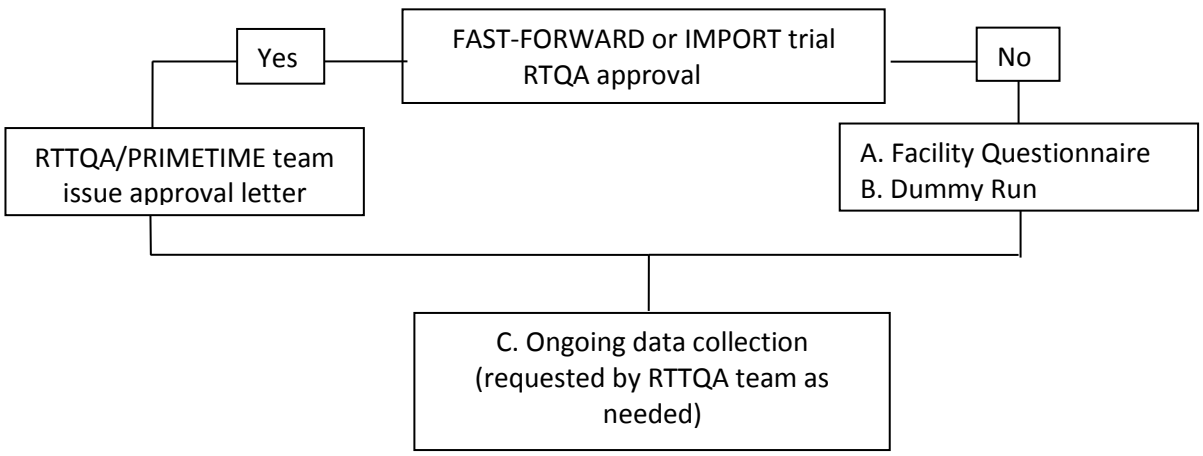
The planning and delivery of radiotherapy for the PRIMETIME study will reflect radiotherapy practice developed as part of the IMPORT and FAST-Forward trials which represent the modern standard for breast cancer radiotherapy practice in the UK.

The PRIMETIME Radiotherapy Quality Assurance (RTQA) programme:

The PRIMETIME RTQA programme is comprised of two parts, a pre-study and an on-study component. In light of the comprehensive RTQA programmes associated with the afore mentioned radiotherapy breast cancer trials, radiotherapy centres may be eligible to undertake a streamlined pre-study RTQA programme based on participation in the IMPORT or FAST-Forward trials.

If a radiotherapy centre has undertaken and received pre-trial QA approval for either the IMPORT or FAST-Forward trials, centres will be granted RTTQA approval without any additional QA procedures requested.. If a centre has not previously undertaken and received pre-trial RTQA approval for either the IMPORT of FAST-Forward trial, a centre will be required to complete a facility questionnaire and submit a 'dummy run' case for review by RTTQA.

Flow diagram summarising RTQA review for PRIMETIME:



*Additional information may be requested by RTTQA.

PRE- STUDY QA:

A. Facility Questionnaire

The Facility Questionnaire must be completed by a member of the radiotherapy staff and submitted to the QA team. The questionnaire will cover details of treatment technique, immobilisation, verification and dosimetry.

B. Dummy Run

Centres should choose one of their own patients to submit to the RTTQA group for technique review. A patient, where the breast only has been treated with radiotherapy, should be selected (please refer to section 9.2).

ON STUDY QA:

C. Ongoing data collection

Radiotherapy plans (CT data, structure set, plan and dose files) may be collected electronically by the QA team if requested by the PRIMETIME study team, TMG or IDMC based on the recurrence rates seen in the study.

Analysis of Radiotherapy data for QA programme

The radiotherapy data from the quality assurance programme may be analysed independently from the main study. Discrepancies from standard of care treatment will be audited and discussed with the chief investigator and participating centres.

A3. Why is this the preferred design of PRIMETIME?

A cohort based study design is proposed in preference to a randomised controlled trial (RCT) testing breast radiotherapy (RT) versus no RT. Such a design is considered preferable for several reasons:

(i) The effect of RT in reducing ipsilateral breast disease risk after breast conservation surgery for early breast cancer (rate ratio at 10 years 0.40, SE 0.09) has been fully quantified by RCTs involving 8000 women and >10 years of follow up (1). The proposed design focuses exclusively on testing the *need* for RT in a patient population considered to have such a low risk of local recurrence that the potential absolute gain from RT is considered so small as to not outweigh the established risks associated with breast RT.

(ii) A review of the worldwide evidence would suppose that - within an appropriately defined low risk patient population - a cohort of patients treated with surgery and endocrine therapy (as standard) but without RT, would result in local control rates which may be a little higher than what would have been observed if all patients had received RT but given the salvageable nature of such relapses would be expected not to have an adverse impact on long term disease-free and overall survival. Designing a randomised trial to assess such outcomes would result in a trial requiring a large number of patients, with expected challenges associated with randomisation and follow up over many years

(iii) Conducting a study whereby one defines the limits of acceptability for the upper threshold for 5 year ipsilateral breast disease rate without RT, is deemed preferable and of greater clinical utility by health care practitioners and patient advocates. This concept has been employed previously in breast cancer trials [26]. The concept has also been discussed and developed with UK clinicians and patient advocates, with a recent survey of UK Breast Intergroup members (September 2014) survey showing more than 90% (50/55) support for a case-cohort design. In addition, the case-cohort design has unanimous support from the NCRI Breast Clinical Studies Group (discussed June & November 2014).

(iv) RCTs testing treatment versus no treatment are difficult to implement, since patients often express have strong preferences. For example, the PRIME RCT randomising women to breast conserving surgery with and without RT recruited 255 patients over 6 years and accrual was challenging, at least in part, by unwillingness of patients to be randomised [27, 28]. The original design was amended to allow non-randomised patients who requested omission of RT to be followed up within a cohort design, which improved recruitment. This challenge of randomising patients to trials of +/- therapy is further illustrated by the ACTION trial, which attempted to randomise patients 70 years or over to breast conserving surgery with and without chemotherapy [29, 30]. The trial failed to recruit with only 4 patients entered and closed early due to patients' declaring strong treatment preferences and being unwilling to accept the uncertainty of randomisation.

(v) The chosen design should facilitate rapid accrual, as there will be no issues of patient acceptance of the uncertainties of randomisation. Instead the patients will be informed that based on their clinic-pathological features they are considered likely to be at very low risk of an ipsilateral breast disease event and may be able

to safely avoid RT. Patients entering the study will be those who consent to have recommendations for their need for RT treatment determined by a biomarker test (used to supplement clinical information) to refine their perceived risk, including the option to recommend standard RT in the case that the biomarker test suggests the patient cannot be deemed very low risk.

(vi) The Canadian cohort study LUMINA (n=500) has a similar design to that proposed for PRIMETIME. This 500 patient study (http://clinicaltrials.gov/show/NCT01791829) is open to recruitment. Discussions with the Chief Investigator, Professor Timothy Whelan recognise the relatively small size of the LUMINA, including its limited power to support investigation of additional prognostic markers, and the future value of an individual patient meta-analysis of the Canadian and UK cohorts in due course (funding dependent).

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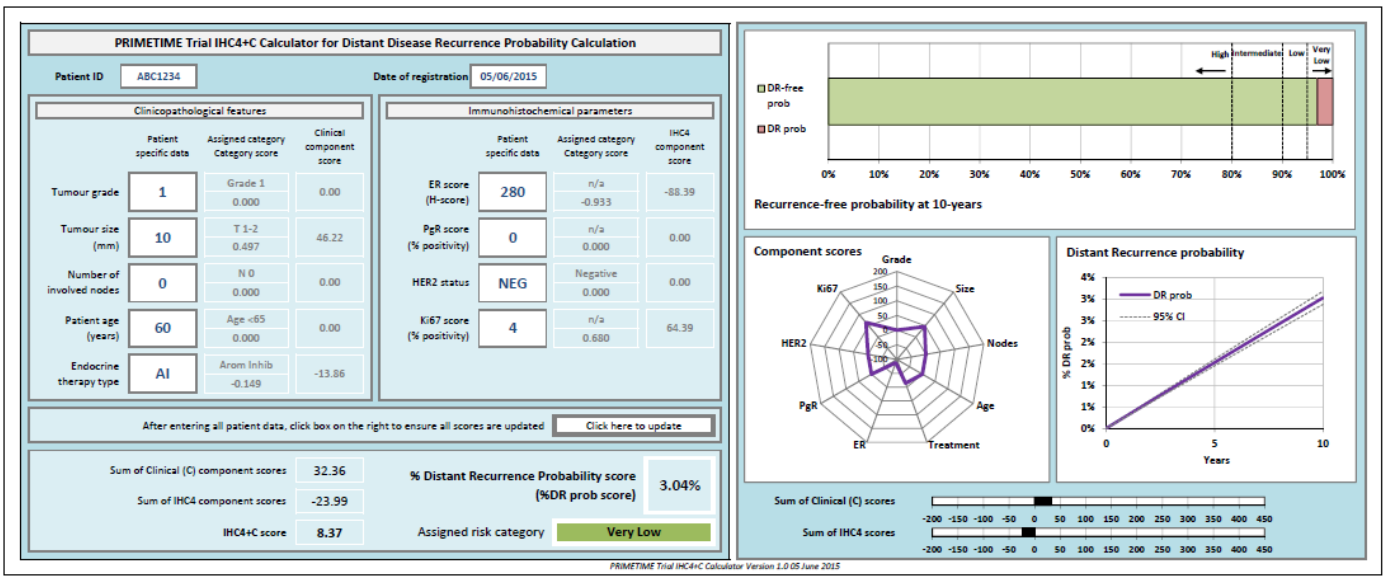
A4. IHC4+C CALCULATOR – EXAMPLE

All clinicopathological data (tumour grade, tumour size, number of nodes involved, patient age, planned endocrine therapy type) and immunohistochemical data (ER, PR and HER2) required to calculate a patient's IHC4+C score will be provided by the local centre to ICR-CTSU at the time of a patient's registration into the PRIMETIME study. In addition, ICR-CTSU will use the patient's Ki67 result obtained during PRIMETIME pre-screening from the relevant central laboratory to complete the IHC4+C calculation.

Each data point will be entered into the PRIMETIME IHC4+C calculator, embedded in the PRIMETIME registration system, as per the example below.

The local centre will be informed of the resulting risk category at registration and a summary of the patient-specific clinicopathological data used to calculate the IHC4+C score will be provided to the centre following registration. A copy of the below schematic representation of the scoring is available on request. Please refer to the Study Guidance Notes for more information.



A5. PRIMETIME Information Giving Study (IGS) Protocol

BACKGROUND

Patient uncertainty regarding de-escalation of treatment studies

PRIMETIME is investigating whether we can identify a highly selected group of women with a very low risk of the breast cancer returning, for whom the side effects of radiotherapy may outweigh the benefits and adjuvant breast radiotherapy can be safely avoided. Research studies are conducted when there is uncertainty regarding the optimal treatment option. Furthermore patients may experience uncertainty regarding whether to participate in a clinical trial. This uncertainty may be compounded in a de-escalation of treatment study where a component of standard treatment is omitted. The state of uncertainty regarding which course of action to take in health-care-related decisions is known as decisional conflict [1]. Defining characteristics of decisional conflict include voicing uncertainty, hesitation between choices, delayed decision making and questioning personal values (personal importance of outcomes) and beliefs when attempting decision making [1]. A number of factors are thought to contribute to decisional conflict which include lack of information regarding alternative treatments and consequences, unclear patient values and the lack of skills to make or implement decisions [1]. Reducing patient uncertainty may facilitate the decision making process for patients.

Use of decision aids to manage patient uncertainty

One way of optimising decision making for patients who face uncertainty is to use decision aids. Decision aids may help patients understand the benefits and risks of treatment options, consider the value they place on benefits and risks and participate actively with their clinicians in deciding treatment options. A Cochrane review of decision aids for people facing health treatment or screening decisions [2] found high quality evidence that decision aids improved patient knowledge regarding treatment options (using study specific questionnaires) and reduced their decisional conflict. There is also evidence that decision aids encourage patients to take a more active role in decision making and improve accurate perceptions of risk. A meta-analysis of cancer related decision aids for patients entering randomised controlled trials demonstrated that patients receiving decision aids had reduced decisional conflict [3].

The IBIS II trial investigated the use of a decision aid in a randomised controlled trial of an aromatase inhibitor in two patient groups; patients at high risk of breast cancer (prevention

group) and patients with Ductal Carcinoma In Situ (DCIS) (treatment group). The authors found there was no difference in their primary outcome of decisional conflict however patients who received the decision aid in the 'treatment' group had higher knowledge post decision compared with patients who did not receive the decision aid. In the 'prevention' group patients who received the decision aid had lower decisional regret at follow-up compared with those who did not receive the decision aid [4]. A study involving women aged 70 or above with stage 1 breast cancer considering radiotherapy after lumpectomy found after using a decision aid that patients had a statistically significant reduction in decisional conflict, increased clarity of the benefits and risks and improved general treatment knowledge [5]. Both studies described are both small single centre studies.

It is not known whether the introduction of a decision aid video in addition to written patient information will reduce decisional conflict within the context of the PRIMETIME study where the risks and benefits of radiotherapy are being discussed and the concept of treatment de-escalation is being introduced. This requires assessment within the context of a prospective research study.

Design of the PRIMETIME Information Giving Study

We propose to introduce a decision aid (in video format) in addition to written patient information, in order to optimise the decision making process for patients who are considering participating in PRIMETIME. The study will investigate the effect of the decision aid on patients' decisional conflict regarding their decision of whether or not to participate in the PRIMETIME main study.

We plan to use a 'study within a trial' approach or 'SWAT' as this can assess different ways of designing, conducting, analysing and evaluating studies through the conduct of research within research [6]. A cluster stepped-wedge trial design will be used for the PRIMETIME Information Giving Study. A cluster stepped-wedge trial consists of the sequential implementation of an intervention (the decision aid video) to participants (or in the case hospital sites) grouped within clusters over a number of time periods [7]. An example of a cluster is a group of hospitals under one National Health Service trust. All clusters will receive the intervention by the end of the study however the order in which clusters initiate the intervention is determined at random [7]. In general, cluster stepped-wedge trials are designed to study the effects of a new intervention implemented at cluster level, but which is experienced and measured at the individual patient level [8]. The justification for

implementing the decision aid video at cluster level is to ensure all patients being treated at a study centre will receive the same information (either written patient information or written patient information in conjunction with video) over pre-specified time periods. If the decision aid was implemented at individual patient level then patients in a centre may discuss the different formats of information they are receiving. This may compromise the interpretation of decisional conflict.

We hypothesise that the decision aid video in addition to written patient information will reduce decisional conflict and the stepped-wedge trial design ensures that by the end of the PRIMETIME Information Giving Study all clusters will have used the decision aid. Furthermore, in a cluster stepped-wedge trial each cluster acts as its own control, increasing the statistical power of the study.

If the PRIMETIME Information Giving Study demonstrates that the introduction of a decision aid can reduce decisional conflict regarding entry into the PRIMETIME main study, this may provide evidence to support increasing resources into the development of decision aids for de-escalation of treatment studies.

STUDY POPULATION

Patients who are approached for the PRIMETIME main study will be eligible for the PRIMETIME Information Giving Study.

STUDY OBJECTIVES

Primary objective;

- To assess whether the introduction of a decision aid video in addition to written patient information reduces patients' decisional conflict.

Secondary objectives;

- Acceptance of entry into the PRIMETIME main study ie. the proportion of participants who consented to the PRIMETIME main study of all patients who were eligible for and given information about the PRIMETIME main study.

- Acceptance of recommended treatment in the PRIMETIME main study ie. the proportion of patients who accepted their recommended treatment of all patients who consented to the PRIMETIME main study

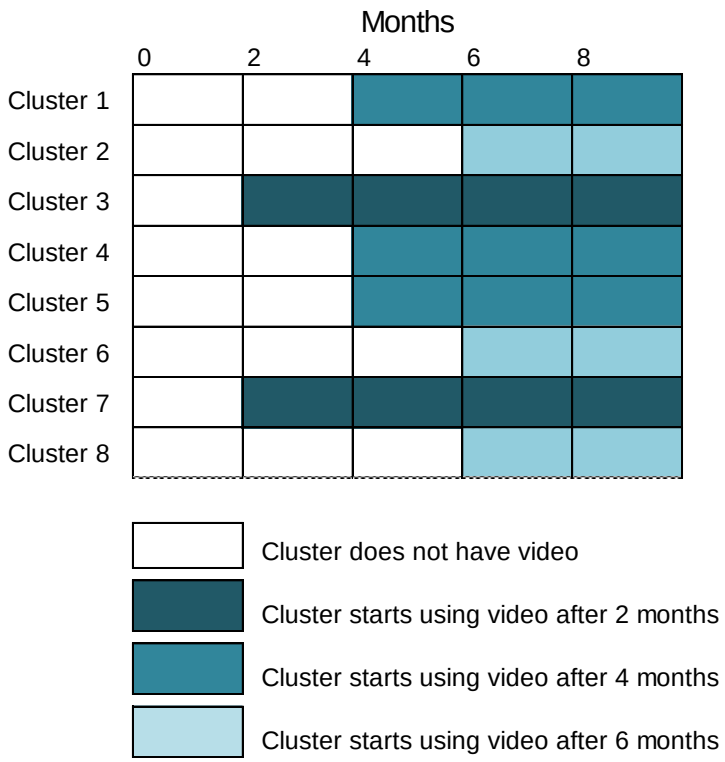
STUDY DESIGN

All centres open to recruitment for PRIMETIME will be included in the PRIMETIME Information Giving Study. The PRIMETIME Information Giving study will open in each centre when the first patient in that centre consents to the PRIMETIME Information Giving Study.

In addition to the written PRIMETIME main study patient information sheet that patients already receive, phased implementation of the decision aid video will take place using a cluster randomised stepped-wedge approach. A cluster consists of the radiotherapy centre and any peripheral centres referring into the radiotherapy centre. Each cluster will receive the PRIMETIME main study patient information sheet and be randomised to receiving the decision aid video at 2, 4, or 6 months after the first patient within the cluster consents to the PRIMETIME Information Giving Study.

Allocation to which time point the cluster will start using the decision aid will be by minimisation (balanced on level of recruitment per centre in previous breast radiotherapy trials) and be performed by the ICR-CTSU. Based on experience with ICR-CTSU trials, clusters included in the PRIMETIME Information Giving Study will be categorised into 'high' versus 'low' recruiters according to average number of patients recruited per month in previous ICR-CTSU trials (eg. the IMPORT HIGH and FAST FORWARD). Recruitment to previous breast radiotherapy trials has been chosen to ensure that higher recruiting centres do not all receive the decision aid at the same time point. The justification for delaying when the intervention will commence is to ensure that there are sufficient participant numbers for the assessment of decisional conflict prior to and after introduction of the decision aid video.

Figure 1: Proposed implementation of PRIMETIME Information Giving Study using a Cluster Stepped-Wedge Trial design



All clusters will begin the study in Group A and switch over to Group B at either 2, 4 or 6 months from when the first patient per cluster enters the PRIMETIME Information Giving Study. Group A will be given Version A of the PRIMETIME main study patient information sheet. Group B will be given Version B of the PRIMETIME main study patient information sheet. The description of the PRIMETIME Information Giving Study will differ between Version A and B with Version B specifying that patients will be provided with a video. This will be the only difference between Version A and B of the PRIMETIME main study patient information sheet.

Please Note – sites should not make patients aware of the availability of the video before the switch over date.

Group A

In Group A clusters, participants will have a discussion with a healthcare professional and be provided with Version A of the PRIMETIME main study patient information sheet. After the patient has made their decision regarding entry into PRIMETIME, they will be presented with Questionnaire A which includes baseline demographics, questions regarding the information provided and the decisional conflict questionnaire [1]. Return of the Questionnaire indicates consent to the PRIMETIME Information Giving Study.

Group B

In Group B clusters, participants will have a discussion with a healthcare professional and be provided with Version B of the PRIMETIME main study patient information sheet and given access to the decision aid video. The video must be viewed after the consultation with the healthcare professional and after the patient has read the PRIMETIME main study patient information sheet. The video must also be viewed prior to the patient making their decision regarding entry into the PRIMETIME main study. After the patient has made their decision regarding entry into PRIMETIME, they will be presented with Questionnaire B which includes baseline demographics, questions regarding the information provided and the decisional conflict questionnaire [1]. Return of the Questionnaire indicates consent to the PRIMETIME Information Giving Study.

ENDPOINTS

Primary Endpoint

The primary endpoint for this study is decisional conflict as measured on the decisional conflict scale [1].

Secondary Endpoints;

- Acceptance of entry into the PRIMETIME main study ie. the proportion of participants who consented to the PRIMETIME main study of all patients who were eligible for and given information about the PRIMETIME main study.

- Acceptance of recommended treatment in the PRIMETIME main study ie. the proportion of patients who accepted their recommended treatment of all patients who consented to the PRIMETIME main study.

FOLLOW-UP

There is no additional follow-up required for the PRIMETIME Information Giving Study.

STATISTICAL CONSIDERATIONS

Statistical design and sample size justification

The target sample size for the PRIMETIME Information Giving Study is 264 patients. This sample size is based on three steps in the cluster stepped-wedge trial design (at 2, 4 and 6 months) of 33 clusters (11 per step), with 2 patients per cluster per 2 month period. There is limited literature on what is a clinically significant reduction in decisional conflict. Two small single centre studies conducted in similar populations to patients in PRIMETIME found effect sizes around 0.40, with standard deviations for the total Decisional Conflict Scale score ranging from 11-25 [4,5]. As this is a cluster randomised trial, the sample size estimation needs to allow for possible clustering effects. However there is no data available on likely values of the intraclass correlation (ICC) for the Decisional Conflict Scale, and so estimates have been calculated across the range of ICC values from 0 to 1. Assuming an alpha of 0.05, 264 patients from 33 clusters would have at least 80% power for all values of the ICC to detect a 10-point difference in total score for the Decisional Conflict Scale (effect size=0.55, assuming standard deviation=18). If this target is not achievable, then 240 patients from 30 centres would provide at least 80% power to detect an effect size of 0.55 across most of the range of ICC values. The figure below illustrates the power for different scenarios according to value of ICC and number of clusters (with total number of patients also shown).

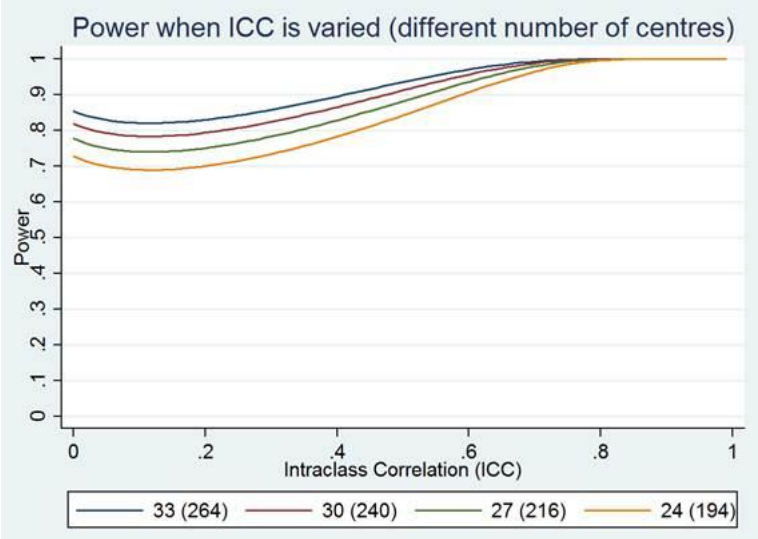


Figure 2: Power when intraclass correlation is varied

Treatment allocation

Each cluster will receive the PRIMETIME main study patient information sheet. Each cluster will be allocated to receive the PRIMETIME main study patient information sheet and

decision aid video at 2, 4 or 6 months from when the first patient consents to the PRIMETIME Information Giving Study. All centres within a cluster will be allocated to receiving the decision aid at the same time point. Clusters will be allocated using minimisation performed by the ICR-CTSU. Each cluster will be allocated a status of high versus low recruiter based on their recruitment into previous ICR-CTSU trials (eg.IMPORT HIGH and FAST FORWARD), and recruitment stratum used as a balancing factor in the minimisation.

STATISTICAL ANALYSIS PLAN

The data will be analysed on the intention to treat (ITT) analysis set. According to the intention to treat principle, clusters will be analysed according to randomised decision aid video start time regardless of when the cluster started using the decision aid video [9].

Primary endpoint

Only patients who return questionnaires (i.e. consent to the PRIMETIME Information Giving Study) will be analysed, regardless of whether they consent to participate in the PRIMETIME main study.

The mean decisional conflict score pre- and post-implementation of the decision aid video will be calculated (with 95% confidence interval). Calendar time is a possible confounder and therefore any effect seen could be (partly or in full) due to underlying temporal trend [9]. To adjust for calendar time and clustering the methods detailed in Hussey and Hughes [10] will be followed, where a linear mixed model will be fitted with a random effect for cluster and a fixed effect for each step.

A sensitivity analysis will be performed to compare the decisional conflict of those who stated they watched the decision aid video (in Questionnaire B) compared to those who stated they did not watch the decision aid video (in Questionnaire B) and those who were not in a cluster using the decision aid video (i.e. were given Questionnaire A to complete).

Secondary endpoints

Acceptance of PRIMETIME main study entry - all participants who were given information and were eligible to enter the PRIMETIME main study will be analysed. This follows an ITT

analysis where patients will be analysed according to the information (PRIMETIME main study information sheet versus PRIMETIME main study information sheet and decision aid video) their cluster was assigned to at that step. Therefore patients will be included regardless of whether they returned a questionnaire.

A sensitivity analysis will be performed to compare the acceptance of PRIMETIME main study entry in patients who stated they watched the decision aid video (in Questionnaire B) compared to those who stated they did not watch the decision aid video (in Questionnaire B) in addition to those who were not in a cluster using the decision aid video (i.e. were given Questionnaire A to complete).

Acceptance of recommended treatment in patients consenting to the PRIMETIME main study - all participants who were recruited into the main PRIMETIME main study will be analysed. This follows an ITT analysis where patients will be analysed according to the information (PRIMETIME main study information sheet versus PRIMETIME main study information sheet and decision aid video) their cluster was assigned to at that step. Therefore patients will be included regardless of whether they returned a questionnaire.

A sensitivity analysis will be performed to compare the acceptance of recommended treatment in patients consenting to the PRIMETIME main study in patients who stated they watched the decision aid video (in Questionnaire B) compared to those who stated they did not watch the decision aid video (in Questionnaire B) in addition to those who were not in a cluster using the decision aid video (i.e. were given Questionnaire A to complete).

Both secondary endpoints will be analysed using a logistic regression model with a cluster level fixed effect for assigned group at that step (PRIMETIME main study information sheet versus PRIMETIME main study information sheet and decision aid video), with a random effect for cluster and a fixed effect for each step [9, 10].

An interim analysis to review emerging data is planned in the first quarter of 2019 and will include the facility to include data in a confidential PhD thesis. The final analysis will take place once all the clusters have received the decision aid.

Data acquisition – Questionnaires will be completed at each centre by the patient and then posted back to the ICR-CTSU for data entry onto the PRIMETIME Information Giving Study database.

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