optima

personalised treatment of breast cancer

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ABBREVIATIONS

Abbreviation	Explanation
AE	Adverse Event
AI	Aromatase inhibitor
BCSS	Breast cancer specific survival
C	Cyclophosphamide
CHI	Community Health Index
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CSG	Clinical Studies Group
D	Day
dd	dose dense
DCIS	Ductal carcinoma in situ
DEXA	Dual energy X-ray absorptiometry
DRFI	Distant recurrence free interval
DRFS	Distant recurrence free survival
E	Epirubicin
ER	Oestrogen receptor
F	Fluorouracil
FACT-B	Functional Assessment of Cancer Therapy for breast cancer patients
FDA	Federal Drug Authority
FNA	Fine needle aspiration
FFPE	Formalin fixed paraffin embedded
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
G-CSF	Granulocyte - Colony Stimulating Factor
GDPR	(The European Union) General Data Protection Regulation
GnRH	Gonadotropin-releasing hormone
GP	General Practitioner
HER2	Human Epidermal Growth Factor Receptor 2
HRA	Health Research Authority
HRT	Hormone Replacement Therapy
HSC	Health and Social Care
HSCIC	Health and Social Care Information Centre

Abbreviation	Explanation
ICH	International Conference on Harmonisation
ICPV	Independent Cancer Patients' Voice
IDFS	Invasive disease free survival
IDMC	Independent Data Monitoring Committee
IHC	Immunohistochemistry
ISH	In-situ hybridisation
ITC	Isolated tumour cells
i.v.	Intravenous
LCIS	Lobular carcinoma in situ
LH	Luteinizing hormone
M	Methotrexate
MPEP	Molecular Pathology Evaluation Panel
MRC	Medical Research Council
NCRI	National Cancer Research Institute
NCRN	National Cancer Research Network
NEQAS	National External Quality Assessment Service
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR HTA	National Institute for Health Research Health Technology Assessment
NPI	Nottingham Prognostic Index
NSABP	National Surgical Adjuvant Breast and Bowel Project
ONS	Office of National Statistics
OPTIMA	**O**ptimal **P**ersonalised **T**reatment of early breast cancer using **M**ulti-parameter **A**nalysis
OS	Overall survival
OSNA	One-step nucleic acid amplification
p.o.	Orally
PCR	Polymerase chain reaction
PIS	Patient Information Sheet
PgR	Progesterone Receptor
PPI	Patient and Public Involvement
Pw/2w	Paclitaxel (administered weekly or 2-weekly)
q.	Every
QA	Quality assurance
QRS	Qualitative Recruitment Study

Abbreviation	Explanation
qRT-PCR	Quantitative reverse transcriptase polymerase chain reaction
RCT	Randomised controlled trial
R&D	Research and Development
REC	Research Ethics Committee
ROR	Risk of Recurrence
RS	Recurrence score
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
T	Docetaxel
TMG	Trial Management Group
TSC	Trial Steering Committee
UCL	University College London
UCLH	University College London Hospitals NHS Foundation Trust
WCTU	Warwick Clinical Trials Unit

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1. Trial Summary

<table>
<tr><td>Title:</td><td>Optimal Personalised Treatment of early breast cancer using Multi-parameter Analysis</td></tr>
<tr><td>Rationale:</td><td>Multi-parameter tumour gene expression assays (or tests) have been shown to provide superior risk predictions to conventional assessment for patients with ER-positive HER2-negative early breast cancer without lymph node metastases and are widely used to assist chemotherapy decisions for this population. Evidence to support test use for patients with higher-risk breast cancer, particularly with lymph node involvement however remains weak.

The OPTIMA trial seeks to advance the development of personalised treatment of early breast cancer by the prospective evaluation of multi-parameter assays as a means of identifying those patients who are likely to benefit from chemotherapy, whilst sparing those who are unlikely to do so from an unnecessary and unpleasant treatment, and to establish the cost-effectiveness of this approach. The OPTIMA study population is at high risk of recurrence and would ordinarily be treated with a combination of chemotherapy and endocrine therapy. The trial compares the management of patients using test-directed allocation to chemotherapy or not with standard management (chemotherapy) in a non-inferiority design. A preliminary phase of the study, OPTIMA prelim, was successfully completed. OPTIMA prelim demonstrated the feasibility of a large-scale trial and selected the test technology to be used in the main trial.</td></tr>
<tr><td>Inclusion Criteria:</td><td>

Female or male, age ≥ 40
Excised invasive breast cancer with local treatment either completed or planned according to trial guidelines.
ER positive (>10% of tumour cells stained positive) as determined by the referring site in a laboratory meeting national external quality assurance standards, and in accordance with national or ASCO-CAP guidelines.
<u>NOTE</u>: Where ER status is reported by Allred (or Quick) Score or by H-Score, tumours with high scores meet the ER-positive definition but the %staining component of the score is required to determine eligibility for intermediate-score tumours. Refer to the table for mapping.
<table>
<tr><td></td><td>Eligible (ER staining >10%)</td><td>Eligibility determined by %staining component of the score</td><td>Ineligible (ER staining ≤10%)</td></tr>
<tr><td>Allred (or Quick) Score</td><td>6, 7, or 8</td><td>4 or 5</td><td>3 or less</td></tr>
<tr><td>H-Score</td><td>>30</td><td>10-30</td><td><10</td></tr>
</table>

HER2 negative (IHC 0-1+, or ISH negative/non-amplified) as determined by the referring site in a laboratory meeting national external quality assurance standards, and in accordance with national or ASCO-CAP guidelines.
Tumour size and axillary lymph node status; one of the following must apply:
<ol type="i">
4-9 lymph nodes involved AND any invasive tumour size.
1-3 nodes involved, with at least 1 node containing a macrometastasis (i.e. deposit >2mm diameter) AND any invasive tumour size.
1-3 lymph nodes involved with micrometastases only (i.e. deposit >0.2-2mm diameter) AND invasive tumour size ≥ 20mm.
node negative AND invasive tumour size ≥ 30mm.

</td></tr>
</table>

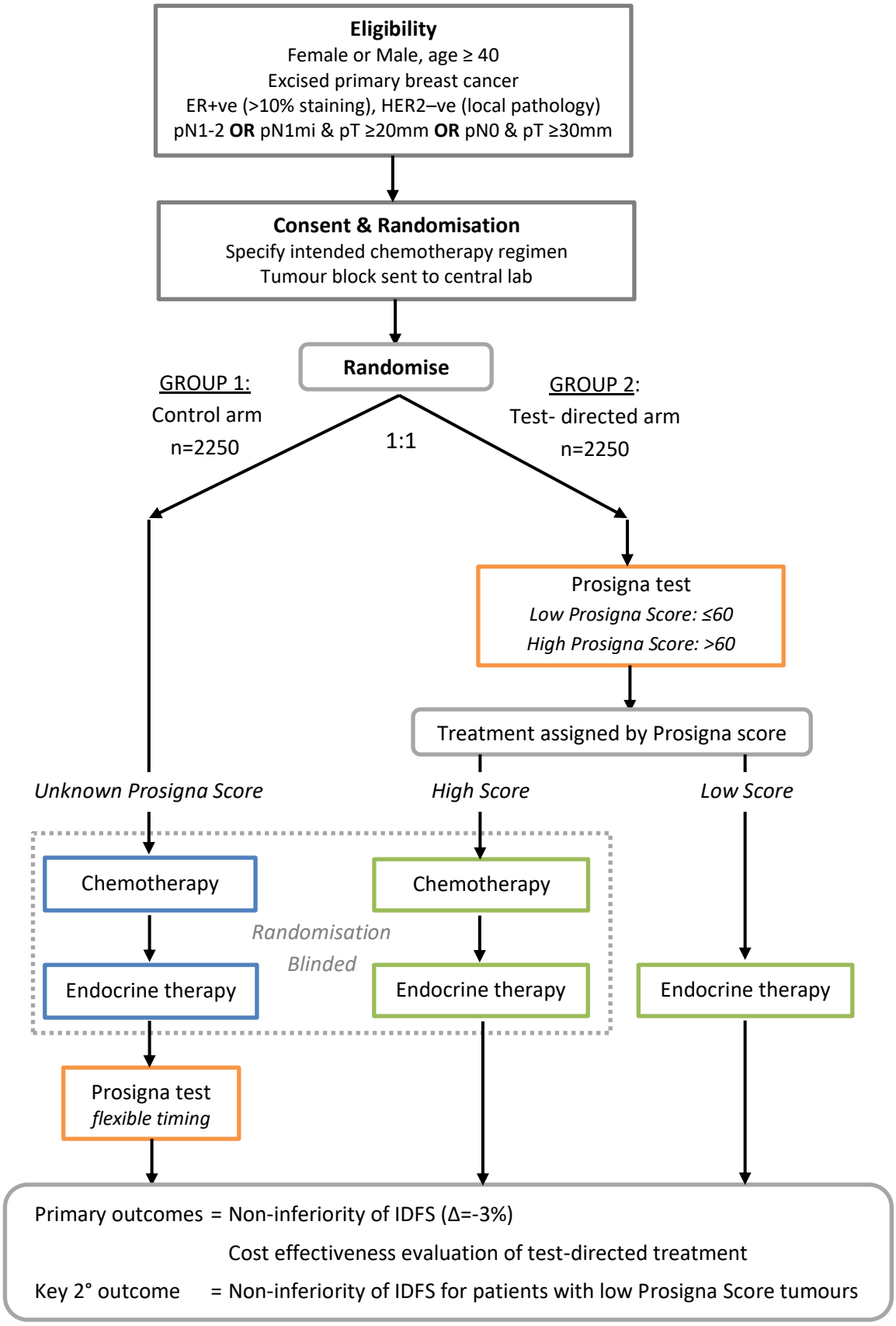
	NOTES: *a. Lymph nodes containing isolated tumour cell clusters (ITC) only (i.e. deposit ≤0.2mm diameter) will be considered to be uninvolved.* *b. Involvement of lymph nodes with macrometastases or micrometastases may be determined either by histological examination or by OSNA or equivalent PCR-based assay.* • Considered appropriate for adjuvant chemotherapy by the treating physician. • Patient must be fit to receive chemotherapy and other trial-specified treatments with no concomitant medical, psychiatric or social problems that might interfere with informed consent, treatment compliance or follow up. • Multiple ipsilateral cancers are permitted provided at least one tumour fulfils the tumour size and axillary lymph node entry criteria, and none meet any of the exclusion criteria. *NOTE: Refer below for guidance on selection of tumour blocks to be sent to the Central Laboratory.* • Bilateral cancers are permitted provided the tumour(s) in one breast meets the eligibility criteria and the other, contralateral tumour is not ER negative and/or HER2 positive and not clinically significant, defined by both of the following: i. The contralateral tumour **does not** fulfil the tumour size and lymph node eligibility criteria required for trial entry; i.e. the following are **not** acceptable: o presence of lymph node macro-metastases; o presence of lymph node micrometastases if the tumour size is ≥20mm; o tumour size ≥30mm when there is no lymph node involvement. ii. The treating physician does not consider that the characteristics of the contralateral tumour alone justify consideration of adjuvant chemotherapy. • Short term pre-surgical treatment with endocrine therapy including in combination with non-cytotoxic agents is allowed providing that the duration of treatment does not exceed 8 weeks. *NOTE: A pre-treatment core biopsy should be sent to the Central Laboratory; a sample from a surgical excision or other on-treatment biopsy is not acceptable.* • Informed consent for the study. • *NOTE: Consent must be received prior to undertaking any trial procedure. Randomisation and tumour block processing may be performed on the basis of formally documented remote verbal consent when written consent will be delayed; written consent is required before proceeding to trial-specified treatment.*
Exclusion Criteria:	• ≥10 involved axillary lymph nodes (with either macrometastases and/ or micrometastases) or evidence for internal mammary lymph node involvement. *NOTE: Internal mammary lymph nodes identified by anatomical imaging studies alone will be considered uninvolved where the diameter is <10mm.* • ER negative/low OR HER2 positive/amplified tumour (as determined by the referring site). • Metastatic disease. *NOTE: Formal staging according to local protocol is recommended for patients where there is a clinical suspicion of metastatic disease or for stage III disease (i.e. tumour >50mm diameter with any nodal involvement OR any tumour size with 4 or more involved nodes).* • Previous diagnosis of malignancy unless:

	i. managed only by surgical treatment with or without local radiotherapy AND disease-free for 10 years. ii. basal cell carcinoma of skin or cervical intraepithelial neoplasia. iii. ductal carcinoma in situ (DCIS) or pleomorphic lobular carcinoma in situ (pleomorphic LCIS) of the breast treated with surgery with or without breast radiotherapy; treatment with anti-oestrogens is not permitted. *NOTE: Isolated classical type lobular carcinoma in situ (LCIS) is not considered in this context to be a diagnosis of malignancy.* • Pre-operative anti-cancer treatments except short-term endocrine therapy administered as per the inclusion criteria. • Adjuvant systemic treatment commenced prior to trial entry* except endocrine therapy, which must be discontinued prior to starting trial-allocated chemotherapy. • Treatment with agents, including ovarian suppression, known to influence breast cancer growth but prescribed for other indications within one year of trial entry* except as follows: i. Use of oestrogen replacement therapy (HRT) provided this is stopped before surgery. ii. Drugs administered for in vitro fertilization or fertility preservation. iii. Use of hormonal contraception. • Trial entry* and randomisation more than 12 weeks after completion of breast cancer surgery. Trial entry should ordinarily be within 8 weeks of final surgery. • Planned further surgery for breast cancer, including axillary surgery, to take place after trial entry*, except either re-excision or completion mastectomy for close or positive/involved margins, which may be undertaken following completion of chemotherapy if given. *NOTE: The timing of radiotherapy to the axilla for lymph-node involvement is not restricted.* *Trial entry is dated from the earlier of participant signature of the consent form or the giving of remote verbal consent.
Hypothesis:	Tumour multi-parameter assays predict chemotherapy sensitivity. Patients with hormone sensitive primary breast cancers that have a low multi-parameter assay score do not have a meaningful chance of benefiting from adjuvant chemotherapy despite other factors that may predict for a high risk of disease recurrence.
Objectives:	1. To identify a method of selection that reduces chemotherapy use for patients with hormone sensitive primary breast cancer without detriment to recurrence and survival. 2. To establish the cost-effectiveness of test-directed treatment strategies compared to standard practice.
Trial Design:	OPTIMA is a multi-site partially blinded randomised international clinical trial with a non-inferiority endpoint and an adaptive design.
Trial arms:	**Experimental:** Test-directed assignment of chemotherapy or not, followed by endocrine therapy. **Control:** Chemotherapy followed by endocrine therapy. **Randomisation will be concealed for patients assigned to chemotherapy**
Test Technology:	Prosigna (Chemotherapy assigned according to Prosigna Score >60 vs. ≤60)

Tumour Block Testing:	Tumour blocks should be selected for testing as follows: • Patients with a unifocal tumour: a representative tumour block should be selected. • Patients who have received pre-operative endocrine treatment: a pre-treatment core biopsy should be selected. • A tumour block from a surgical excision or other on-treatment biopsy is not acceptable: treated tumours are likely to have a lower Prosigna Score than untreated tumours, which could change the treatment allocation. • Patients with multiple ipsilateral tumours: blocks from more than one lesion should be submitted to the laboratory when the lesions are considered to be clinically significant by the referring site and they are interpreted as synchronous primary cancers (based either on the site of the lesions, i.e. in different quadrants, or if they are of differing morphology, i.e. histological type or grade). It is anticipated that laboratories will, as per standard good practice, assess ER and HER2 on the different lesions. Clinical management will be based on the highest Prosigna score for patients randomised to test-directed treatment. *<u>NOTE</u>: Involved lymph nodes are not suitable for trial-specified laboratory investigation.*
Trial Treatments:	**Chemotherapy** (permitted regimens): Anthracycline non-taxane • FEC75-80 • FEC90-100 • EC90-100 • E-CMF Taxane non-anthracycline • TC Combined anthracycline-taxane • (F)EC-T • (F)EC-Pw/P2w • TAC Dose-dense • dd AC/EC-P Paclitaxel-albumen (nab-paclitaxel) may be substituted for docetaxel/ paclitaxel. Platinum salts may be added to chemotherapy regimens for patients identified as having a homologous DNA repair deficiency. **Endocrine therapy:** Endocrine therapy should be planned for a minimum of 5 years; the recommended duration is 10 years. <u>Initial treatment period (years 0-5)</u> • Postmenopausal at trial entry: aromatase inhibitor for 5 years. • Premenopausal at trial entry: tamoxifen or an aromatase inhibitor for 5 years; combined with either ovarian suppression with GnRH agonist for at least 3 years OR bilateral surgical oophorectomy. Ovarian suppression may be deferred in the event of chemotherapy-induced amenorrhoea but should be initiated for those who resume menses up to 2 years from trial entry. • Male: tamoxifen for 5 years. <u>Extended treatment period (years 6-10)</u>

	Endocrine therapy of physician's choice appropriate for sex and menopausal status up to a total of 10 years.
No. patients:	4500 patients (2250 patients per arm) *(Sample size does not include patients recruited into OPTIMA prelim)*
Stratification:	1. Country: each country will be represented as a separate category 2. Chemotherapy regimen 3. Number of involved lymph nodes 4. Histological grade 5. Tumour size 6. Menopausal status
Outcome measures:	**Primary outcomes:** • Invasive disease free survival (IDFS): non-inferiority of test-directed chemotherapy treatment and endocrine therapy compared to chemotherapy followed by endocrine treatment. • Cost effectiveness evaluation of protocol specified multi-parametric assay driven treatment against standard clinical practice. **Secondary outcomes:** • IDFS for patients with low-score tumours (defined as tumours for which the Prosigna score is below the cut-off [≤60] for chemotherapy use). • Distant recurrence free interval (DRFI) and distant recurrence free survival (DRFS). • Breast cancer specific survival (BCSS) and Overall survival (OS). • Health Resource Use, and Quality of Life as measured by EQ-5D & FACT-B questionnaires and Distress thermometer. • Patient compliance with long-term endocrine therapy.
Analysis:	The primary outcome of invasive disease free survival (IDFS, defined as: loco-regional invasive breast cancer relapse, distant relapse, ipsilateral or contralateral new invasive primary breast cancer or new invasive primary non-breast cancer or death by any cause) will be calculated from the date of trial entry to the date of first IDFS event or the date last known to be alive. The primary outcome of IDFS will be assessed using Kaplan-Meier survival curves and compared using Cox models after adjustment for stratification variables. The analysis will test the non-inferiority hypothesis that the IDFS rate for test-directed chemotherapy is not more than 3% lower than the IDFS rate for standard chemotherapy, which is assumed to be 85% after 5 years of follow-up. A secondary analysis of non-inferiority of IDFS will be performed for those patients with tumour Prosigna Scores of ≤60.

2. Trial Schema



3. Introduction

In recent decades, adjuvant chemotherapy has been widely used in the treatment of early breast cancer to reduce the risks of relapse and death. The Oxford Overview meta-analysis of adjuvant chemotherapy trials suggests that the reduction in the relative risk of relapse and death is similar for all breast cancers, but the absolute benefit is greater for those at highest risk. Patients at high risk of relapse, either from having involved axillary lymph nodes and/or large tumour size, have usually been recommended adjuvant chemotherapy on the expectation that they would benefit from this treatment. A major focus of research in recent years has been to develop tests of sensitivity to chemotherapy so that patients who would not benefit from such treatment could avoid unpleasant side effects and health care funders could be spared unnecessary costs. Whilst oestrogen receptors and Human Epidermal Growth Factor Receptor 2 (HER2) expression are used to determine sensitivity to endocrine therapy and trastuzumab respectively, no similar tests exist for chemotherapy sensitivity.

A number of 'multi-parameter' prognostic tests for breast cancer have been developed that use molecular techniques, mostly applied to paraffin-embedded tissue. These tests are established as providing superior prognostic information to conventional histopathology assessment of node-negative breast cancer for patients with ER positive and HER2 negative breast cancer. They are widely used to help guide chemotherapy decisions in this population. Limited evidence additionally suggests that the tests may be predictive of chemotherapy benefit.

OPTIMA aims to assess the value of multi-parameter tests in women and men aged 40 or older who have tumours that are ER positive and HER2 negative and who are currently offered adjuvant chemotherapy in addition to endocrine therapy because they are at high risk of recurrence. In this study they are randomised either to receive standard treatment (chemotherapy) or to "test-directed treatment". In the test-directed option, a decision on chemotherapy treatment is made based on the tumour test score: patients with a high-score tumour will be assigned chemotherapy, those with a low score tumour will not.

4. Background

4.1 THE CURRENT TREATMENT OF BREAST CANCER

Breast cancer is a major public health problem. It is the most commonly occurring cancer in the United Kingdom with an annual incidence of 55,000 in 2015-17, and with about 11,500 deaths annually in the same period, it is the second most frequent cause of cancer death in women (1). 80% of women who develop breast cancer are older than 50 years at diagnosis and most deaths occur in this age group. Other developed nations report comparable incidence and mortality figures.

The treatment of primary breast cancer, which is undertaken with curative intent, is divided into local (surgery and radiotherapy) and systemic (including chemotherapy, endocrine treatment and HER2-targeted drugs) therapies. The goal of systemic treatment is to eliminate occult microscopic metastatic disease and thus prevent incurable distant relapse. Decisions on adjuvant treatment depend on an individual patient's risk of developing future overt metastatic disease. The risk is affected by tumour stage (size and number of involved axillary lymph nodes) and by tumour biology. Relevant biological features include tumour grade, and its oestrogen receptor (ER) and HER2 status. These latter two also predict sensitivity to anti-oestrogen drugs and HER2-targeted therapy respectively. Distant relapse, which affects a minority of patients, typically occurs after an interval of several years; late (after 5 years) relapse is a particular feature of both ER positive and lower grade tumours (2). Although male breast cancer is comparatively rare and therefore much less studied, there are no reasons to believe that it is in any way fundamentally different from female breast cancer; the treatment is the same.

Endocrine therapy with tamoxifen and more recently aromatase inhibitors (AIs) is considered to be the mainstay of treatment for postmenopausal women with ER positive disease, the commonest presentation of breast cancer. AIs have been shown to be superior to tamoxifen in a number of large randomised clinical trials; current National Institute for Health and Clinical Excellence (NICE) guidance recommends that these drugs should be offered to the majority of postmenopausal patients (3, 4).

In recent years there has been a large expansion in the use of adjuvant chemotherapy, especially for postmenopausal women. In the UK as in many other countries it has become standard to offer chemotherapy with anthracyclines and/or taxanes to most women with axillary node involvement. Although undoubtedly highly effective for some, chemotherapy is extremely unpleasant with side effects such as hair loss, fatigue, nausea, painful mouth ulcers, weight gain, muscle pain, diarrhoea or constipation and loss of sensation in hands and feet. About one in six patients require admission to hospital with serious complications and there is a small risk of death from treatment. Patients are frequently unable to work during and for some time after treatment, which has a considerable cost to society. Many are left with anxiety, fatigue and depression, which severely affect their quality of life for months or even years afterwards. There is also a small long-term risk of treatment induced leukaemia and cardiomyopathy.

Chemotherapy itself is expensive. Estimates for the cost of delivering a course of fluorouracil, epirubicin and cyclophosphamide (FEC) – Docetaxel (T) and of FEC alone, which are the two most commonly used adjuvant chemotherapy regimens in the NHS, are £4600 and £3800 respectively ((5) updated to 2014 prices). This includes drug costs, outpatient visits and hospital admissions for the management of complications. Approximately 18,500 patients (41% of diagnoses) received chemotherapy in the UK in 2006 (6). As a result, adjuvant chemotherapy treatment for breast cancer imposes a very substantial financial burden on the NHS.

Several computerised tools have been developed to aid adjuvant therapy decision making, particularly chemotherapy. All of these tools use individual patient and pathological data combined with population data to assess baseline risk. Clinical trial efficacy data are then used to predict individual patient treatment benefit. The best known of these tools are PREDICT (7) and Adjuvant! (8) (not currently available), which are recommended in NICE guidance (3, 4). Both PREDICT and Adjuvant! however, refine existing practice rather offering a fundamentally new approach to selecting patients who are likely to benefit from chemotherapy.

The underlying assumption behind OPTIMA is that new tumour gene-expression based technologies which test multiple parameters allow the identification of a sizeable subgroup of women with breast tumours that are intrinsically insensitive to chemotherapy and for whom chemotherapy offers toxicity without a clinically meaningful benefit.

4.2 REDEFINING BREAST CANCER

The traditional classification of breast cancer is based on morphology. The most useful component of this classification is histological grade which, when combined with stage information (tumour size and extent of nodal involvement), provides valuable prognostic information as exemplified by the Nottingham Prognostic Index (NPI) (9). In recent years, multiple additional prognostic markers have been defined through studies of tumour protein and gene expression. The best established are receptors for steroid hormones – oestrogen (ER) and progesterone (PgR), and HER2. ER and PgR expression are good prognostic markers and predict sensitivity to anti-oestrogen drugs. HER2 gene amplification and protein over-expression, which is an adverse prognostic feature, predicts sensitivity to HER2-targeted drugs such as trastuzumab (Herceptin). The value of Ki67, a marker of proliferation which is not routinely measured, is more controversial (10) and is subject to difficulties in assay standardisation (11).

Since 2000 with the invention of the technology of microarray profiling, a new molecular classification of breast cancer has been developed (12, 13). This classification divides breast cancers into four main

"intrinsic subtypes": luminal A, luminal B, HER2 enriched and basal-like (table 1). These subtypes differ markedly in their clinical behaviour and response to therapy, as shown in the summary table. This goes some way to explaining the highly heterogeneous clinical behaviour of the disease. Within the intrinsic subtypes, luminal A breast cancer has a significantly better prognosis than the other subtypes. Most breast cancers with a lower proliferation rate (typically grade 1 or 2) that are both strongly positive for ER expression and which express HER2 at normal levels will fall into the luminal A category.

Table 1: Clinical features associated with the intrinsic classification subtypes

	Luminal A	**Luminal B**	**HER2-E**	**Basal-like**
Prognosis	Good	Moderate	Poor	Poor
Proliferation	Low	Moderate or High	High	High
Chemosensitivity	?Low /nil	?Moderate	?High	?High
Oestrogen receptor	Strong	Variable	Nil	Nil
HER2 amplification	Uncommon	In subset	Frequent	Nil

The original research into intrinsic subtypes required complex microarray analysis using frozen tissue samples to analyse the simultaneous expression of thousands of genes within each breast cancer with associated bioinformatic challenges. This technology is widely regarded as too complex and variable to bring into the clinical setting. The microarray based system maps onto immunohistochemical markers (table 1) that can be used in routine pathology laboratories (2, 14), although correlation is imperfect (15). Considerable progress has also been made with developing RNA-based assays (e.g. Prosigna (PAM50) and MammaPrint/ BluePrint – see section 4.3) that allow the determination of intrinsic subtype using formalin-fixed paraffin-embedded (FFPE) material (which is the standard tissue handling protocol for histopathology laboratories). These assays are available commercially.

4.3 MULTI-PARAMETER ASSAYS IN BREAST CANCER

The emergence of the intrinsic classification has transformed understanding of breast cancer and is changing clinical management to a more individualised approach. There have been intensive research efforts to develop simple tools that allow both molecular subtyping of breast cancers and more importantly a molecular classification of relapse risk following treatment; these new tests typically involve the measurement of multiple gene expression parameters simultaneously. A number of multi-parameter assays have been developed, by both academic groups and commercial organisations, many of which are available for clinical use (table 2). The main focus of this development has been in ER positive HER2 negative and mostly node-negative tumours.

Many of these assays, particularly Oncotype DX (16), Mammostrat (17, 18) and MammaPrint (16, 19), offer a simple numerical estimate of risk and/or risk categorisation information rather than information about a broad pathological classification. Most are strongly influenced by steroid hormone receptor, HER2 and proliferation marker expression.

The majority of the assays have been developed primarily as prognostic tests. Most validation studies have been performed by retrospective testing of archival material from historical trials; a number of retrospective cohort studies of outcomes in patients whose management has been influenced by testing, and two prospective trials evaluating multi-parameter assay have been published. Additionally, there is little data on the cross-comparison between the assays but it is perhaps significant that there is considerable overlap between the markers included in many of these tests. Most critically, there is very little data that allow the performance of the assays to be compared with

best routine pathological practice. Nevertheless, the available comparisons suggest that all assays classify tumours with strongly positive ER and PgR expression, normal HER2 and low proliferation rate/histological grade as carrying the lowest risk; most of these tumours would be in the luminal A group.

Table 2: Summary of multi-parametric tests for breast cancer.

Assay (Provider)	Details of Multi-parametric assay	Test Output	Availability	Ref.
Perou and Sorlie (academic)	The original description of the intrinsic classification using 495 genes.	subtype		(12, 13)
Oncotype DX (Exact Sciences Corp.)	A 16 (+5 normalisation) gene qRT-PCR expression assay for ER positive breast cancer.	risk score & category	Central lab (US)	(16)
MammaPrint + BluePrint (Agendia)	A 70 + 80 gene microarray based expression signature.	risk category, subtype	Central lab (NL)	(19, 20)
Prosigna (PAM50) (Veracyte Inc.)	A 50 (+5 normalisation) gene expression assay using the NanoString platform.	risk score & category, subtype	Regional labs	(15, 21)
Breast Cancer Index (BCI) (bioTheranostics)	A 7 gene qRT-PCR expression assay for ER positive breast cancer.	risk score & category	Central lab (US)	(22, 23)
Mammostrat (Clarient - NeoGenomics Laboratories)	A 5 gene immunohistochemical assay.	risk score	Not currently available.	(17, 18)
IHC4 (non-proprietary/ Genoptix - NeoGenomics Laboratories)	Quantitative immuno-histochemical assay for ER, PgR, Her2, Ki67; conventional immunohistochemistry/ AQUA™ fluorescence IHC.	risk score & category	Local labs/ Not currently available.	(24)
MapQuant (Genomic Grade Index) (Bordet Institute)	A 97 gene microarray based expression assay.	risk score & category	Not currently available.	(25, 26)
EndoPredict (Myriad Genetics)	A 8 (+3 normalisation) gene qRT-PCR expression assay.	risk score & category	Regional labs	(27)
NPI plus	A 10 gene immunohistochemical assay.	risk score	In development	(28)
MammaTyper (BioNTech Diagnostics GmbH)	A 4-gene qRT-PCR assay for ER, PgR, HER2 & Ki67.	subtype	Regional labs	(29)

qRT-PCR=quantitative reverse transcriptase polymerase chain reaction. ER=oestrogen receptor, PgR=Progesterone receptor. Ki67 is a proliferation marker.

A more detailed description of selected tests follows:

Oncotype DX: This is a polymerase chain reaction (PCR) based expression assay measuring expression of 21 genes, 16 of which are cancer-related and 5 are controls (16). The test output is the "Recurrence Score" (RS), a continuous variable which predicts the risk of distant recurrence at 10 years following

tamoxifen treatment of ER positive node negative breast cancer. Individual patient risk can be estimated from the calibration provided with the results. Additionally, patients are divided into 3 risk categories: low, intermediate and high, where intermediate is defined as a 10-20% risk of developing distant metastases over 10-years. The test is performed by Exact Sciences Corp. (trading as Genomic Health Inc., the developer, in some jurisdictions) in a single US laboratory.

Multiple studies (reviewed in (30-34)) have confirmed the value of Oncotype DX as a predictor of residual risk following endocrine therapy. Oncotype DX reclassifies risk defined by Adjuvant!, a well-validated risk prediction nomogram that utilises conventional histopathology parameters. Oncotype DX has also been shown to predict chemotherapy sensitivity in the neoadjuvant setting (35, 36) as well as risk of local recurrence with a possible interplay with radiotherapy (37).

Retrospective analyses of individual patient Oncotype DX Recurrence Scores from a subset of participant tumour blocks from the NSABP B-20 trial of women without axillary nodal involvement (38) and the SWOG88-14/ INT0010 trial of women with node-positive disease (39) have been undertaken. These show that there is no evidence for a clinically significant chemotherapy benefit for women with an RS in the "low" or "intermediate" risk groups. The analysis of the SWOG88-14 trial is particularly important as it shows that even in heavily (≥4) node-positive patients who have a particularly poor prognosis by virtue of stage, there is no benefit from the addition of chemotherapy to adjuvant endocrine therapy alone, if the RS is low. These data are widely interpreted to suggest that Oncotype DX is able to predict whether or not tumours are likely to be sensitive to chemotherapy. Incorporating clinical data (tumour stage, grade and age) for patients with node-negative disease into the test improves its performance as a prognostic test but crucially does not improve its ability to predict chemotherapy sensitivity (30, 40).

Limitations of Oncotype DX, as highlighted by 4 systematic reviews (31-34) include the relative paucity of data on the performance of the test in node-positive patients and that the data supporting the ability of the test to predict chemotherapy benefit are not robust, as they are based on small patient cohorts and/or there are potential confounding factors in the study design and included patient cohorts (33, 34). Additionally, Oncotype DX taken alone is only able to predict risk of recurrence within 5 years of diagnosis (41). The test has not been prospectively trialled against alternatives and there is no evidence that the Oncotype DX assay is any more informative than other gene expression assays (42). The prospective randomised controlled TAILORx trial, discussed in detail below (43), partially alleviates these criticisms.

Prosigna (PAM50): PAM50 is a qRT-PCR expression assay developed in an academic setting using 50 genes selected from the original set identified in the pioneering microarray studies of intrinsic subtype (15). The assay provides subtyping information and additionally a numerical "Risk of Recurrence" (ROR) score; there are several variants of the ROR score incorporating varying amounts of clinical and conventional histological information. The basic ROR score algorithm includes parameters indicating how closely a sample lies to the centroid of each intrinsic subtype and is therefore more informative than subtype alone. PAM50 has been commercialised by NanoString Technologies (subsequently transferred to Veracyte Inc.) as Prosigna, an assay that can be performed in suitable local laboratories using proprietary hardware and reagents (21). The analytical validity of the assay has been demonstrated in this distributed environment (44) and NanoString Technologies was granted the necessary FDA (Federal Drug Authority) approval for its marketing as a prognostic assay in postmenopausal patients in 2013. The FDA-approved signature (Prosigna Score or ROR_PT) includes parameters derived from expression of the PAM50 proliferation-related genes and tumour size. There are no direct comparisons between the performance of PAM50 and Prosigna although it seems reasonable to assume that the two are very similar. The PAM50 algorithms are available in the public domain but their recalibration as Prosigna is proprietary.

PAM50, and by inference Prosigna, apply to all subtypes of breast cancer but the detailed validation studies have been performed on patients with ER positive disease. PAM50 has been validated as a

predictor of residual risk in 3 studies (15, 45, 46) and has been shown to reclassify risk defined by Adjuvant! using conventional pathology. Similarly, Prosigna has been shown both to predict residual risk and reclassify risk using the large transATAC cohort and approximately 1500 mostly node negative patients treated with endocrine therapy alone in the ABCSG08 study (47, 48). Prosigna, in contrast to Oncotype DX and IHC4, is also able to predict late (beyond 5 years) recurrence in these 2 patient cohorts (41, 49). Both of these cohorts were postmenopausal and the terms of the FDA approval of Prosigna reflects this. Further validation of the ability of Prosigna to predict outcome in patients has been generated by analysis of a cohort of approximately 2500 post-menopausal Danish women treated with endocrine therapy alone of whom 55% had lymph-node involvement (46). Other validation studies of both PAM50 and Prosigna have been performed in cohorts that include premenopausal patients (50, 51). Both assays have also been shown to predict response to neoadjuvant chemotherapy and to distinguish response rates between higher and lower risk groups with ER positive disease (15, 52, 53). Other studies have explored the ability of PAM50 to predict long-term outcome in trials comparing two chemotherapy regimens, two of which were conducted in early breast cancer (54, 55) and one in advanced disease (56). None of the three studies selected patients by receptor expression, so the number of patients analysed with luminal disease was comparatively small. Two of the three studies failed to show a statistically significant benefit for patients with luminal B vs. luminal A disease whilst the trial exploring the addition of a taxane to an anthracycline regimen in the adjuvant setting showed that patients with low ROR scores appeared to benefit more from taxane treatment than those at higher risk (55), which is a counterintuitive finding.

MammaPrint: The MammaPrint assay is based on 70 genes identified by expression profiling that were shown to predict outcome in a small mixed population of young breast cancer patients, of whom all sporadic cases were node-negative and none were treated with adjuvant tamoxifen (57). The test is marketed by Agendia Inc. as part of the SYMPHONY profile and is performed in central laboratories located in the Netherlands and in the USA. The output from MammaPrint is a simple binary division into “low risk” and “high risk”. MammaPrint has been reported to provide valid prognostic information in a number of studies and there is evidence that it is able to re-classify risk against existing prognostic variables (reviewed in (30-34)). Several studies have shown that MammaPrint is able to predict response to neoadjuvant chemotherapy including differentiating between high and low risk ER positive disease (52, 58, 59). A study of patients pooled from several data sets suggests that MammaPrint is able to predict chemotherapy benefit in patients with ER positive disease and up to 3 involved lymph nodes (30, 60), although this approach is open to criticism.

Overall the evidence supporting MammaPrint is convincing but in comparison with studies validating the use of Oncotype DX, is less comprehensive, particularly in respect of its potential utility as a predictive marker, with individual studies tending to have a lower quality (30-34). The publication of the randomised study, MINDACT, in 2016 is however the first prospective evidence showing that any multi-parameter assay is superior to conventional risk assessment (61). The limitations of the evidence supporting Oncotype DX also apply to MammaPrint.

IHC4 and fluorescence IHC4: There is evidence that 4 conventional immunohistochemistry (IHC) markers, ER, PgR, HER2 and Ki67 (14) are able to identify patients at increased residual risk following adjuvant endocrine therapy. The IHC4 test relies on quantitative IHC for these markers integrated into a viable predictor of residual risk in postmenopausal women with ER positive disease who had participated in the ATAC trial (24). IHC4 using conventional manual colorimetric (DAB) IHC has been developed in an entirely academic setting. The output from IHC4 is a numerical score with a division into 3 risk groups using the same definitions as Oncotype DX.

The original IHC4 validation study was performed on a large (1125) patient cohort and the report included a second validation performed on an independent cohort from Nottingham. Another completely independent study has been performed on approximately 4500 patients recruited from the TEAM study using both DAB IHC and quantitative immunofluorescence (62). Both methods of

detection provided significant prediction of residual risk following endocrine therapy with reasonable correlation.

The low estimated cost (£150 at 2014 prices) of performing IHC4 using conventional IHC (33) and its portability are potential advantages for IHC4 over other multi-parameter assays. However its portability is also its principal weakness as the reproducibility of manual quantitative IHC, particularly for Ki67, is limited (63). It is possible that the use of image analysis software supported by machine learning in local laboratories will improve reproducibility, but this is yet to be established.

MammaTyper: This is a 4-gene qRT-PCR expression assay developed commercially by BioNTech Diagnostics GmbH. The assay measures ER, PgR, HER2 and Ki67 mRNA (29). These data are combined to allocate tumours to an intrinsic subtype rather than provide a risk score as IHC4. The definition of intrinsic subtype is based on an immunohistochemical definition, which does not map accurately onto PAM50/Prosigna defined subtypes (45). MammaTyper has been provided for clinical use since 2015 by a number of laboratories in Europe and Asia.

4.4 DIFFERENTIAL SENSITIVITY OF BREAST CANCER SUBTYPES TO CHEMOTHERAPY

The strongest evidence for the effectiveness of adjuvant chemotherapy comes from the meta-analyses of over 100,000 patients in 123 chemotherapy trials conducted around the world, known as the Oxford Overview. For node positive, postmenopausal women with hormone sensitive breast cancer treated with tamoxifen, the Overview suggests that 10-year mortality is reduced from about 31% to 25% by anthracycline chemotherapy (64). Whilst this is highly significant, 17 patients need to be treated for one life to be saved.

All historic published adjuvant chemotherapy trials in breast cancer have made the assumption that breast cancer is a single entity and that the proportional benefits of chemotherapy apply uniformly to all cancers irrespective of histological characteristics of the tumour. The development of the intrinsic classification requires re-evaluation of all of the available evidence on adjuvant chemotherapy treatment; now that different subtypes of breast cancer, which behave in different ways, are recognised, it is necessary to investigate the appropriate use of chemotherapy within the new classification.

Evidence that chemotherapy response is influenced by tumour biology comes from analysis of response to pre-surgical (neo-adjuvant) chemotherapy. Analysis of the outcome of treatment according to intrinsic subtype of individual tumours is particularly striking with a pathological complete response rate of 6% in luminal tumours compared to 45% in basal type (65). Two independent studies showed that the chances of achieving a pathological complete response for patients with luminal B tumours was more than double that for patients with luminal A tumours (15, 52).

A particularly relevant line of evidence comes from the retrospective analysis of historical trials comparing chemotherapy plus tamoxifen with tamoxifen alone in ER positive breast cancer according to the results of the Oncotype DX test performed on archival tumour tissue. Analysis of individual patient Oncotype DX Recurrence Scores (RS) in the NSABP B-20 trial in women without axillary nodal involvement and SWOG 88-14 trial in women with node positive disease has shown that there is no chemotherapy benefit for women with an RS in the “low” or “intermediate” risk groups. The analysis of the SWOG 88-14 trial is particularly important as it shows that there is no chemotherapy benefit if the RS is low, even in heavily (≥4) node positive patients who have a poor prognosis by virtue of stage. This suggests that Oncotype DX is able to predict tumour chemotherapy sensitivity. These studies however have been criticised on methodological grounds (33, 34)

4.5 THE CONTRIBUTION OF ENDOCRINE THERAPY TO OUTCOME

Endocrine therapy is an essential component of the treatment of ER positive breast cancer, and in the overall population makes a greater contribution to improvements in outcome than does chemotherapy (66). In postmenopausal women, whilst both treatment with tamoxifen and AIs significantly reduce the risk of relapse and death, a number of large-scale trials have demonstrated superiority of AI treatment either given for 5 years or for about 3 years after about two years of tamoxifen ("AI switch") over 5 years of tamoxifen alone (67). Two trials, BIG 1-98 (68) and TEAM (69) have compared an AI switch strategy with 5 years of AI; neither trial showed an overall difference between the two treatment strategies at 8 and 5 years of follow-up respectively, although there were more relapses during the initial treatment phase with tamoxifen in comparison to women randomised to initial AI. For women with higher risk disease, there is also clear evidence for a benefit from continuation of tamoxifen to 10 years (70) or for a switch from tamoxifen to AI (compared to no further endocrine treatment) after 5 years (71). Additionally, more limited data show that continuation of AI therapy for a total duration of 10 years is modestly superior to treatment for 5 years (72). The benefits of endocrine therapy are largely independent of those of chemotherapy in the postmenopausal population.

In premenopausal women, for whom AI therapy is ineffective unless combined with reversible ovarian suppression, endocrine therapy with tamoxifen is also well established as reducing the risk of relapse. There is also a significant body of evidence that ovarian suppression, oophorectomy and chemotherapy-induced ovarian failure also reduce relapse risk. Chemotherapy induced ovarian failure is common in the over 40's.

The principal randomised trials to investigate the benefit of ovarian suppression in the context of contemporary breast cancer treatment are the companion SOFT and TEXT trials (73, 74). Patients joining SOFT were premenopausal following chemotherapy, if given, and were randomised between tamoxifen, ovarian suppression + tamoxifen and ovarian suppression + AI, all given for 5 years. The primary end point was a test for superiority of 5-year disease-free survival of patients treated with ovarian suppression + tamoxifen compared with tamoxifen alone. The comparison between ovarian suppression + AI with tamoxifen alone was a secondary end point. The TEXT trial compared ovarian suppression + AI with ovarian suppression + tamoxifen and the primary analysis included patients enrolled in SOFT.

The SOFT trial allowed women who resumed menstruation after up to 8 months of post-chemotherapy amenorrhoea to participate. A subsequent trial with a similar design but conducted in a younger patient group and which reported comparable findings to SOFT allowed amenorrhoea of up to two years in participants (75).

SOFT and TEXT have been analysed after a median 8 years of follow-up (74). In the SOFT trial, the addition of ovarian suppression to tamoxifen or the combination ovarian suppression and AI reduced the risk of recurrence compared with tamoxifen alone. In subgroup analyses of the relative benefits of ovarian suppression in both comparisons, there were comparable gains for women who had received prior chemotherapy, or not. The chemotherapy-treated subgroup had both a higher absolute recurrence rate and gain from ovarian suppression. The majority of patients with node-positive disease enrolled in SOFT were treated with chemotherapy. SOFT has additionally shown that combination ovarian suppression and AI reduces distant disease recurrence in comparison to tamoxifen alone. Combined analysis of SOFT and TEXT has confirmed the overall superiority of ovarian suppression + AI over ovarian suppression + tamoxifen both in improving disease-free survival and freedom from distant recurrence. The relative benefits were comparable irrespective of whether patients were treated with chemotherapy, or not.

4.6 AVAILABILITY OF MULTI-PARAMETER TESTING IN THE UK

NICE evaluated 4 multi-parameter assays, Oncotype DX, MammaPrint, IHC4 and Mammostrat for potential use in the NHS. The resulting guidance ("Gene expression profiling and expanded immunohistochemistry tests for guiding adjuvant chemotherapy decisions in early breast cancer management: MammaPrint, Oncotype DX, IHC4 and Mammostrat [DG10]") was published in 2013 (76). DG10 recommends that Oncotype DX is "an option for guiding adjuvant chemotherapy decisions for people with oestrogen receptor positive (ER+), lymph node negative (LN−) and Human Epidermal Growth Factor Receptor 2 negative (HER2−) early breast cancer". The appraisal was limited to patients with node negative disease, as the evidence for the use of the tests was considered less robust in the node-positive population and the recommendation for Oncotype DX was further restricted to patients at "intermediate risk". The three other tests evaluated were recommended for use in research only. Oncotype DX testing is available to NHS patients meeting the criteria defined in the NICE DG10 guidelines in England, Wales and Northern Ireland and by Molecular Pathology Evaluation Panel (MPEP) advice in Scotland. The DG34 guidance (77), an update of DG10 was published in December 2018; of the five tests (Oncotype DX, MammaPrint, Prosigna, EndoPredict and IHC4) evaluated, Prosigna and EndoPredict were recommended for use in the NHS in addition to Oncotype DX. The population eligible for testing is essentially the same as DG10 but additionally allows patients with lymph-node micrometastases (pN1mi) to be treated as node negative. NICE again evaluated the use of tests for patients with 1 to 3 involved lymph nodes (pN1) but considered the evidence to be insufficient to justify an extension of the eligible population.

4.7 OPTIMA AND OPTIMA PRELIM

The OPTIMA trial seeks to advance the development of personalised treatment in breast cancer by identifying an appropriate and effective method, using multi-parameter analysis, to identify people with ER positive HER2 negative primary breast cancer who are likely to benefit or not benefit from chemotherapy. OPTIMA has an adaptive design that allows more than one technology to be evaluated and will run in 2 phases with (1) an initial feasibility study, now completed, to compare the performance of technologies, to establish their candidacy for inclusion in the main trial and to evaluate the acceptability of the approach to patients and its cost-effectiveness and (2) a main efficacy trial. Both phases of the study are covered by a single protocol and ethical approval. Patients recruited into both phases of the trial will contribute to the final analyses. In versions of the protocol (version 4 onwards) following the completion of OPTIMA *prelim*, the feasibility phase, details that are specific to OPTIMA *prelim* have been removed from the body of the protocol to an appendix to reduce the risk of confusion. Additionally, a number of outputs from OPTIMA *prelim* have been separately reported and are summarised below.

The specific objectives of OPTIMA *prelim* were:

- To evaluate the performance and health-economics of alternative multi-parameter tests to determine which technology(s) are to be evaluated in the main trial.
- To establish the acceptability to patients and clinicians of randomisation to test-directed treatment assignment.
- To establish efficient and timely sample collection and analysis essential to the delivery of multi-parameter tests driven treatment.

OPTIMA *prelim* opened in September 2012. The database was locked on 3 June 2014 with 350 participants registered and 313 randomised into the study, recruited from 35 UK hospitals. The detailed conduct of OPTIMA *prelim* and its outputs are described in the final report (78).

The main conclusions from OPTIMA *prelim* were:

- OPTIMA *prelim* succeeded in its aim of demonstrating that a large-scale study of multi-parameter test-directed chemotherapy allocation in a high-risk population of patients with ER

positive HER2 negative invasive breast cancer is feasible in the UK by meeting all pre-defined success criteria.

- Receptor determination (ER and HER2) is accurate in local sites in this patient population with an acceptable predicted error rate of 3.7%.
- Public-Patient Involvement and the Qualitative Recruitment Study (QRS) have contributed substantially although in an unquantifiable manner to the success of the project and should continue into a large-scale study.
- There is considerable discrepancy between the outputs of a selection of multi-parameter assays performed on individual participant tumour blocks.
- There is considerable uncertainty regarding the cost-effectiveness of all tests considered.
- There is substantial value to the UK NHS in comparative research into all tests, although Prosigna may currently be considered the highest priority.

5. Rationale

The OPTIMA trial seeks to advance the development of personalised treatment of early breast cancer by the prospective evaluation of multi-parameter analysis, as a means of identifying those patients with ER positive HER2 negative disease who are likely to benefit from chemotherapy and those who are not, and to establish the cost-effectiveness of this approach. The majority of patients will have node positive disease.

The NICE DG34 (and DG10) guidance recommend that Oncotype DX, Prosigna and EndoPredict testing are made available to patients with ER positive HER2 negative invasive breast cancer who do not have axillary node involvement and who are at "intermediate risk". This recommendation is based on retrospective analyses that demonstrate that the tests provide superior prognostic information to conventionally assessed histological grade. The economic analyses conducted for DG34, and previously for DG10, showed that none of the tests were cost-effective when applied to the entire potentially eligible population of patients with node negative disease. The recommendation for their use was therefore as prognostic tests, restricted to patients with larger or higher grade tumours, but even so this was anticipated to result in a net cost to the NHS that could only be brought within the NICE thresholds after the providers offered a discounted price to the NHS.

The output from the majority of multi-parameter assays used in validation studies is the risk of distant recurrence at 10 years. A significant proportion of such events occur between 5 and 10 years from initial diagnosis. These later events are little influenced by the use of adjuvant chemotherapy (64). The predefined risk categories for the assays therefore potentially lead to an over-estimate of chemotherapy benefit in the tested population. In the absence of any prospective randomised trials, selection of a threshold for chemotherapy use is therefore at best intelligent guesswork. The assay providers offer limited guidance over this question.

Patients with node positive disease, for whom chemotherapy use is far more widespread than for those with node negative disease are only likely to benefit significantly from multi-parameter assays if these have the ability to predict chemotherapy sensitivity. This is because lymph node involvement is independently prognostic for recurrence, and the additional prognostic information provided by the tests decreases with increasing numbers of involved nodes (79). The ability of the available tests to predict chemotherapy sensitivity above and beyond providing prognostic information was reviewed in detail during the development of the NICE DG34 guidance (34). The evidence that was available to NICE, and the studies published subsequently, has been obtained from retrospective analysis of registry data, re-analysis of historic RCT data and prospective cohorts. Although all of the data from patients with both node negative (pN0) and up to 3 involved nodes (pN1) support the predictive hypothesis, none of the studies provide evidence of better than limited strength. NICE considered the

evidence to be suggestive and recommended that further research be performed on this topic: OPTIMA sets out to answer this important question.

The evidence for multi-parameter assay use in the node-positive population overlaps with data supporting the predictive hypothesis but additionally includes studies in which nodal status is incorporated into test outputs (particularly Prosigna and EndoPredict). Again this evidence was reviewed by Harnan et al (34) for NICE who concluded that although suggestive, it was insufficiently strong to recommend its routine use. OPTIMA, by studying a largely node positive population including patients with 4-9 involved nodes (pN2) for whom almost no data exist, will provide this evidence.

Three ongoing international randomised controlled trials (RCTs) will generate prospective evidence for the validity of test-directed treatment assignment.

• **TAILORx** (43): This US intergroup trial randomised patients to chemotherapy followed by endocrine therapy or endocrine therapy alone based on an Oncotype DX test result. Eligible patients had ER positive breast cancer without nodal involvement. All patients underwent Oncotype DX testing and those with a Recurrence Score in the range 11-25 were eligible for randomisation. The majority of patients randomised in TAILORx would not currently be offered chemotherapy in the NHS and would not qualify for Oncotype DX testing under the terms of the NICE DG10 guidance. The TAILORx study showed no overall difference in outcome between patients who were randomised to chemotherapy in addition to endocrine therapy, or not. Event rates were low, with more unrelated second cancers being reported than breast cancer metastases or death. Pre-menopausal women and/ or those aged under 50 appeared to benefit from chemotherapy with the relative benefit increasing with Recurrence Score; this effect was not seen in post-menopausal/ older study participants. A secondary analysis of trial data concluded that this provided evidence in support of the predictive hypothesis (80). Ovarian suppression was infrequently given to pre-menopausal participants and no data on the incidence of chemotherapy-induced ovarian failure were collected. It is plausible that the benefit of chemotherapy in the pre-menopausal population can be explained as an indirect endocrine effect.

• **MINDACT - EORTC 1004** (61): This pan-European trial compared adjuvant chemotherapy treatment decisions based on the MammaPrint test with decisions based on clinical risk calculated using "Adjuvant!" applying a pre-defined risk categorisation. The study aims to validate MammaPrint as a prognostic marker and to allow a modest reduction in chemotherapy use. A protocol modification made during recruitment allowed entry of patients with up to 3 involved axillary lymph nodes. The patient cohort, unlike that of OPTIMA, included patients with any ER and HER2 status. The trial population of 6693 patients included 21% with lymph node involvement, and 12% with ER-negative and 10% with HER2-positive disease. The primary analysis, published in 2016, showed that chemotherapy allocated on the basis of clinical vs genomic risk was reduced by 14% in the entire trial population (61). For patients classified as having high clinical risk, chemotherapy use was reduced by 46% for those additionally classified as having low vs. high genomic risk without detriment in their outcome. Overall event rates were low with over 90% of patients classified as having both high clinical and genomic risk, all of whom were treated with chemotherapy, remaining metastasis-free with an average follow-up of 5 years. The trial was underpowered to be able to demonstrate a chemotherapy benefit in the subpopulations classified as having low clinical but high genomic risk and vice versa. Overall the results support the use of test-directed chemotherapy allocation in a comparatively low-risk population.

• **RxPONDER** (81): This is a US Intergroup study that opened in 2011. Eligible patients have ER positive HER2 negative tumours with 1-3 involved axillary lymph nodes. All patients undergo Oncotype DX testing; those with a RS of 25 or less are eligible to be randomised between chemotherapy followed by endocrine therapy or endocrine therapy alone. The trial aims to test over 10,000 patients and to randomise 4,500. The primary analysis is currently intended to take place in 2022. The design of the study means that there is likely to be a preponderance of patients with low RS tumours.

Once the results of these studies become available, the opportunity to conduct any further prospective studies in the field will be severely limited. However significant questions will remain unanswered. Specifically, the cost-effectiveness of multi-parameter assay test-directed treatment in the NHS will be addressed only by OPTIMA.

Whilst the OPTIMA *prelim* study was not able to exclude the potential for any of the candidate tests to be cost effective in the context of the NHS, there was a preference for the use of a validated and established test with a significant potential for improved dissemination throughout the NHS. "Value of Information" (VoI) analysis performed in OPTIMA *prelim* indicates that the value to the NHS in conducting further research on Prosigna is particularly high (78). Although evidence to support the use of Prosigna was not available for inclusion in the NICE DG10 evaluation in 2011, a number of important validation studies have been published recently, as described above. Prosigna has therefore been selected as the primary discriminator for use in OPTIMA.

The approach taken in OPTIMA is to randomise patients between standard therapy (chemotherapy and endocrine therapy) and test-directed treatment. OPTIMA is designed to test both the validity of multi-parameter test directed therapy and the performance of specific assay(s) in detail. The adaptive design of the study will facilitate this. As such it should be considered complementary to the 3 ongoing international studies which are committed to a specific assay from the outset and can only provide information about and justification for the use of that assay. An evaluation of the cost-effectiveness of the assay used in the main study is central to the OPTIMA design and is reflected in the randomisation to have a test performed rather than randomisation according to test result as in the other 3 trials. OPTIMA will therefore add to the sum-total of knowledge on treatment selection based on the use of multi-parameter assays.

6. Trial Design

OPTIMA is a multi-site partially blinded randomised international clinical trial with a non-inferiority endpoint and an adaptive design. The preliminary or feasibility phase of the study, which had the same structure as the main trial, is referred to as OPTIMA *prelim*.

OPTIMA *prelim* was intended to establish whether a large efficacy trial of multi-parameter test-based treatment allocation ("test-directed" treatment) is acceptable to patients and clinicians and to select multi-parameter test(s) to be used in the main study. This phase of the trial was designed to recruit a total of 300 patients, randomised in a 1:1 ratio over two years. A 200 patient extension phase was built into the design to allow a smooth roll through into the main trial.

OPTIMA will compare standard treatment of chemotherapy followed by endocrine therapy with multi-parameter test-directed treatment allocation to either chemotherapy followed by endocrine therapy or endocrine therapy alone. The randomisation of patients allocated to chemotherapy will be concealed from treating sites. In the main trial, 4500 patients (2250 patients per arm) will be randomised to a two-arm design. Patients will be followed up for ten years.

The test technology used in OPTIMA to allocate patients to chemotherapy or to no chemotherapy is Prosigna with a Prosigna Score (or ROR_PT) cut-off of >60 vs. ≤60; the cut-off is the pre-defined boundary between high and intermediate risk for node-negative tumours. OPTIMA is an adaptive trial designed to allow additional multi-parameter test technology to be evaluated in the future.

7. Trial Hypothesis and Objectives

Hypothesis

- Tumour multi-parameter assays predict chemotherapy sensitivity. Patients with hormone sensitive primary breast cancers that have a low multi-parameter assay score do not have a meaningful chance of benefiting from adjuvant chemotherapy despite other factors that may predict for a high risk of disease recurrence.

Objectives

- To identify a method of selection that reduces chemotherapy use for patients with hormone sensitive primary breast cancer without detriment to recurrence and survival.
- To establish the cost-effectiveness of test-directed treatment strategies compared to standard practice.

8. Outcome Measures

Primary outcomes

- Invasive disease free survival (IDFS): non-inferiority of test-directed chemotherapy treatment and endocrine therapy compared to chemotherapy followed by endocrine treatment.
- Cost effectiveness evaluation of protocol specified multi-parameter assay driven treatment against standard clinical practice.

Secondary outcomes

- Distant recurrence free interval (DRFI) and Distant recurrence free survival (DRFS).
- Breast cancer specific survival (BCSS) and Overall survival (OS).
- IDFS for patients with low-score tumours (defined as tumours for which the Prosigna score is below the cut-off [≤60] for chemotherapy use).
- Health resource use, and Quality of life as measured by EQ-5D & FACT-B questionnaires and distress thermometer.
- Patient compliance with long term endocrine therapy.

Table 3 provides definitions of each of the outcome measures (82).

Table 3: Definition of outcome measures

Outcome measure	Definition
Invasive Disease Free Survival	ipsilateral loco-regional invasive breast cancer recurrence; distant breast cancer recurrence; contralateral new invasive primary breast cancer; new invasive primary non-breast cancer (excluding squamous and basal cell skin cancers); death from any cause
Distant recurrence free interval	distant recurrence of breast cancer; death from breast cancer
Distant recurrence free survival	distant recurrence of breast cancer; death from any cause
Breast cancer specific survival	death from breast cancer
Overall survival	death from any cause

9. Patient Selection, Eligibility & Treatment

9.1 INCLUSION CRITERIA

- Female or male, age ≥ 40
- Excised invasive breast cancer with local treatment either completed or planned according to trial guidelines.
- ER positive (>10% of tumour cells stained positive) as determined by the referring site in a laboratory meeting national external quality assurance standards and in accordance with national or ASCO-CAP guidelines (83).
  NOTE: Where ER status is reported by Allred (or Quick) Score or by H-Score, tumours with high scores meet the ER-positive definition but the %staining component of the score is required to determine eligibility for intermediate-score tumours. Refer to the table for mapping.

	Eligible (ER staining >10%)	Eligibility determined by %staining component of the score	Ineligible (ER staining ≤10%)
Allred (or Quick) Score	6, 7, or 8	4 or 5	3 or less
H-Score	>30	10-30	<10

- HER2 negative (IHC 0-1+, or ISH negative/non-amplified) as determined by the referring site in a laboratory meeting national external quality assurance standards and in accordance with national or ASCO-CAP guidelines (84).
- Tumour size and axillary lymph node status; one of the following must apply:
  i. 4-9 lymph nodes involved AND any invasive tumour size.
  ii. 1-3 nodes involved, with at least 1 node containing a macrometastasis (i.e. deposit >2mm diameter) AND any invasive tumour size.
  iii. 1-3 lymph nodes involved with micrometastases only (i.e. deposit >0.2-2mm diameter) AND invasive tumour size ≥ 20mm.
  iv. node negative AND invasive tumour size ≥ 30mm.

  NOTES:
  a. Lymph nodes containing isolated tumour cell clusters (ITC) only (i.e. deposit ≤0.2mm diameter) will be considered to be uninvolved.
  b. Involvement of lymph nodes with macrometastases or micrometastases may be determined either by histological examination or by OSNA or equivalent PCR-based assay.
- Considered appropriate for adjuvant chemotherapy by the treating physician.
- Patient must be fit to receive chemotherapy and other trial-specified treatments with no concomitant medical, psychiatric or social problems that might interfere with informed consent, treatment compliance or follow up.
- Multiple ipsilateral cancers are permitted provided at least one tumour fulfils the tumour size and axillary lymph node entry criteria, and none meet any of the exclusion criteria.
  NOTE: Refer to section 10 for guidance on selection of tumour blocks to be sent to the Central Laboratory.
- Bilateral cancers are permitted provided the tumour(s) in one breast meets the eligibility criteria and the other, contralateral tumour is not ER negative and/or HER2 positive and not clinically significant, defined by both of the following:
  i. The contralateral tumour **does not** fulfil the tumour size and lymph node eligibility criteria required for trial entry; i.e. the following are **not** acceptable:
     - presence of lymph node macro-metastases;
     - presence of lymph node micrometastases if the tumour size is ≥20mm;

- tumour size ≥30mm when there is no lymph node involvement.

ii. The treating physician does not consider that the characteristics of the contralateral tumour alone justify consideration of adjuvant chemotherapy.

- Short term pre-surgical treatment with endocrine therapy including in combination with non-cytotoxic agents is allowed providing that the duration of treatment does not exceed 8 weeks.
  NOTE: A pre-treatment core biopsy should be sent to the Central Laboratory; a sample from a surgical excision or other on-treatment biopsy is not acceptable. Refer to section 10.
- Informed consent for the study.
  NOTE: Consent must be received prior to undertaking any trial procedure. Randomisation and tumour block processing may be performed on the basis of formally documented remote verbal consent when written consent will be delayed; written consent is required before proceeding to trial-specified treatment. Refer to section 10.

9.2 EXCLUSION CRITERIA

- ≥10 involved axillary lymph nodes (with either macrometastases and/ or micrometastases) or evidence for internal mammary node involvement.
  NOTE: Internal mammary lymph nodes identified by anatomical imaging studies alone will be considered uninvolved where the diameter is <10mm.
- ER negative/low OR HER2 positive/amplified tumour (as determined by the referring site).
- Metastatic disease.
  NOTE: Formal staging according to local protocol is recommended for patients where there is a clinical suspicion of metastatic disease or for stage III disease (tumour >50mm with any nodal involvement OR any tumour size with 4 or more involved nodes).
- Previous diagnosis of malignancy unless:
  i. managed only by surgical treatment with or without local radiotherapy AND disease-free for 10 years.
  ii. basal cell carcinoma of skin or cervical intraepithelial neoplasia.
  iii. ductal carcinoma in situ (DCIS) or pleomorphic lobular carcinoma in situ (pleomorphic LCIS) of the breast treated with surgery with or without breast radiotherapy; treatment with anti-oestrogens is not permitted.
  NOTE: Isolated classical type lobular carcinoma in situ (LCIS) is not considered in this context to be a diagnosis of malignancy.
- Pre-operative anti-cancer treatments except short-term endocrine therapy administered as per the inclusion criteria.
- Adjuvant systemic treatment commenced prior to trial entry* except endocrine therapy, which must be discontinued prior to starting trial-allocated chemotherapy.
- Treatment with agents, including ovarian suppression, known to influence breast cancer growth but prescribed for other indications within one year of trial entry* except as follows:
  i. Use of oestrogen replacement therapy (HRT) provided this is stopped before surgery.
  ii. Drugs administered for in vitro fertilization or fertility preservation.
  iii. Use of hormonal contraception.
- Trial entry* and randomisation more than 12 weeks after completion of breast cancer surgery. Trial entry should ordinarily be within 8 weeks of final surgery.
- Planned further surgery for breast cancer, including axillary surgery, to take place after trial entry*, except either re-excision or completion mastectomy for close or positive/involved margins which may be undertaken following completion of chemotherapy if given.
  NOTE: The timing of radiotherapy to the axilla for lymph-node involvement is not restricted.

*Trial entry is dated from the earlier of participant signature of the consent form or the giving of remote verbal consent.

9.3 CHEMOTHERAPY REGIMENS

Chemotherapy to be chosen from a list of allowed regimens: the intended regimen must be stated at randomisation.

Chemotherapy is recommended to start within 2 weeks of treatment allocation. Monitoring and dose modifications during treatment is according to local guidelines. This includes the use of anti-emetics and other supportive care including the use of Granulocyte - Colony Stimulating Factor (G-CSF).

<u>Anthracycline non-taxane regimens</u>

- FEC75-80:
  fluorouracil [F] 500-600 mg/m^2, i.v. q.3weeks x 6 cycles
  epirubicin [E] 75-80 mg/m^2,
  cyclophosphamide [C] 500-600 mg/m^2
- FEC90-100:
  fluorouracil [F] 500 mg/m^2, i.v. q.3weeks x 6 cycles
  epirubicin [E] 90-100mg/m^2,
  cyclophosphamide [C] 500mg/m^2
- EC90-100:
  epirubicin [E] 90-100mg/m^2, i.v. q.3weeks x 4-6 cycles
  cyclophosphamide [C] 600mg/m^2
- E-CMF:
  epirubicin [E] 100mg/m^2 i.v. q.3weeks x 4 cycles
  followed by
  cyclophosphamide [C] 600mg/m^2 i.v. D1,8 q.4weeks x 4 cycles
  OR 100mg/m^2 p.o. daily x14 days
  methotrexate [M] 40mg/m^2
  fluorouracil [F] 600mg/m^2

<u>Taxane non-anthracycline regimens</u>

- TC:
  docetaxel [T] 75mg/m^2 i.v. q.3weeks x 4 (-6) cycles
  cyclophosphamide [C] 600mg/m^2

<u>Combined anthracycline-taxane regimens</u>

- (F)EC-T:
  FEC90-100 ***OR*** EC90-100 (as above) i.v. q.3weeks x 3-4 cycles
  followed by
  docetaxel [T] 100mg/m^2 i.v. q.3weeks x 3-4 cycles
  note – the order of (F)EC and docetaxel administration may be reversed
- (F)EC-Pw/P2w:
  FEC90-100 ***OR*** EC90-100 (as above) i.v. q.3weeks x 3-4 cycles
  followed by
  paclitaxel 80-90mg/m^2 i.v. q.1week x 8-12 cycles
  OR 175mg/m^2 q.2weeks x 4-6 cycles
  note – the order of (F)EC and paclitaxel administration may be reversed

- TAC:

  docetaxel [T] 75mg/m^2 — i.v. q.3weeks x 6 cycles
  doxorubicin [A] 50mg/m^2
  cyclophosphamide [C] 500mg/m^2

Dose-dense regimens

- dd AC/EC-P: [dd = dose dense] :

  doxorubicin [A] 60mg/m^2 ***OR*** — i.v. q.2weeks x 4 cycles
  epirubicin [E] 90mg/m^2 — (with G-CSF support)
  cyclophosphamide [C] 600mg/m^2
  followed by
  paclitaxel [P] 175mg/m^2 — i.v. q.2weeks x 4 cycles
  OR 80-90mg/ m^2 — q.1week x 8 cycles

Paclitaxel albumin (nab-paclitaxel) at appropriate dose and schedule may be used in place of either docetaxel or solvent-based paclitaxel in the allowed regimens.

Platinum salts can be added to any of the allowed regimens with appropriate adjustments to other components if a patient carries a germline BRCA1/2 or PALB2 mutation or has a tumour with evidence of homologous recombination deficiency.

9.4 ADJUVANT ENDOCRINE THERAPY

Initiation

Endocrine therapy is recommended to be started within 2 weeks of treatment allocation in patients assigned to no chemotherapy or 4 weeks after day 1 of the final cycle of chemotherapy for all other patients. Concomitant endocrine therapy and chemotherapy is not allowed. Initiation of endocrine therapy should not be delayed until after radiotherapy.

Endocrine therapy should be planned for a minimum of 5 years; the recommended duration is 10 years.

Initial treatment period (years 0-5)

Recommended endocrine therapy is based on the patient's menopausal status at trial entry (defined as the date of informed consent).

- Postmenopausal at trial entry:
  All postmenopausal women should be treated with an aromatase inhibitor (anastrozole, exemestane or letrozole). Tamoxifen may be given where aromatase inhibitor therapy is contraindicated or not tolerated.
- Premenopausal at trial entry:
  All premenopausal patients should receive ovarian suppression, either with a licensed Gonadotropin Releasing Hormone (GnRH) agonist, such as goserelin 3.6mg subcutaneously once a month or leuprorelin acetate 11.25mg subcutaneously once every 3 months, for at least 3 years, or undergo bilateral surgical oophorectomy. Radiation menopause is not permitted.

  Ovarian suppression may be deferred for patients who experience chemotherapy-induced amenorrhoea but should be initiated in the event of resumption of menses up to 2 years from trial entry.

In addition, women should receive either tamoxifen or an aromatase inhibitor (anastrozole, exemestane or letrozole) for 5 years. Investigators must declare prior to randomisation whether they plan to use tamoxifen or an aromatase inhibitor.

NOTE: Ovarian suppression is mandated for all premenopausal women within the OPTIMA trial to ensure: (i) that the patients within both arms receive equally balanced endocrine treatment and (ii) to eliminate the risk of confounding from different rates of chemotherapy induced menopause between the arms.

NOTE: Most GnRH agonist SmPCs recommend monitoring FSH and oestradiol levels to confirm ovarian suppression when used in combination with an aromatase inhibitor. Investigators are advised to confirm that oestradiol levels lie within the locally defined post-menopausal range after 3 months of treatment. See note on interpretation of FSH and oestradiol levels during endocrine therapy, below.

- Male:
  Tamoxifen for 5 years.

Assessment of menopausal status at trial entry

Women who fulfil the following criteria at trial entry will be considered postmenopausal:

- Age >45 and natural amenorrhoea of at least 1 year's duration.
- Bilateral surgical oophorectomy.
- For amenorrhoea not fulfilling the above criteria the diagnosis of postmenopausal status should be supported by hormone measurement: FSH levels must be > 25IU/L with low oestradiol (i.e. within the locally defined postmenopausal range), in the event of doubt measured on 2 occasions preferably 4-6 weeks apart. This applies to women who have undergone hysterectomy without bilateral surgical oophorectomy and are age <60; those ≥60 may be considered postmenopausal.

NOTE: Hormonal contraception will suppress FSH and oestradiol levels. In those taking oral contraception, levels will recover rapidly on discontinuation. Depo-Provera injectable contraception lasts many months: all women receiving this agent should be considered premenopausal.

Extended treatment period (years 6-10)

As the OPTIMA population is considered to be at high risk of late relapse, all patients are advised extended adjuvant endocrine therapy up to a total of 10 years as follows:

- Female:
  Aromatase inhibitor or tamoxifen.
- Male:
  Tamoxifen

For women deemed premenopausal at trial entry who are considered for extended endocrine therapy with an aromatase inhibitor, the following considerations apply to determination of menopausal status:

- Age ≥ 55 on tamoxifen monotherapy with intact ovaries and with amenorrhoea for 2 years may be considered postmenopausal.
- Age < 55 on tamoxifen monotherapy with intact ovaries and with amenorrhoea for 2 years. Assay FSH and oestradiol; consider the patient to be postmenopausal if FSH is > 25IU/L and oestradiol is within the locally defined postmenopausal range.

- Age <60 and on GnRH agonist combined with either tamoxifen or an aromatase inhibitor, discontinue GnRH agonist, allowing at least 4 months from final treatment prior to measurement of FSH and oestradiol. Discontinuation of tamoxifen for 8-12 weeks or aromatase inhibitor for 2 weeks is advised before hormone measurement. Consider the patient to be postmenopausal if FSH is > 25IU/L and oestradiol is within the locally defined postmenopausal range. Women age ≥60 may be considered postmenopausal.

Notes on interpretation of FSH and oestradiol levels in women with amenorrhoea receiving endocrine therapy.

1. Tamoxifen

Tamoxifen may suppress FSH levels in postmenopausal women and cause elevation in premenopausal women. Women with FSH ≤25IU/L measured whilst taking tamoxifen should be considered premenopausal regardless of oestradiol level. If the FSH lies close to 25 then consider repeating measurements in 6 months or following interruption of tamoxifen for 8-12 weeks. Women with FSH >25IU/L and oestradiol above the menopausal range are likely to be peri-menopausal; consider repeating measurements in 6 months.

2. Aromatase inhibitors

Aromatase inhibitors should suppress the oestradiol level to below the lower limit of detection for all women thought to be postmenopausal on clinical grounds and additionally cause modest elevation of FSH levels in both pre- and postmenopausal women (secondary to the suppressed oestradiol production). If measurements of FSH and oestradiol are made to confirm postmenopausal status for women whilst taking an aromatase inhibitor, and the FSH level lies close to 25IU/L then measurements should be repeated after a two-week interruption of aromatase inhibitor treatment to avoid an incorrect diagnosis of a postmenopausal state.

3. Ovarian suppression

GnRH agonists suppress both FSH and serum oestradiol. If following discontinuation of a GnRH agonist, FSH is ≤25IU/L and oestradiol is within the locally defined postmenopausal range then it is likely that there is ongoing GnRH agonist activity; repeat analysis should be performed at 4-6 week intervals until menopausal status is clear.

Measurements of FSH and oestradiol when made early, i.e. within 6 months of discontinuation of a GnRH agonist, are much more reliably interpretable where the analysis is performed following washout of tamoxifen or an aromatase inhibitor.

Bone Health

Ovarian suppression in premenopausal women and aromatase inhibitor therapy in postmenopausal women are known to cause accelerated bone loss (85). For this reason, careful attention should be paid to bone health for all patients randomised into the OPTIMA protocol. It is advised that sites follow the recommendations for monitoring and maintenance of bone health including the use of Dual Energy X-ray Absorptiometry (DEXA) studies contained UK national (4, 85) and other relevant guidelines, taking into account any planned use of adjuvant bisphosphonates.

9.5 ADJUVANT BISPHOSPHONATES

A meta-analysis has demonstrated a survival benefit for women with early breast cancer receiving adjuvant bisphosphonates (86). This benefit is seen in postmenopausal women and those who become postmenopausal as a result of their treatment. The meta-analysis does not demonstrate superiority of one agent over another or an optimal duration of therapy.

In the OPTIMA trial, all patients are eligible for treatment with a bisphosphonate as they are either postmenopausal or are treated with ovarian suppression.

It is recommended that patients in the OPTIMA trial receive a bisphosphonate (oral or intravenous) for 2-5 years according to UK national (4) and other relevant guidelines.

NOTE: To avoid potential treatment imbalance, sites should ensure that the bisphosphonate treatment schedule is the same for all patients irrespective of treatment allocation.

9.6 SURGERY

Appropriate surgery should be performed according to local guidelines.

- Breast Conservation:
  If breast conservation is undertaken then margins should be clear. If re-excision is required to gain clear margins this further surgery can take place either before or after chemotherapy.
- Mastectomy:
  If mastectomy is performed, immediate reconstruction should be offered according to local guidelines with consideration of all factors including patient choice and without inappropriate delay in delivering systemic therapy.
- Margins:
  The acceptable circumferential and deep/superficial margin widths are determined by local guidelines.
- Axillary Surgery:
  All patients should undergo pre-operative axillary staging with an ultrasound scan and needle biopsy or fine needle aspiration (FNA) of any suspicious or indeterminate nodes.

  Patients with pre-operative pathologically proven axillary lymph node involvement should undergo axillary clearance. Selection for sentinel lymph node biopsy should be according to local guidelines.

  Patients with axillary lymph node macrometastases identified at sentinel node biopsy should have further management (including entry into clinical trials of further axillary surgery versus no further surgery) according to local guidelines. Isolated tumour cell clusters (ITC) and micrometastases should be treated according to local guidelines. All planned axillary surgery must be completed before trial entry.

9.7 RADIOTHERAPY GUIDELINES

Radiotherapy should be given as part of breast cancer treatment as per standard good clinical practise and in accordance with local guidelines and the Royal College of Radiologists 2016 Consensus Statement (87), the NICE 2018 NG101 guidelines (4) and any other applicable national guidelines. The purpose of this section is to summarise current opinion on best practice.

CT-based treatment planning is recommended.
Sites may enter patients into clinical trials of post-operative radiotherapy.

- Breast Conserving Surgery:
  Breast radiotherapy is standard management for all patients who have had breast-conserving surgery. Whole breast including the primary tumour bed is the target volume. A tumour bed boost in conjunction with whole breast radiotherapy may be given as per local guidelines. Partial breast radiotherapy may be used, but only for patients who have a negative sentinel node biopsy, or a full axillary clearance.
- Post mastectomy Radiotherapy:

Chest wall radiotherapy is standard management for patients with ≥4 positive axillary nodes, T3 tumours with any node positivity and is recommended for tumours with a positive deep margin. The chest wall is the target volume.

Chest wall radiotherapy may be considered for patients with 1-3 positive axillary nodes, or high-risk node negative disease.

- Regional lymph node radiotherapy:
  There are three options for patients who have had a sentinel lymph node biopsy and at least one node is positive. These options are (1) axillary clearance, (2) axillary radiotherapy, or (3) observation. Practice in this area is changing rapidly and treatment selection should therefore be as local guidelines / physician choice. Levels I/II of the axilla should not be routinely irradiated after an axillary clearance.

  Treatment of the supraclavicular fossa is standard management when ≥4 axillary lymph nodes are involved and may be used according to local guidelines for patients with 1-3 involved axillary nodes.

  Internal mammary nodes should be treated according to local guidelines.

- Dose fractionation:
  Recommended schedules after breast conserving surgery or mastectomy:
  1. 40Gy in 15 fractions, 5 fractions per week
  2. 50Gy in 25 fractions, 5 fractions per week
  3. 45Gy in 20 fractions, 5 fractions per week
  4. 26Gy in 5 fractions, 5 fractions per week

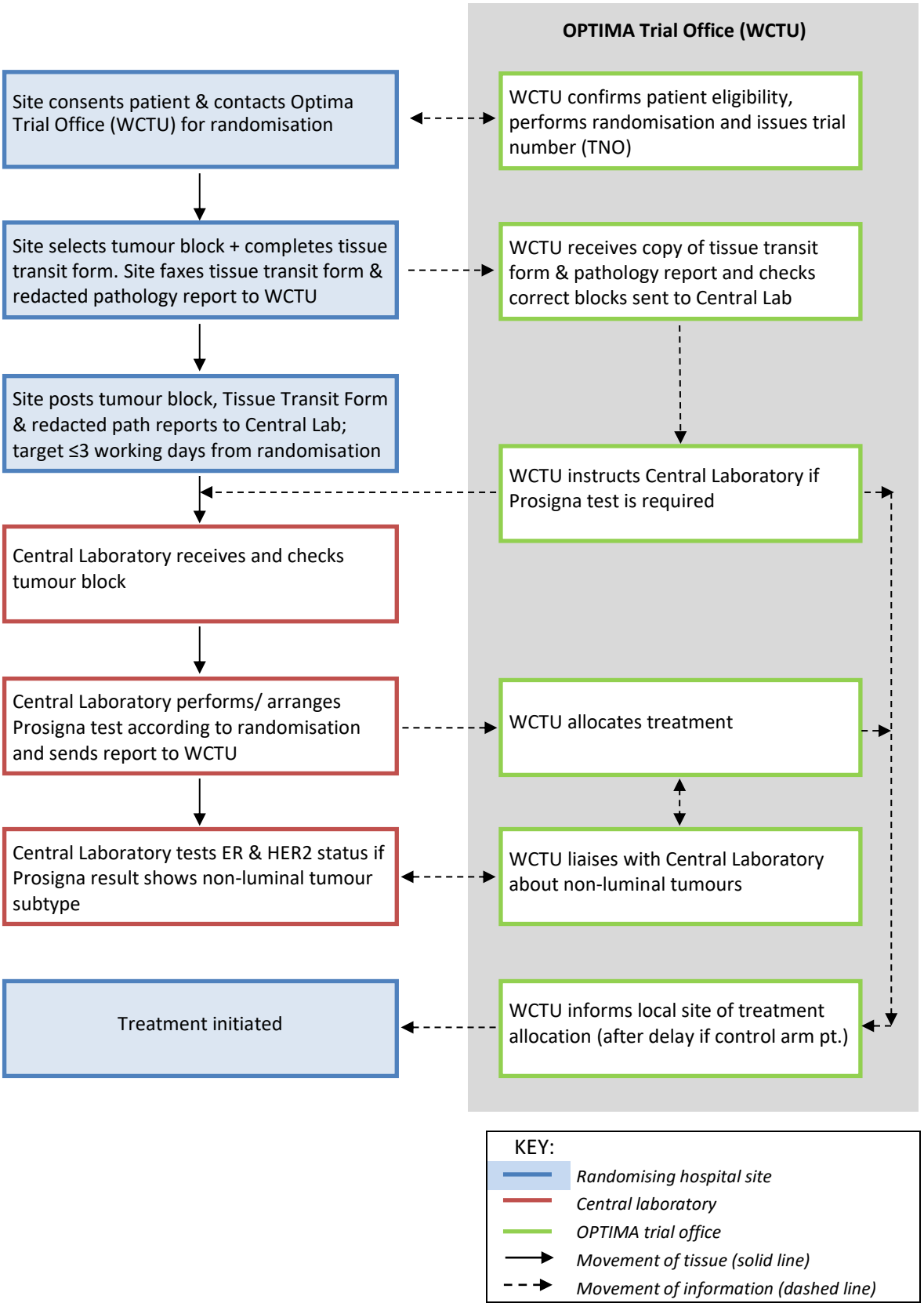
  Dose fractionation for tumour bed boost and regional lymph nodes should be given according to local guidelines.

- Intraoperative Radiotherapy (IORT):
  Patients who have received IORT are eligible for OPTIMA enrolment provided that they then receive standard external beam radiotherapy to the whole breast after chemotherapy is completed. The OPTIMA trial is designed for higher risk patients than those who participated in the IORT trials, and for this reason IORT alone is deemed inadequate treatment.

10. Consent and Randomisation Procedures

The information flow and tissue handling necessary for randomisation and treatment allocation is summarised in the flowchart (figure 2, below).

Figure 2. Tissue handling and treatment allocation flow diagram



The randomisation and treatment allocation process from the date of consent to treatment allocation will take approximately 2 weeks for most participants.

Detail of procedures may differ for non-UK sites*:* please refer to footnote* and to country-specific appendix.

10.1 INFORMED CONSENT

It is the responsibility of the local Principal Investigator (or designee as listed in the Site Signature and Delegation Log) to obtain informed consent in compliance with international requirements from each patient prior to entry into the trial. Discussions about trial participation may take place during an in-person consultation or remotely, i.e. during a telephone or video consultation. In all settings, the trial must be discussed in detail with the patient, and the patient provided with a copy of the Patient Information Sheet. Patients should be offered sufficient time to consider the trial, allowing time for discussion with family/friends/GP. The patient must be given the opportunity to ask questions and to be satisfied with the responses prior to consent being given.

Ethically approved patient facing information such as printed leaflets and on-line information sources, designed to inform potential participants of the existence of the trial are not part of the formal informed consent process. This includes the OPTIMA website (optimabreaststudy.com). Access to these sources will not be restricted to patients who have been approached about trial participation.

Full consent must be given in writing. This may be during an in-person consultation or alternatively, the patient may complete the consent form remotely. When completed remotely, the patient should return the signed form, or a scan or legible photograph of all sections of it, to a named person at the recruiting site using one of the following methods:

i. by post
ii. electronically (e.g. to an institutional email address)
iii. in person

The local Principal Investigator or designee receiving consent must countersign the consent form. There is no requirement that the counter signature date match the date of the participant signature where this has been completed remotely, but the counter signatory must be satisfied that the consent is genuine. Where the participant has returned an image of the signed form, this should be printed and if unsuitable for countersignature, the investigator should sign a blank consent form and attach the printed image to it. The consent form may be completed and signed electronically where an approved mechanism is available.

A potential participant who is unable to attend an appointment in person may, for convenience, also give *initial* remote verbal consent to the local Principal Investigator or qualified designee during a telephone or video consultation. The patient must be provided with a copy of the PIS and afforded the same opportunities to consider joining the study and to ask questions as they would be when attending in person. A documentation of remote verbal consent form must be completed to record verbal consent.

Remote verbal consent has limited scope. Specifically, participants may be entered into the trial, randomised by the OPTIMA Trial Office and tumour samples sent to the lab for testing. To release details of the treatment allocation however, the randomising site will need to confirm to the Trial Office that written consent has been received.

The Patient Information Sheet and Consent Form are available in electronic format to facilitate printing onto local headed paper. Signed original consent forms (or forms which have been received electronically, printed and counter signed) must be retained on site and should be stored in the trial site file with a copy filed in the patient's hospital notes. Completed Consent Forms **must not** be sent to the OPTIMA Trial Office at Warwick Clinical Trials Unit (WCTU) or to the Central Laboratory.

A copy of the fully signed consent form and where applicable, the documentation of remote verbal consent form, must be given to the patient. Copies may be in paper or electronic format according to site standard procedures. Sites must ensure that patients' participation in the trial is recorded in the patient notes and is communicated to the patient's General (or family) Practitioner.
If the Patient Information Sheet and/or Consent Form are modified during the course of the trial, sites will be notified of any required procedure to follow for patients already consented.

For non-UK sites: Informed Consent Forms and Patient Information Sheets will be translated into the national language of each international collaborator. Local Clinical Leads for each country will be responsible for the accuracy of the translation as well as obtaining approval of each form by the appropriate country-specific ethics committee(s).

10.2 RANDOMISATION

The randomisation procedure will commence after informed consent has been given ('trial entry'). During randomisation, eligibility will be confirmed by a trial investigator using the results of local pathology testing. Participants will be stratified according to country, intended chemotherapy regimen, number of involved nodes, histological grade, tumour size and menopausal status. This information must be available at randomisation. Before contacting the OPTIMA Trial Office at WCTU, a Randomisation Form and Eligibility Form must be completed. Randomisation can be conducted by telephone or fax to WCTU. Non-UK sites will use the WCTU online randomisation application.

Warwick Clinical Trials Unit Randomisation Service
Telephone 02476150402 (Mon-Fri 9am-5pm)
Fax: 024 7615 1586

Trial entry will be recorded by WCTU at the time of randomisation but is dated from the giving of informed consent, i.e. the earlier of participant signature of the consent form or the giving of remote verbal consent.

Participants will be randomised to standard treatment (control arm) or to test-directed treatment.

Randomisation will be by computer using a minimisation algorithm. The randomisation system will ensure that there is no bias between the two trial groups. Patients will be randomised strictly sequentially, and allocation between trial arms will be undertaken at a ratio of 1:1. The randomisation system will allocate each patient a unique trial number. The Trial Office will send a confirmation fax/email to the research site containing the randomisation details.

Following randomisation, the research site should send a partially anonymised copy of the participant's relevant histopathology reports to the OPTIMA Trial Office. To assist linkage with tumour blocks, in addition to the participant's trial number and initials, the report should show the date of birth, the hospital name and histopathology numbers. All other patient identifiable data (name, NHS and hospital numbers etc) should be redacted before the report is sent to the Trial Office. A copy of the redacted report should accompany the tumour block(s) sent to the Central Laboratory.

The Trial Office will check all pathology reports and any other necessary source documents, and in the event that patient identifiable information has not been fully removed, this will be redacted by the trial team.

Following randomisation, the research site will promptly send a tumour block to the Central Laboratory. The Trial Office will inform the Central Laboratory of the participant's randomisation. The laboratory will inform the Trial Office of receipt of the tumour block.

10.3 TUMOUR BLOCK SELECTION AND DOCUMENTATION

The collection and subsequent testing of an archival tumour block is integral to patient care in OPTIMA. A suitable tumour block should be sent without delay to the Central Laboratory following patient randomisation, target within 3 working days.

Tumour block selection should be performed as follows:

- Patients with a unifocal tumour: a representative tumour block should be selected.
- Patients who have received pre-operative endocrine treatment: a pre-treatment core biopsy should be selected.

  A tumour block from a surgical excision or other on-treatment biopsy is not acceptable: treated tumours are likely to have a lower Prosigna Score than untreated tumours, which could change the treatment allocation.
- Patients with multiple ipsilateral tumours: blocks from more than one lesion should be submitted to the laboratory when the lesions are considered to be clinically significant by the referring site and they are interpreted as synchronous primary cancers (based either on the site of the lesions, i.e. in different quadrants, or if they are of differing morphology, i.e. histological type or grade). It is anticipated that laboratories will, as per standard good practice, assess ER and HER2 on the different lesions.

  Clinical management will be based on the highest Prosigna score for patients randomised to test-directed treatment.

NOTE: Involved lymph nodes are not suitable for trial-specified laboratory investigation.

Tumour blocks will be accompanied by a transit document which must be completed by a member of staff trained in the interpretation of pathology reports. This should be either a trial investigator or pathologist who is a member of the breast multidisciplinary team. The transit document will record permissions agreed by the patient for future research (section 15), which will constitute evidence of consent to the receiving laboratory.

The site should additionally send a redacted copy of the histopathology reports to accompany the tumour block; this should be a copy of the redacted report that has been sent to the OPTIMA Trial Office

The address of the Central Laboratory service (UK) to send specimens to is:

HSL Advanced Diagnostics
Ground Floor
60 Whitfield Street
London W1T 4EU

Tel: 020 3912 0280
Fax: 020 3912 0288
email: AD@hslpathology.com
Web: hsl-ad.com

Additional details of the processing and delivery of tissue blocks to the Central Laboratory including the transit document to accompany the sample, and packaging and shipping instructions are provided in the OPTIMA Site Sample Collection Standard Operating Procedure (SOP) document.

10.4 CENTRAL LABORATORY PROCEDURES

The Central Laboratory will in the first instance assess the block(s) for invasive tumour content irrespective of randomisation. If any tissue block is deemed as insufficient or unsuitable a further tissue block will be requested from the recruiting site via the OPTIMA Trial Office.

For patients randomised to test-directed treatment, the Central Laboratory will either perform or despatch tissue to a second laboratory for Prosigna testing. The laboratory will inform the Trial Office of the result of the Prosigna test(s) if performed or if suitable tumour cannot be obtained from the recruiting site. In the ordinary course of events, the laboratory will make 2 attempts to obtain suitable tissue and/or perform a Prosigna test.

A small (estimated as approximately 4%, from OPTIMA *prelim*) proportion of patients may require confirmation of tumour ER and HER2 status because of the Prosigna test result, most commonly because the tumour has a non-luminal phenotype. The Central Laboratory will perform receptor re-testing in such cases.

10.5 TREATMENT ALLOCATION

For patients randomised to test-directed treatment, the Trial Office will inform the research site, by fax/email, whether the patient is to receive chemotherapy or not, based on the Prosigna Score. Where the Central Laboratory tests more than one tumour block, the block with the highest Prosigna Score will determine treatment allocation.

The research site will be blind to randomisation for those patients allocated chemotherapy. For patients randomised to standard treatment, the trial office will delay informing the research site of the treatment allocation by a time period equivalent to that taken to perform the Prosigna test for those randomised to test-directed treatment.

In the event that the Central Laboratory is unable to obtain sufficient or suitable tissue from the referring site, or if the Prosigna test should fail for any other reason, then the participant will be assigned to chemotherapy.

If the patient is found to have an ER negative/low or HER2 positive/amplified tumour as a result of procedures performed by the Central Laboratory then the Trial Office will inform the research site. In such cases, the patient must be treated appropriately for the tumour characteristics but will be continued to be followed-up for outcome measures and will be included in the primary analysis on an intention-to-treat basis. This will also apply in the event that additional (not pre-planned) analyses performed by the research site following randomisation result in the identification of an ER negative/low or HER2 positive/amplified tumour.

10.6 RANDOMISATION DOCUMENTATION

After patients have been randomised, the investigator should send the patient's General Practitioner (GP) a letter and copy of the Patient Information Sheet to inform them of their participation in the trial.

The completed Randomisation Form and Eligibility Form must be sent to the OPTIMA Trial Office, with copies retained at site. The patient's details must be entered onto the local site's Patient ID Log. The patient's trial number and initials will be used on all subsequent CRFs and correspondence relating to that patient. For sample tracking and pathology forms, the date of birth will additionally be included.

A Screening Log should be maintained to document all patients considered for the trial but not entered. Where possible, the reason for non-entry to the trial should be documented. Screening logs should be faxed to OPTIMA Trial staff on a regular basis as requested. Patient names or hospital numbers must not be recorded on the Screening Log (use initials only).

* The process of randomisation is the same for all participating countries but procedures may differ. For non-UK sites, the procedure is described in the country-specific appendix which includes details of the local coordinating centre (if any) and designated testing laboratory/ laboratories. These should be substituted for the terms “Central Laboratory” and “OPTIMA Trial Office” above.

11. Data Collection

Each site will be provided with an Investigator File containing Case Report Forms (CRFs). Copies of the CRF’s are also available from the OPTIMA website. Data collected on each patient must be recorded by the local Principal Investigator, or her/his designee, as accurately and completely as possible. The members of staff responsible for this must be appropriately recorded on the Site Signature and Delegation Log. The Principal Investigator is responsible for the timing, completeness, legibility, accuracy and signing of the CRF and he/she will retain a copy of each completed form. The Principal Investigator must allow study staff access to any required background data from hospital records (source data e.g. medical records) on request.

All fields MUST be completed. If a test or measurement was not done, please indicate why that was omitted on the CRF. Entries must be made in **black ballpoint pen**. Errors must be **crossed out with a single line** leaving the original data un-obscured (i.e. without overwriting), the correction inserted and the change initialled and dated. An explanatory note should be added if necessary. Correction fluid/tape/labels must not be used. All data submitted on CRFs must be verifiable in the source documentation. Any deviation from this must be explained appropriately. CRFs should be sent to the Trial Office by post or electronically (i.e. by email or fax), with a copy retained at site.

Completed CRFs should be returned to
OPTIMA Trial Office
Warwick Clinical Trials Unit
University of Warwick
Gibbet Hill Road
Coventry, CV4 7AL

At the discretion of WCTU, CRFs may be completed on-line where a mechanism is provided.

Non-UK sites: please refer to your country-specific appendix for details of data collection arrangements.

11.1 SCHEDULE OF EVENTS

Table 4 summarises the schedule of events within OPTIMA.

Table 4: Schedule of Events

	Pre-randomisation	Pre-treatment allocation	Following treatment allocation	3-months from trial entry	6 months from trial entry	12 months from trial entry	24 months from trial entry	Annually from 3 to 10 years
Inclusion criteria satisfied	X							
Informed trial consent received	X							
Archival tissue block sent to Central Laboratory		X						
Chemotherapy planned		X[a]						
Chemotherapy treatment			X[b]					
Endocrine treatment and compliance			X[c]			X[d]	X[d]	X[d]
OPTIMA Patient Questionnaire Booklet (Quality of Life & Health Resource Use)		X[e,f]		X[f]	X[f]	X[f]	X[f]	
Follow-up						X[g]	X[g]	X[g]

Notes:

Trial entry is dated from informed consent (i.e. the earlier of participant signature of the consent form or the giving of remote verbal consent).

a. Chemotherapy must be specified at the time of randomisation. In order to avoid delays, sites are advised to make arrangements for chemotherapy treatment in advance of treatment allocation, accepting that patients may be allocated endocrine therapy alone.
b. Chemotherapy is recommended to start within 2 weeks of treatment allocation. Monitoring during treatment is according to local guidelines.
c. Endocrine therapy recommended to start within 2 weeks of treatment allocation or within 4 weeks of day 1 of the final cycle of chemotherapy. Monitoring during treatment is according to local guidelines.
d. Information on current endocrine treatment and compliance with treatment to be collected as part of annual follow-up.
e. The initial Patient Questionnaire Booklet may be completed at any time point between Informed Consent and treatment allocation.
f. The Patient Questionnaire Booklet can be completed at all time points either in clinic or at home by post for patients who are not due in clinic or have been discharged from clinical review. If no reply is received to the postal questionnaire, sites are permitted to telephone patient and complete the form over the phone. Completion of questionnaires outside the expected timeframe will not be considered as protocol non-compliance.
g. Patients are followed-up annually. It is recommended that the annual follow-up is scheduled for the anniversary of trial entry where possible; follow-up undertaken outside this expected timeframe will not be considered as protocol non-compliance. Telephone or video follow-up is permitted. Follow-up by email is permitted subject to local information governance policies.

11.2 ADVERSE EVENT MANAGEMENT

Definitions

An Adverse Event (AE) is defined as any untoward medical occurrence in a randomised trial participant and which does not necessarily have a causal relationship with their involvement in the trial.

A Serious Adverse Event (SAE) is an AE that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical condition

Recording and Reporting

Information about AE's and SAE's are collected through routine data capture on CRFs (on the Chemotherapy Form and Annual Follow-up Form). Recurrence of and/or death from breast cancer and the diagnosis of new cancers in participants are outcome measures of the trial that will be collected on CRFs (the Event Form and Notification of Death Form) and are treated as expected events.

All treatment administered to trial participants according to the protocol is identical to the treatment given in normal clinical practice, for which there is extensive safety data already available. Therefore all AEs are expected and, for the purposes of this trial, further adverse event data is not collected as it is not required for trial analysis.

There is no requirement for expedited reporting of any SAEs in the trial.

11.3 QUALITY OF LIFE & HEALTH RESOURCE USE ASSESSMENT

Patients will be asked to complete the OPTIMA Patient Questionnaire Booklet incorporating FACT-B, EQ-5D, a distress thermometer, as well as health resource use information and a blank page to collect any further patient reported experiences. The first OPTIMA patient questionnaire should be given to patients after informed consent is received but prior to treatment allocation. Further OPTIMA patient questionnaires will be administered at 3, 6, 12 and 24 months from the date of consent. The Patient Questionnaire Booklet can be completed at all time points in clinic or at home by post for patients who are not due in clinic or have been discharged from clinical review. If no reply is received to the postal questionnaire, sites are permitted to telephone patient and complete the form over the phone. Completion of questionnaires outside the expected timeframe will not be considered as protocol non-compliance.

Each participating site will be responsible for providing patients with the Patient Questionnaire Booklets. The local Principal Investigator or their designee must explain the requirements, ensure the patient understands how to complete the questionnaires and the time-frames within which they are required, and ensure the booklets are submitted to the OPTIMA Trial Office at WCTU following completion. The member of staff responsible for this must be appropriately recorded on the Site Signature and Delegation Log.

Non-UK sites: please refer to your country-specific appendix.

11.4 FOLLOW-UP

Follow-up will be annually for 10 years from trial entry. Telephone follow-up is permitted for patients who have been discharged from clinical review. Follow-up by email is permitted subject to local information governance policies. For UK patients, information will also be obtained where possible

from Hospital Episode Statistics in conjunction with the National Cancer Intelligence Network. UK Patients will also be flagged with the ONS.

12. Post Randomisation Withdrawals, Exclusions and Moves Out of Region

Patients have the right to withdraw from the trial at any time for any reason. Patients should be encouraged to remain within the trial. However, if a patient wishes to withdraw, the OPTIMA Trial Office should be notified immediately. Full details of the reasons for withdrawal must be recorded on the relevant CRF.

Patients who have given remote verbal consent but who do not subsequently give written consent will be treated as withdrawn. Tumour blocks will be returned to the referring site in this event.

Patients may be withdrawn from trial treatment at the discretion of the Investigator and/or Trial Management Committee. If a patient is only withdrawn from trial treatment, they must be followed-up in accordance with the protocol.

Patients moving away from the region of the local site should NOT be withdrawn from the trial. Should this occur, please contact the OPTIMA Trial Office with the relevant details, and they will endeavour to assign the patient's follow-up to a site close to their new location.

13. End of Trial

The end of trial is defined as the date of completion of all trial procedures on all participants.

The trial will be stopped prematurely if:

- Mandated by the Ethics Committee
- Following recommendations from the IDMC
- Funding for the trial ceases

The Research Ethics Committee will be notified in writing within 15 days if the trial has been concluded or terminated early.

14. Statistical Considerations

14.1 STRATIFICATION

- Country: each country will be represented as a separate category
- Chemotherapy regimen (anthracycline- non-taxane [(F)EC75-80, (F)EC90-100, E-CMF] vs. taxane- non-anthracycline [TC] vs. combined anthracycline-taxane [(F)EC-T, (F)EC-Pw/2w, TAC] vs. dose dense [dd AC/EC-P])
- Number of involved nodes (node negative [includes isolated tumour cells] vs. positive sentinel node biopsy with micrometastases only and without axillary clearance vs. positive sentinel node biopsy with macrometastases and without axillary clearance vs. 1-3 nodes vs. 4-9 nodes)
- Histological grade (1, 2 vs. 3)
- Tumour size (≥ 30mm vs. < 30mm)
- Menopausal status (premenopausal vs. postmenopausal vs. male sex)

14.2 POWER AND SAMPLE SIZE

OPTIMA *prelim* informed the type of patients that would be entered into OPTIMA. The tumour characteristics of the population were similar to node-positive patients with HER2 negative disease enrolled in the ATAC and TEAM studies and who received 5 years of an AI. The 5-year disease free survival for patients in the transATAC study, with ER positive HER2 negative tumours with axillary lymph node involvement who were not treated with chemotherapy was 82% and the 5-year DRFS was 84% (Dowsett, Cuzick & Sestak, unpublished).

The power calculations assume a 5-year recruitment period with a minimum of 21 months follow-up. On this basis, a trial randomising 2250 patients in each treatment arm (4500 in the 2-arm study) will have the ability to demonstrate non-inferiority of test directed treatment, defining non-inferiority as 'no worse than 3%' below the estimated 85% 5-year invasive disease-free survival (IDFS) for the control arm with a one sided 5% significance level and 77% power. This sample size is sufficient to consider a variety of scenarios if the population changes (Table 5). The inclusion of the 412 OPTIMA prelim patients (206 in each arm) or 6 months additional follow-up will increase the power of assessing test directed therapy to 81%.

Table 5: Power calculations assuming 5 years recruitment, minimum of 21 months follow-up and non-inferiority defined as no worse than 3% below the control arm.

Control arm 5-year IDFS	Test guided arm 5 year IDFS	HR	Power with 2250 patients in each arm	Power including OPTIMA prelim patients
83%	80%	1.20	74%	80%
85%	**82%**	**1.22**	**77%**	**81%**
87%	84%	1.25	80%	84%
88%	85%	1.27	82%	85%
90%	87%	1.32	86%	89%
92%	89%	1.40	91%	93%
93%	90%	1.45	92%	95%
95%	92%	1.63	95%	96%

Key: IDFS = Invasive disease free survival; HR=non-inferiority limit for the hazard ratio.

If all control arm participants were tested, a 4500 patient sample size would have at least 80% power to demonstrate non-inferiority of IDFS for patients with tumours categorised as low score using the multi-parameter test (estimated at 65% of patients, based on OPTIMA *prelim*) at 3.5% with a one sided 5% significance level and a 5 year IDFS in the control arm of at least 87%.

OPTIMA is designed as an adaptive trial to allow the inclusion of another multi-parameter test or tests, should any additional multi-parameter test(s) become sufficiently validated, reasonably priced and warrant further research in the future. The adaptive trial design will be dependent on the available additional funding and the current recruitment rates.

14.3 ANALYSIS PLAN

The primary outcome is invasive disease free survival (IDFS), as defined in Table 3 (82). All time to event outcomes will be calculated from the date of trial entry to the date of first event, or the date last known to be alive. The time to event outcomes will be assessed using the Kaplan-Meier survival curves. Cox proportional hazards models will be used to compare trial arms after adjustment for stratification variables as well as exploring important prognostic factors and trial arm/marker interactions. The primary hypothesis of non-inferiority of IDFS between test-directed therapy and standard chemotherapy will be tested with adjustment for the stratification variables in a Cox regression model and the hazard ratio obtained. Non-inferiority may be conferred if the 95% quantile of the estimated hazard ratio is less than the non-inferiority limit for the hazard ratio of 1.22 assuming the control IDFS rate is 85% at 5 years (Table 5). Kaplan-Meier survival curves will also be produced

for IDFS by trial allocation for the patients with low-score tumours only and the 95% quantile of the estimated hazard ratio obtained from fitting a Cox regression model to assess whether having no chemotherapy in this population is non-inferior to having chemotherapy.

The quality of life FACT-B scale will be scored and analysed using longitudinal methods and appropriate statistical tests. Compliance with endocrine therapy will be assessed as the proportion of patients stopping endocrine treatment early and compared using a chi-squared test. In addition, the time to stopping endocrine therapy will be assessed using Kaplan Meier survival curves and compared between trial arms using the Cox regression model after adjustment for the stratification variables. The impact of endocrine therapy use on IDFS and overall survival will also be assessed.

All analyses will be carried out on an intention-to-treat basis using all randomised patients. Patients considered ineligible post-randomisation and those patients for whom multi-parameter testing on submitted tumour blocks cannot be completed will be included in the analysis. Patients from the *prelim*inary study will be included in the analysis of the test-directed therapy versus control without inflating the error rate (88). It is estimated that the analysis will be at 624 IDFS events.

Two interim analyses of the primary outcome measure are planned, equally spaced in terms of numbers of IDFS events and the final analysis. At each, it may be concluded that the experimental trial arm (test-directed therapy) is non-inferior to the control arm. The 5% Type I error rate for testing non-inferiority will be controlled by an O'Brien-Fleming-like alpha-spending rule set at p = (0.004, 0.007 and 0.047). A futility analysis based on conditional power to determine the value of continuing the study may also be considered at these times. Conditional power limits are likely to be set at 10%, to be decided after discussion with the Independent Data Monitoring Committee (IDMC); anything below this level would be unlikely to prove non-inferiority at the 3% margin. The sample size assumptions will be assessed at each interim analysis.

15. Pathology research

Tissue blocks for all patients will be stored in the OPTIMA Tissue Bank. In the event of tissue being required by the treating site for diagnostic use then the remaining tissue block will be returned. The UK tissue bank is located at the University of Edinburgh. Alternative arrangements may apply for non-UK sites (refer to appendix 3).

Prosigna testing on stored tumour samples from patients randomised to the control arm is planned to allow the analysis of the secondary outcome of IDFS for patients with low-score tumours. Additional pathology research designed to develop and improve multi-parameter assays is integral to the OPTIMA study. Intended research includes undertaking additional multi-parameter testing on stored samples to allow evaluation of these tests in predicting study outcome and the evaluation of tumour within lymph nodes.

Patients will additionally be asked to "gift" their tumour samples for unspecified future research. Patients are asked for permission to allow the future retrieval of additional stored tumour samples which may include lymph nodes from their treating hospital as part of their "gift". These donations are optional. The research may include genetic testing performed on the tumour tissue. It is the intention of the OPTIMA Trial Management Group (TMG) to make gifted samples available to third party researchers in the future. A tissue access mechanism will be developed to manage this process.

16. Economic Evaluation

Non-UK sites: please refer to your country-specific appendix for details of Economic Evaluation.

Preference-based utility data from the EQ-5D will be collected at baseline and every 3 months for the

first year then again at 2 years. Information will be collected using CRFs on all hospital-based chemotherapy, other drugs prescribed, inpatient stays and outpatient visits during the initial treatment phase and those associated with subsequent short and long-term toxicities. Other health and social care services used up to 12 months post-randomisation will be recorded using questionnaires posted to patients that will ask about primary care consultations, out of pocket expenses, social care contacts, and employment status. These will be administered at the same time as the quality of life questionnaires. Unit costs will be obtained from NHS reference costs, PSSRU Unit Costs for Health and Social Care, and other national sources, supplemented if necessary by unit cost data from participating sites.

16.1 MAIN STUDY ECONOMIC ANALYSIS PLAN

At the time of the final analysis of the main trial two cost-effectiveness analyses will be conducted.

1. A within-trial analysis will report the incremental cost-effectiveness ratio (cost per QALY) using data collected within the trial only. Methods recommended at the time of analysis will be followed to account for missing data and censoring (89). Uncertainty will be calculated using bootstrapping and presented as a cost-effectiveness acceptability curve.
2. A model based analysis will be considered the method of choice for calculating the primary economic outcome measure, the incremental cost-effectiveness ratio (cost per QALY). The model will consist of a decision model used to simulate costs and outcomes and will be based on that developed for analysis of the preliminary stage. The model will adopt a lifetime horizon and will be populated wherever possible using data from the trial but will be supplemented with external data where necessary or desirable on the basis of an updated literature review. Uncertainty will be evaluated by probabilistic analysis using Monte Carlo simulation and presented as a cost-effectiveness acceptability frontier. The precise methods (e.g. discount rate for costs and benefits) will be implemented in line with best practice for cost-effectiveness analysis at the time of the analysis, as specified by the updated methods guidance of the National Institute for Health and Clinical Excellence (90). For a full description of the modelling methods upon which the analysis will be based see Hall et al (5).

The primary perspective for all analyses will be the UK NHS and personal social services. Additional analyses will be conducted from a societal perspective.

17. Qualitative Recruitment Study

Non-UK sites: please refer to your country-specific appendix.

Some of the recruitment difficulties encountered in OPTIMA *prelim* are likely to re-emerge in the main trial, which may also encounter new challenges in light of the opening of new sites, and the different multi-parametric test under investigation (e.g. issues of equipoise, logistics of testing). To this end, an integrated qualitative recruitment study (QRS) will build on the findings from OPTIMA *prelim,* with a focus on implementing transferrable findings from the feasibility study, and identifying unique challenges that arise in the main trial. Emerging challenges will be reported to the Chief Investigator (CI) and Trial Management Group (TMG), with a view to formulating tailored solutions as the trial proceeds. This work will be undertaken with support from theme II of the Medical Research Council (MRC) ConDuCT-II (**Co**llaboration and i**n**novation in **D**ifficult and **C**omplex randomised controlled **T**rials **I**n **I**nvasive procedures) methodology hub.

The QRS methods employed will be similar to those used in OPTIMA *prelim*, based on methods developed by Donovan in the National Institute for Health Research Health Technology Assessment (NIHR HTA) Programme-funded ProtecT (**Pro**state **te**sting for **c**ancer and **T**reatment) study (91). The QRS will proceed in two iterative phases.

17.1 PHASE 1

Phase 1 will focus on implementing findings of OPTIMA *prelim* and identifying new challenges that arise in the main trial. Investigation of emerging challenges will be undertaken in a select sample of sites experiencing recruitment difficulties, with some high recruiting sites selected for comparison. A multi-faceted, flexible approach will be adopted, using one or more of the following methods:

1. Mapping of eligibility/recruitment processes

Previous research has shown that logistical and other local issues can sometimes lead to more or less efficient recruitment pathways. Patient eligibility and recruitment pathway details will be mapped for select sites, to include: the point at which patients receive information about the trial, members of the clinical team encountered, and the timing and frequency of appointments. Logs of eligible and recruited patients will be assembled using simple flow charts and counts to display numbers and percentages of patients at each stage of the eligibility and recruitment process. Logs will be analysed by the QRS researcher and trial co-ordinator and compared with the trial protocol.

2. In-depth interviews

In-depth, semi-structured interviews will be conducted and audio-recorded with three groups:

(a) Members of the TMG, including the CI and those most closely involved in the design, management, leadership and coordination of the trial.

(b) Clinical and recruitment staff across a range of clinical sites involved in the RCT.

(c) Patients eligible for recruitment to the RCT, including those who accept or reject randomisation.

Interview topic guides will be used to ensure similar areas are covered in each interview within each group. Informants in group (a) will be asked about the background, development and purpose of the RCT, interpretation of evidence and perceptions of equipoise; and their views on key recruitment challenges and how these may be addressed.

In addition to these topics informants in group (b) who directly recruit to the trial will also be asked the questions about their personal sense of equipoise when faced with individual eligible patients; the recruitment pathway in their sites and how they feel the protocol integrates into their clinical setting. Informants in group (b) will also be asked how they explain the RCT, the multi-parametric tests, and key trial processes (e.g. randomisation, blinding) to patients.

Informants in group (c) will include patients who have agreed to or rejected randomisation who are willing to discuss their views about the trial and how they reached their decision about participation. Patients will be probed to discuss: their individual pathway, from diagnosis until their decision about trial participation; their interpretation of the trial rationale and perceptions of equipoise, and their views on trial processes (such as randomisation and blinding). Attempts will be made to obtain a sample of maximum variation on the basis of age (i.e. extremes of the eligibility criteria), clinical characteristics (e.g. those with a small/large number of positive lymph nodes), decision about trial participation (accept/decline), and socio-demographic characteristics.

Information Sheets have been developed to inform staff and patients about the QRS including interviews. Consent Forms for staff and for patient interviews may be completed in person or alternatively, remotely by a researcher during a telephone interview; when completed remotely, the researcher will audio-record the consent process.

3. Observation of TMG and investigator meetings

The QRS researcher will regularly observe TMG and investigator meetings to obtain an overview of trial conduct and overarching challenges (logistical issues, etc.). Based on experiences from OPTIMA *prelim*, these meetings can elucidate new solutions to recruitment difficulties, and add a new dimension to challenges that have emerged through other data collection methods.

4. Audio-recording of recruitment appointments

Audio-recording of recruitment consultations is an important component of the QRS. The QRS researcher will work closely with the CI/TMG to identify sites where audio-recording of recruitment appointments would be most appropriate and feasible. These will be based on the existing screening log information, initially focusing on sites that have attempted recruitment; and later driven by theoretical sampling following data analysis and continued scrutiny of screening log information. There will be an attempt to sample a wide range of sites that vary in terms of recruitment rates.

One main point of contact (usually the lead research nurse) will be identified per site, and digital audio-recorders will be provided. The number of recorders required for each site will depend on the number of recruiting staff and the logistics and geographic location of recruiters. Recruitment staff will be requested to audio-record all appointments where they provide information to patients and attempt to recruit them to the RCT.

Documents explaining the ethical requirements of audio-recording of patient appointments (Patient and Staff Information Sheets and consent forms for audio-recording) and Standard Operating Procedures (SOPs) to help with the operation of the recorder, dictation of patient/recruiter/recording identifiers, naming and securely transferring of the recording to the computer and then to the QRS researcher will be provided to sites in 'Recruiter Packs'.

Recordings will be analysed through thematic, content, and targeted conversation analysis to identify aspects of information provision that are unclear, disrupted, and hinder recruitment. The QRS researcher will document findings and provide a summary of key issues to be fed back to the CI/TMG. These findings will form an important basis for individual and group feedback and training programmes to be initiated in Phase 2.

5. Study documentation

Patient information sheets (PIS) and consent forms will be scrutinised to identify aspects that are unclear or potentially open to misinterpretation, assess the clarity of the lay presentation of the evidence, and the balance of information on the different arms in the RCT and its adverse events. The information from the study documents will be compared with the findings from the interviews and recorded appointments, to identify any disparities or improvements that could be made.

17.2 PHASE 2: FEEDBACK TO CI/TMG

Findings from Phase 1 will be presented to the TMG. If recruitment difficulties are evident across the study or in particular sites, the TMG and QRS team will formulate a 'plan of action' to improve recruitment and information provision. The specific plan implemented will be grounded in the findings from the main trial and OPTIMA *prelim*. Generic forms of intervention may include 'tips' documents that provide suggestions about how to explain trial design and processes. Supportive feedback will be a core component of the plan of action, with the exact nature and timing of feedback dependent on the issues that arise. Site-specific feedback may cover institutional barriers, while multi-site group feedback sessions may address widespread challenges that would benefit from discussion. All group feedback sessions will be aided by anonymised data extracts from interviews and audio-recorded consultations. Individual confidential feedback will also be offered – particularly where recruiters experience specific difficulties, or where there is a need to discuss potentially sensitive issues. Investigator meetings and site visits may also be employed to discuss technical or clinical challenges (e.g. discomfort surrounding eligibility criteria).

Evaluating changes in recruitment practice and randomisation

The QRS team will evaluate the impact of QRS interventions implemented in phase 2 and consider further opportunities for action. Evaluation will constitute mixed approaches, including 'before/after' comparisons (eligible patients identified, number of recruited patients, patients accepting allocation) and investigation of changes in recruiter practice (through continued analysis of audio-recorded

consultations). Semi-structured interviews will be conducted with recruiting staff and TMG members to explore their views on QRS interventions, and suggestions for areas that would benefit from continued QRS input.

18. Data Management & Patient Confidentiality

18.1 Data acquisition

Case Report Forms (CRFs) will be designed by the Trial Coordinator in conjunction with the Chief Investigator and Statistician. Original CRFs must be sent to the coordinating team at WCTU and copies retained on site.

18.2 Data quality monitoring and audit

On receipt, all forms will be checked for completeness and congruity. Forms containing empty data fields or data anomalies will be queried with the site for resolution. Data will be entered onto the trial database and any further anomalies will be identified and queried with the site. Periodically, data will undergo additional checks to ensure consistency between data submitted on CRFs.

Trial staff will maintain regular communication with sites, through routine calls, mailings and/or meetings. In the event of persistent issues with the quality and/or quantity of data submitted, an on-site monitoring visit may be arranged. In such circumstances, patient notes and the investigator site file must be available during the visit. The representative from the OPTIMA Trial Office will work with the site staff to resolve issues, offer appropriate training if necessary, and to determine the site's future participation in the trial.

An audit may be arranged at a site if the Trial Management Group feels it is appropriate. Audits will be conducted by an independent team, determined by the Trial Management Group.

18.3 Participant Identifiable Data and Confidentiality

Personal data collected during the trial will be handled and stored in accordance with the UK Data Protection Act (2018), GDPR and all other applicable legislation and regulations. Participants (potential and actual) should be assured that their confidentiality will be respected at all times. WCTU will maintain the confidentiality of all patient data and will not disclose information by which patients may be identified to any third party, other than those directly involved in the treatment of that individual.

Details of the use made of participant's data within the study, arrangements for protection of data and participant's legal rights in accordance with legislation are contained in the Patient Information Sheet and Data Transparency Statement.

Data Collection and Use

To preserve patient anonymity, only the minimum patient identifiable data will be collected. For all routine communication including identification on CRF's, participants will be referred to by trial number (TNO) and initials only.

Participant full date of birth and National Health Service (NHS) number/ Community Health Index (CHI)/ Health and Social Care (HSC) number or other unique identifier (where applicable) will be collected at baseline.

Copies of pathology reports sent to the OPTIMA Trial Office and the Central Laboratory should contain in addition to TNO and initials, the participant's date of birth and histology number(s) and name of randomising/ pathology hospital. All other patient identifiable data should be redacted from these documents as described in Section 10 (Consent and Randomisation Procedures). For clarity, in the event that copies of pathology reports sent to the OPTIMA Trial Office contain incompletely redacted participant identifiable data, this will not be treated as a protocol violation.

Participant identifiable data will be used as follows:

- Date of Birth is used together with histology number as an identifier for tissue samples sent to the Central Laboratory and Tissue Bank to help ensure that tissue samples are associated with the correct patient. Both are used in communications between the Trial Office and Central Laboratory (and Tissue Bank). This procedure increases patient safety. Date of birth is additionally used to calculate participant age.
- National Health Service (NHS) number/ Community Health Index (CHI)/ Health and Social Care (HSC) number and date of birth will be used for flagging with NHS Digital, Office of National Statistics (ONS) and other relevant bodies that collect long-term health data. This data is vital for analysis of the primary outcome of the trial.

In addition, patients will be asked if they would be willing to be contacted to be interviewed about their decision to enter the trial (or not). Patients who agree to be contacted to be interviewed will be asked to provide their name and address to enable a Qualitative Recruitment Study researcher from the University of Bristol to contact the patient. These details will be sent directly from the site to the University of Bristol. Interviews may be audio recorded and will be stored electronically and identified by trial number only.

18.4 DATA STORAGE

The local investigator must maintain documents not for submission to the Trials Unit (e.g. patients' written consent forms) in strict confidence. In the case of special problems and/or regulatory queries, it will be necessary to have access to the complete trial records, provided that patient confidentiality is protected.

WCTU will maintain a trial database. This will contain all information related to trial participants including patient identifiable data and scanned copies of patient reports from the referring site. The database will be set up by the Programming Team at WCTU and all specifications (i.e. database variables, validation checks, screens) will be agreed between the Programmer, Statistician and Trial Coordinator. The database will meet industry-standard security criteria and will only be accessible to authorised personnel.

Data from OPTIMA participants which may include patient identifiable data that are held at other authorised sites including the University of Bristol, the Central Laboratory and the University of Edinburgh in the UK, will be stored in locally approved secure arrangements and in accordance with current legislative and regulatory requirements.

18.5 DATA SHARING

The OPTIMA Trial Management Group supports the sharing of outcome data with other researchers wishing to undertake additional analyses such as meta-analysis once the primary analysis of the trial has been published. The OPTIMA Trial Management Group additionally supports the sharing of data generated by tumour sample analysis with other researchers.

All data sharing will be governed by contract between the Sponsor and recipient to ensure that relevant intellectual property and the identity of individual trial participants are protected.

Where tumour (and any other biological) samples collected as part of the trial are made available to third party researchers (section 15), contractual arrangements between the Sponsor and researcher will be made to preserve the anonymity of trial participants. Specifically, attempts to identify individuals through analysis of data generated by researchers and the sharing and/or publication of data that could be used for this purpose will be prohibited.

18.6 ARCHIVING

All essential documentation and trial records will be stored by WCTU in conformance with the applicable regulatory requirements, and access to stored information will be restricted to authorised personnel.

Trial documentation and data will be archived for at least 10 years after completion of the trial in accordance with the University of Warwick's Research Data Management Policy.

19. Trial Organisation & Oversight

19.1 SPONSOR AND GOVERNANCE ARRANGEMENTS

University College London (UCL) will act as Sponsor for the OPTIMA trial.

The trial will be conducted in accordance with the principles and guidelines of the International Conference on Harmonisation (ICH), Good Clinical Practice (GCP), UK legislation, WCTU SOPs and the Protocol. GCP-trained personnel will conduct the trial.

19.2 ESSENTIAL DOCUMENTATION

A Trial Master File will be set up and held securely at the WCTU, in accordance with WCTU SOPs.

WCTU will provide Investigator Site Files to all recruiting sites involved in the trial. Investigator Site Files for non-UK sites will be supplied according to country-specific arrangements (appendix 3).

19.3 SITE STAFF TRAINING

Prior to activating a site to recruitment, it is necessary for all staff members working on the trial to participate in an induction session. This will be carried out during the initial launch meeting. For sites unable to attend the trial launch, or for sites opening to recruitment at a later date, this will be carried out via telephone or video conference or by site initiation visit.

Support will be offered to staff at participating sites to ensure they remain fully aware of trial procedures and requirements. Additional support and training will be offered to sites where necessary (e.g. recruitment rate lower than expected).

19.4 ETHICAL & REGULATORY REVIEW

Approvals

All required approvals for the trial will be sought using the Integrated Research Application System. The OPTIMA Trial has obtained ethical approval from the National Research Ethics Committee South East Coast - Surrey (NHS REC) in the UK. Before enrolling patients into the trial, each trial site must ensure that the local conduct of the trial has the permission of the relevant NHS/Health and Social Care (HSC) Organisation's research management function (e.g. R&D department). NHS/HSC management permission will be obtained through Health Research Authority (HRA) Approval for NHS Organisations in England and via the coordinated NHS/HSC permissions systems in the devolved administrations. UCL and WCTU will only activate a site to recruitment once written confirmation of the NHS/HSC Organisation's permission to participate in the study has been received.

Non-UK sites will require country-specific ethical approvals. UCL and WCTU will require written confirmation that the necessary ethical approvals are in place before recruitment can commence. Responsibility for managing local approvals may be delegated to the country-specific coordinating centre where applicable.

Amendments

All amendments will be documented by the OPTIMA Trial Office. Substantial amendments will be submitted for HRA Approval, which includes NHS REC review, prior to communication to relevant

participating NHS Organisations. Non-substantial amendments will be submitted to the HRA, and the applicable national coordinating functions in the devolved administrations, for review. Each trial site must ensure that they are using the most up to date version of the protocol, the Patient Information Sheet and Consent Form. All previous versions of the protocol, and other trial documents should be crossed out with 'this version is now superseded' written on cover page.

Annual Report

OPTIMA Trial staff will send an annual trial update report to the NHS REC, which will be distributed to the local research team at each trial site. It is the responsibility of the local research team at each site to send a copy of this report to the research management function (e.g. R&D Office) in accordance with local requirements and recommendations made by the NHS REC. Any additional local information required must also be submitted. Additional data required by NHS Trusts are available from the OPTIMA Trial Office on request.

19.5 TRIAL REGISTRATION

OPTIMA is registered with the International Standard Randomised Controlled Trial Number (ISRCTN) Register: ISRCTN42400492

19.6 INDEMNITY

NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial in the UK. UK NHS bodies carry this risk themselves or spread it through the Clinical Negligence Scheme for Trusts, which provides unlimited cover for this risk. All sites should ensure that they carry insurance allowing them to conduct studies including this one.

The UCL will indemnify the trial in relation to the design and management of the research.

19.7 TRIAL TIMETABLE AND MILESTONES

The main OPTIMA trial will randomise 4500 patients over a 5- year period from both UK and international sites in addition to patients randomised into OPTIMA *prelim*.

A 24-month recruitment feasibility phase has been incorporated into OPTIMA where we aim to have recruited 835 patients in total. Within the UK we aim to have 100 sites open, 790 patients recruited, and reach an average recruitment rate of 0.5 patients or more per site per month during the last 6 months of this phase (months 33 to 39).

The trial timetable is as follows where month 0 = (1st) October 2015.

Months 0-15:	HTA Grant activation and new site set up. Main Trial launch meeting.
Month 16:	Trial open to recruitment
End month 26:	74 sites open; 300 patients randomised; IDMC followed by Trial Steering Committee (TSC) to monitor recruitment and progress
End month 39:	End of recruitment feasibility phase: 835 patients randomised in total IDMC followed by TSC to monitor recruitment and progress.
End month 75:	4500 patients randomised. IDMC/TSC meetings.
Month 76-96:	Follow-up of patients, data collection & data cleaning and start analysis.
Month 96:	Analysis, preparation of trial report for HTA and manuscript for publication, presentation at national and international clinical conferences, dissemination through patient and consumer groups.
End month 195:	Planned final overall survival analysis (10 years from recruitment of last patient)

19.8 FUNDER

The OPTIMA trial has been funded by a grant from the NIHR HTA programme. Although funding from additional sources may be acquired to support non-UK recruitment and translational research projects, this will not affect the position of NIHR as the primary funder.

19.9 TRIAL ADMINISTRATION

The Chief Investigator for the trial is Professor Rob Stein, University College London Hospitals NHS Foundation Trust (UCLH) and UCL. The Chief Investigator is chair of the TMG. The trial will be co-ordinated from the OPTIMA Trial Office at WCTU, under the direction of Professor Janet Dunn (WCTU lead).

19.10 TRIAL MANAGEMENT GROUP (TMG) AND CORE TRIAL MANAGEMENT GROUP (CTMG)

The Trial Management Group (TMG) are the OPTIMA investigators and are responsible for trial design and monitoring trial progress. The TMG is a multidisciplinary team whose members include clinicians, statisticians, a translational scientist and a patient advocate, and has considerable expertise in all aspects of design, running, quality assurance and analysis of the trial. The core TMG (cTMG) consists of members of the TMG and the WCTU and is responsible for the day-to-day conduct of the trial. The TMG will report to the Trial Steering Committee through the cTMG.

19.11 TRIAL STEERING COMMITTEE (TSC)

The Trial Steering Committee (TSC) is an oversight committee appointed by the Trial Funder. The TSC will have an independent Chairperson and majority independent membership. The Chief Investigator and WCTU lead represent the TMG to the TSC. Additional members of the TMG will be co-opted onto the TSC as appropriate. Face to face meetings will be held at regular intervals determined by need but not less than once a year. Routine business is conducted by email, post or teleconferencing.

The TSC will take responsibility throughout the trial for:

- Proposals for substantial protocol amendments and provision of advice to the funder regarding approvals of such amendments
- Monitoring and supervising the progress of the trial
- Reviewing relevant information from other sources
- Considering recommendations from the Independent Data Monitoring Committee (IDMC)
- Informing and advising on all aspects of the trial

19.12 INDEPENDENT DATA MONITORING COMMITTEE (IDMC)

An Independent Data Monitoring Committee (IDMC) will be established for this trial and will advise the Trial Steering Committee. The IDMC will review the main trial for trial progress, recruitment, protocol compliance and interim assessment of outcomes, annually or more frequently if requested. The IDMC will advise on whether the trial should continue, be amended or stop prematurely based on the trial data monitored and any future publications or emerging worldwide evidence.

19.13 NCRI CLINICAL STUDIES GROUP

National Cancer Research Institute (NCRI) Breast Clinical Studies Group (CSG) developed and approved the trial and provided input into responses to reviewers of the funding applications.

19.14 PATIENT AND PUBLIC INVOLVEMENT (PPI)

Patient and Public Involvement is integral to the design of OPTIMA, and the patient advocacy group Independent Cancer Patients' Voice (ICPV) has contributed to study design, the patient information sheet and is represented on the TMG.

The effect of chemotherapy on patient's quality of life, adherence to endocrine therapy and reasons for non-adherence, and their experience of the use of multiparameter tests for decision making are issues that have been discussed in ICPV focus groups and the NCRI Breast Clinical Studies group symptom management subgroup, of which some of OPTIMA team are members. Any ethical approvals for national surveys to explore these issues further will be sought on a case by case basis.

20. Dissemination & Publication

The results of the trial will be published in peer-reviewed journal(s) and presented at national and international meetings and will be widely disseminated amongst the research community. The results will be presented first to the trial collaborators. The main trial report will be drafted by the trial co-ordinating team at the WCTU on behalf of the TMG, and the final version will be agreed by UCL prior to public presentation and/or submission for publication. Publication will be on behalf of the OPTIMA collaboration. The trial will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines (www.consort-statement.org), the Vancouver guidelines and the Helsinki Declaration.

The success of the trial depends on the collaboration of researchers from across the UK and other participating countries. Equal credit will be given to those who have wholeheartedly collaborated in the trial. All participating investigators and sites will be acknowledged in the primary publication(s). No investigator may present or publish data relating to OPTIMA without prior permission from the OPTIMA TMG.

The impact of various scenarios of results on investigators, and the potential change of practice, will be ascertained by surveys.

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Appendix 1: OPTIMA *prelim*-specific features of protocol

This appendix lists the features of the protocol that are specific to OPTIMA *prelim* and that are not current from version 4 onwards. Features of OPTIMA *prelim* that are applicable to the entire study and have been amended are summarised in Appendix 2: Protocol history

TRIAL DESIGN (Protocol Section 6, Trial Design – original wording)

OPTIMA is a multi-site partially blind randomised clinical trial with a non-inferiority endpoint and an adaptive design. The preliminary or feasibility phase of the study, which has the same structure as the main trial is referred to as OPTIMA *prelim*.

OPTIMA *prelim* will establish whether a large efficacy trial of multi-parameter test-based treatment allocation ("test-directed" treatment) is acceptable to patients and clinicians. A total of 300 patients will be randomised in a 1:1 ratio. The recruitment phase will last for up to two years. A 400 patient extension phase is built into the design of OPTIMA *prelim* to allow a smooth roll through into the main trial. OPTIMA *prelim* has an adaptive design. The performance of alternate multi-parameter tests will be compared to allow the selection of multi-parameter tests to be evaluated in the main trial.

OPTIMA will compare standard treatment of chemotherapy followed by endocrine therapy with multi-parameter test-directed treatment allocation to either chemotherapy followed by endocrine therapy or endocrine therapy alone. The randomisation of patients allocated to chemotherapy will be concealed from treating sites. In the main trial, 1860 patients will be randomised to each arm in a two or three arm design (with either one or two test arms). Patients will be followed up for ten years.

The test technology used in OPTIMA *prelim* to allocate patients to chemotherapy or to no chemotherapy is Oncotype DX (with a Recurrence Score cut-off of >25 vs. ≤25). The test technology or technologies and their cut-offs will be selected according to outcome of the preliminary study

OPTIMA *PRELIM* OBJECTIVES (Protocol Section 7, Objectives)

- To evaluate the performance and health-economics of alternative multi-parameter tests to determine which technology(s) are to be evaluated in the main trial.
- To establish the acceptability to patients and clinicians of randomisation to test-directed treatment assignment.
- To establish efficient and timely sample collection and analysis essential to the delivery of multi-parameter tests driven treatment.

OPTIMA *PRELIM* OUTCOME MEASURES (Protocol Section 8, Outcome Measures)

- Identification of a multi-parameter test technology that is suitable for validation in the main study.
- Recruitment of 300 patients in not more than 2 years from the first site opening to recruitment, and, for the final 150 patients: (1) patient acceptance rate will be at least 40%; (2) recruitment will take no longer than 6 months; (3) chemotherapy will start within 6 weeks of signing the OPTIMA consent form for no less than 85% of chemotherapy assigned patients.

STATISTICAL CONSIDERATIONS (Protocol Section 14, Statistical Considerations)

Preliminary study sample size (Protocol Section 14.2)

The feasibility study requires 300 patients to be recruited over the first 2 years (6 month set-up and 18 month recruitment phase). These numbers are sufficient to be able to detect concordance between tests, assuming that at least 70% of all 'test-directed' patients will be allocated to not requiring chemotherapy, taking into account the expected type of patients entered into the study. Oncotype DX is the current "Gold Standard" test from which the decision not to receive chemotherapy is acceptable. It is anticipated that the Oncotype DX test will be used prospectively to make the decision to receive chemotherapy or not, whilst the other tests will be applied retrospectively to the first 300 patients before a decision of which test(s) to take forward in the main trial is made. The extension of 400 patients will allow recruitment to continue at an estimated 30 patients per month for 12 months whilst the main trial is activated if the TSC decides for the TMG to proceed. Some further evaluation of test performance will be undertaken during the extension phase.

Assuming that 70% of patients randomised to test-directed treatment will be assigned to no chemotherapy as the result of the Oncotype DX test, then out of the 150 patients randomised to test-directed arm it is estimated that 105 of these will start endocrine therapy immediately. The true efficacy of this test will not be known until all patients have been followed up for 5 years and invasive disease free survival is compared. However all alternative tests (and combination of tests) will be compared against the Oncotype DX test for concordance. The study requires 150 patients to be randomised to the test-driven arm to be able to estimate the kappa value with reasonable accuracy. If the true kappa value was 0.8, this would give a lower 95% confidence limit of 0.7. In addition patients randomised to the control arm will also have Oncotype DX testing (retrospectively) and the pooling of all 300 patient's results at the end of the pilot phase will considerably improve the stability of the concordance estimate, lower 95% confidence limit of 0.73.

Analysis plan (Protocol Section 14.3)

The selection of the tests to be included in the main trial will be based on observations from the feasibility study. It is anticipated that this decision will be informed by a combined primary outcome measure including concordance of test results, cost-effectiveness and deliverability of pathology services. The Kappa concordance coefficient will be used to assess agreement between tests, whilst multivariate models will be produced to determine factors influencing concordance. Each test (and combinations of tests) will be compared with the Oncotype DX "gold standard". The planned economic evaluation is described in section 15.

Independent Data Monitoring Committee (IDMC) (Protocol Section 14.4)

An independent data monitoring and ethics committee will be established for this trial. Its main objective will be to advise the Trial Steering Committee as to whether there is evidence or a reason why the trial should be amended or terminated based on recruitment rates, compliance and delivery of tests. All centres should be set up within the first 6 months and the IDMC will review progress 7 months after grant activation when reports containing recruitment, protocol compliance and delivery of test results will be reviewed by the IDMC. The second IDMC review will be prior to discussions with funders to see if it is feasible to continue with the main trial. This decision will be based on the combined primary outcome of concordance of test results, cost-effectiveness and deliverability of pathology services.

Trial timetable and milestones for OPTIMA *prelim* (Protocol Section 14.5)

OPTIMA *prelim* will randomise 300 patients from 6-7 NCRN research networks in the UK. Up to 400 additional patients will be randomised in the preliminary study extension. Recruitment milestones assume at least 3 new centres activated per month up to at least 25 centres (30 maximum) which each recruit at least 1 patient per month. This enables 300 patients to be recruited within the 2 year funding period with the ability to recruit a further 400 patients in the best case scenario.

May 2012 Grant activated

May-Oct 2012	Site set-up and screening
Sept 2012	IDMC and TSC joint meeting to review protocol & timelines
Oct 2012	1st patient randomised
April 2013	72 patients, IDMC followed by TSC review
Oct 2013	210 patients, IDMC followed by TSC review
Dec 2013	Discussion with HTA re application for main trial
Feb 2014	300 patients recruited
April 2014	IDMC followed by TSC review

OPTIMA *prelim* will inform the timetable and milestones for the main trial.

PRELIMINARY STUDY ECONOMIC ANALYSIS PLAN (Protocol Section 15, Economic Evaluation)

The objective of the preliminary economic analysis will be to confirm that there is societal value in conducting further research into the cost-effectiveness of Oncotype DX or alternative test-directed therapy. An algorithm will be used to prioritize candidate tests for inclusion the main trial. The basis of this will be the model developed in preparation for the OPTIMA trial (5). The model will be updated with contemporary evidence from the feasibility study and appropriate external data at the time of the feasibility analysis. It will then be evaluated and outcomes presented in a number of stages, taking Oncotype DX as the initial gold-standard test:

1. The probability of cost-effectiveness of the gold-standard test in comparison to standard care (control arm) will be calculated. The gold-standard test will only be offered for inclusion in the main trial if there is an adequate probability of the gold-standard test being demonstrated cost-effective.
2. The probability of cost-effectiveness of alternative tests in comparison to standard care will be calculated from the same adapted model. Tests with an adequate probability of cost-effectiveness will be offered for inclusion in the main trial.
3. A test selection process will compare the expected value of including each test in the main trial as follows:
    a. Data on discordant selection of patients by candidate tests will be used in the cost-effectiveness model in light of a best-case scenario to ascertain if they can ever be demonstrated cost-effective.
    b. A fully probabilistic evaluation of the model will quantify the decision uncertainty around the cost-effectiveness of each test. Tests exhibiting a realistic probability of cost-effectiveness will be assessed by value of information (VoI) analysis. VoI analysis will be used to describe the societal value of including each test in the main OPTIMA trial.

Appendix 2: Protocol history

Version 1:

Version	Version date	REC Submission date	Submission ID	REC opinion	Comments
V1.0	08 Mar 2012	14 Mar 2012	Initial application	08 May 2012: Provisional favourable opinion subject to specified changes.	n/a
V1.2	22 May 2012	22 May 2012	Re-submission of initial application	22 Jun 2012: approved	Addressed REC comments on V1.0

Version 2:

Version	Version date	Amendment date	REC Submission ID	REC opinion	Comments
V2.0	23 Jul 2013	24 Jul 2013	SA#1	24 Jul 2013: Unfavourable opinion on amended PIS	Protocol approved but implementation delayed pending revision to PIS
		3 Oct 2013	Modified SA#1	16 Oct 2013: approved	Permission to implement protocol V2.0

Summary of changes made in V2.0:

- Clarification of inclusion/exclusion criteria (section 9.1/9.2)
- Addition of chemotherapy regimen FEC-Pw.
- Minor text changes to section 9.6 Surgery for clarification purposes.
- Addition to section 9.7 Radiotherapy to confirm compatibility with trial of post-operative radiotherapy.
- Tissue handling process modified to minimise opportunity for additional delays in randomisation process.
- Minor changes to schedule of delivery of intervention and data collection (section 12.1) to reflect changes to inclusion/exclusion criteria.
- Addition of telephone as a method of completion of follow-up Patient Questionnaire Booklets (all time points except baseline).
- Re-wording of section 13 Post Randomisation Withdrawals for clarification purposes.
- Trial Milestones updated (section 14.5).

Number of patients randomised when V2.0 approved: 130

Version 3:

Version	Version date	Amendment date	REC Submission ID	REC opinion	Comments
V3.0	18 Jul 2014	18 Jul 2014	SA#2	11 Aug 2014: Unfavourable opinion	Unfavourable opinion due to safety concern identified between submission of amendment and REC review.
V3.0	18 Jul 2014	20 Feb 2015	SA#4	26 Mar 2015: approved	Version not activated at sites.

Summary of changes made in V3.0:

- Increased sample size of the roll through phase (between feasibility and main study) from 200 to 400 participants.
- Discontinued central eligibility confirmation of ER and HER2 status.
- Correction regarding time points where patient questionnaire data is collected.

Number of patients randomised when V3.0 approved: 412

Version 4:

Version	Version date	Amendment date	REC Submission ID	REC opinion	Comments
V4.0	09 Sep 2015	9 Sep 2015	SA#5	18 Sep 2015: approved	Version not activated at sites.

Summary of changes made in V4.0:

- Features of the protocol specific to OPTIMA *prelim* removed from the main body into Appendix 1 (l sections 1, 2, 4.7, 5, 6, 7, 8, 11, 14, 15 & 16).
- Replacement of Oncotype DX by Prosigna as the primary test used to allocate treatment (sections 1, 2, 4.7, 5, 6, 10 & 14.2).
- Increase in sample size from 3,720 to 4,500 patients.
- Introduction of Breast Cancer Specific Survival and Invasive Disease Free Survival in low risk patients as secondary outcome measures (sections 1 & 8).
- Eligibility criteria extended to include men (sections 1, 19.1, 9.5 & 14.1).
- Lymph nodes containing micrometastases now considered as uninvolved for eligibility purpose (sections 1, 9.1 & 9.7).
- Clarification of eligibility rules for patients with bilateral and multiple ipsilateral cancers and allowing multi-parameter testing of more than one lesion (sections 1 & 9.1).
- Fluorouracil made optional component of anthracycline combination chemotherapy (FEC) regimens (sections 1, 9.4 & 14.1).
- Modification to recommended endocrine therapy with increase in duration from 5 to 5-10 years, permission for use of aromatase inhibitors in combination with ovarian suppression for premenopausal patients and recommendation for tamoxifen for men (sections 1, 2 & 9.5).
- Recommendation for use of adjuvant bisphosphonate therapy for all patients; no recommendation for specific drug and schedule made (section 9.6).
- Update to surgery and radiotherapy guidance made to changes in “best practice” arising from new evidence (sections 9.7 & 9.8).
- Update of background and rationale to the study (sections 4 & 5) with current relevant evidence and addition of information about the contribution of endocrine therapy to outcome (section 4.5), availability of multi-parameter testing in the UK (section 4.6) and the results of OPTIMA *prelim* (section 4.7).
- Update to sections: Statistical Considerations (section 14) to justify changes in sample size, Economic Evaluation (section 15) and Qualitative Recruitment Study (section 16) required for efficacy part of the study
- Minor changes of administrative nature

Number of patients randomised when V4.0 approved: 412

Version 5:

Version	Version date	Amendment date	REC Submission ID	REC opinion	Comments
V5.0	27 Sep 2016	30 Sep 2016	SA#6	4 Oct 2016: approved	Main study recruitment opened with version 5

Summary of changes made in V5.0:

- Administrative updates to contact details (pages 2-3).
- Update of background and rationale to the study with current relevant evidence (sections 4 & 5).
- Re-phrase of a secondary outcome measure to clarify that Quality of Life is measured by EQ-5D and FACT-B (sections 1 & 8).
- Formal definitions of the outcome measures have been added for clarity and to align with internationally accepted terminology (section 8).
- New eligibility category added to allow participation by patients with micrometastatic only nodal involvement provided that the tumour is above a minimum size (sections 1, 2, 9.1, 9.2 & 15.1).
- Removal of exclusion criteria to allow participation by patients with more than two involved axillary nodes (as defined in the inclusion criteria) identified by sentinel node biopsy or axillary sampling where further axillary surgery is not planned (sections 1, 9.2 & 9.8).
- Permitted chemotherapy regimens updated to include TAC and dose-dense AC/EC-paclitaxel. Regimens (F)EC-T and (F)EC-Pw adjusted from 100 to 90-100 (sections 1, 9.4 & 15.1).
- Modifications to detail of adjuvant endocrine therapy (sections 1 & 9.5):
  i. Clarification of when endocrine therapy is to be started for participants who are assigned to receive chemotherapy.
  ii. Re-insertion of statement that radiation is not permitted as a form of ovarian suppression after it was removed from V4.0 of the protocol in error.
  iii. Information added regarding extended endocrine therapy.
  iv. Definition of menopause simplified and updated to be consistent with NICE NG23 guidance (Nov 2015).
  v. New information added on determination of menopausal status in women receiving anti-oestrogen treatment.
- Further detail added to the recommendation for use of adjuvant bisphosphate therapy (section 9.6).
- Changes made to clarify that no ionising radiation is required as part of the research protocol (sections 9.5, 9.8 & 12.1).
- Detail added to describe management of randomised participants whose tissue samples are found to have insufficient invasive tumour content for Prosigna testing (sections 10 & 15.3).
- Modification to consent requested from participants for the use of personal data (sections 10 & 18.3):
  i. Consent for the trial office at WCTU to hold a record of patient date of birth and NHS/CHI number has been made a required (rather than optional) part of the patient consent to participate in the trial.
  ii. Permission to collect patient's name and address will only be sought from those patients who consent to be interviewed as part of the Qualitative Recruitment Study.
- Detail added to specify which members of site staff can complete the transit document that accompanies a participant's tissue block to the Central Laboratory (section 11.1).
- Addition of email as a method of follow-up for participants discharged from clinical review, in accordance with local information governence requirements (section 12.1 & 12.4).
- Information added regarding the management of adverse events (section 12.2).
- Study records will be archived and retained for at least 10 years following the conclusion of the study, in accordance with the University of Warwick's Research Data Management Policy (section 18.4).
- Previous sections Trial Organisation, Patient Protection & Ethical Conduct and Research Governance have been combined into section now titled Trial Organisation & Oversight (section 19), and content has been re-ordered.
- Updates to reflect introduction of HRA Approval (section 19.4).
- Trial timetable and milestones moved from Statistical Considerations (section 15) to Trial Organisation and Oversight (section 19). Trial milestones updated to reflect a change to start of participant recruitment into the main trial (section 19.7).
- Administrative updates to details of the trial administration, and trial management and oversight committees (sections 19.5, 19.9 – 19.12).

Number of patients randomised when V5.0 approved: 412

Version 6:

Version	Version date	Amendment date	REC Submission ID	REC opinion	Comments
V6.0	8 Nov 2018	8 Nov 2018	SA#8	21 Jan 2019: approved	n/a

Summary of changes made in V6.0:

- Protocol adjustment to allow for international involvement with the addition of an appendix to contain country-specific administrative arrangements where these differ from the UK (sections 1, 6, appendix 3 with references to appendix throughout protocol).
- Replace the term "risk" with "score" where used in the context of Prosigna test results and treatment (e.g. "low-score" not "low-risk") to avoid potential confusion (section 1, 2, 3, 8, 14, 15 and also in PIS)
- Update of study background and rationale with recent relevant evidence (*sections 4, 5, 21*).
- Distant recurrence free interval (DRFI) added as an additional secondary end point (section1, 8).
- Addition of distress thermometer to Patient Questionnaire Booklet (section 1, 8, 11.3).
- Allow short term pre-surgical endocrine therapy (maximum 8 weeks) including participation in window studies provided these do not involve chemotherapy (section 1, 9.1, 9.2).
- Extend limit for trial entry following final surgery from 8 to 12 weeks (1, section 9.2).
- Additional inclusion and exclusion criteria amendments, with re-ordering and division where necessary to maintain clarity (section 1, 9.1, 9.2)
    i. Definitions of what constitutes an ER positive and HER2 negative tumour updated to be consistent with current ASCO guidance.
    ii. Rules on allowed tumour size and lymph node involvement re-phrased for greater clarity. No change in criteria.
    iii. Rules on bilateral cancers amended to disallow ER-positive HER2-negative contralateral tumours that fulfil the entry criteria or are considered clinically significant by the randomising site.
    iv. Allow local radiotherapy treatment for previously diagnosed cancers including in situ breast cancers. No changes to the rules on systemic therapy.
    v. Clarify that classical LCIS is not a diagnosis of malignancy where this occurs as an isolated event.
    vi. Amend the exclusion criteria on the use of systemic treatment liable to affect breast cancer prior to trial entry in the so as not to conflict with the allowed use of pre-surgical endocrine therapy.
    vii. Allow IVF/ fertility preservation and hormonal contraception within 12 months of trial entry.
- Update to permitted Chemotherapy Regimens (section 1, 9.4).
    i. Allow the addition of platinum salts to chemotherapy regimens for patients identified as having a homologous DNA repair deficiency.
    ii. Allow EC90 x4.
    iii. Allow paclitaxel 2-weekly as alternative to weekly administration in (F)EC-Pw (now (F)EC-Pw/2w).
    iv. Allow reversal of order of administration of anthracyclines and taxanes in sequential anthracycline-taxane regimens ((F)EC-T, (F)EC-Pw/P2w).
    v. Allow paclitaxel-albumen (nab-paclitaxel) to be used as substitute for docetaxel/ paclitaxel.
- Restructuring of protocol sections 10 & 11 to ensure that information related to randomisation and laboratory procedures is more logically organised and with insertion of hyper-links to cross references in electronic copies of the protocol to aid navigation (section 9.1, 9.2, 10, 11, 15, re-numbering former sections 12-15 now 11-14).
- Revision of information on tumour block selection with inclusion in the summary (section 1, 9.1, 10.2).
- Recruitment period extended to 5 years with adjustment to trial milestones and power calculation (revised table 5) (section 1, 14 [formerly 15], 19.7)
- Recruitment country added as a stratification factor (section 14.1).
- Dose-dense chemotherapy made an additional chemotherapy regimen stratification factor (section 14.1).
- Statement that multi-parameter assays in lymph node metastases will be investigated as part of future research (section 15)
- Additional detail on data confidentiality and sharing with references to 2018 regulations (section 18).
- Update to dissemination and publication policy (section 20)
- Administrative updates to contact details (pages 2-3).
- Additional minor corrections and changes of an administrative nature.

Activation date = 12 Mar 2019; number of patients randomised when V6.0 activated: 936

Version	Version date	Amendment date	REC Submission ID	REC opinion	Comments
V6.1	5 Feb 2019	5 Feb 2019	NSA#17	12 Mar 2019: approved	Non-substantial amendment
Summary of changes made in V6.1: • Correction of significant typographical error & change to contact details (pages 2-3)					
Activation date = 27 Mar 2019; number of patients randomised when V6.1 activated: 953					

Version 7

Version	Version date	Amendment date	REC Submission ID	REC opinion	Comments
V7.0	11 Aug 2020	20 Aug 2020	SA#10	14 Sept 2020: Approved	

Summary of changes made in V7.0:

- Restructuring of protocol sections 9 & 10 by moving section 9.3 (Informed Consent) to new section 10.1 (re-numbering former sections 9.4-9.8, 10.1-10.5).
- Update of study background and rationale with recent relevant evidence (sections 1, 3, 4, 5, 21).
- Addition of statement of trial hypothesis (section 7)
- Amend definition of ER-positive tumours in inclusion and exclusion criteria to exclude ER-low tumours (≤10% staining) as defined in the 2020 ASCO-CAP guidance on the advice of the IDMC (section 1, 9.1, 9.2)
- Allow endocrine therapy initiated following surgery to be continued up to the time of starting chemotherapy (if allocated) rather than require this to be discontinued at trial entry (sections 1, 9.2).
- Re-defined allowed chemotherapy regimens: replace (F)EC75-80 and (F)EC90-100 by FEC75-80, FEC90-100 and EC90-100 to clarify standard cyclophosphamide doses for FEC90-100 and EC90-100 and disallow EC75-80 (section 9.3).
- Endocrine therapy (Ovarian Suppression) (sections 1, 9.4)
  i. Allow ovarian suppression to be deferred for patients who experience chemotherapy-induced amenorrhoea with requirement to commence this in the event of resumption of menses up to 2 years from trial entry.
  ii. Allow the prescribing of licensed 3-monthly GnRH agonist preparations (limited to leuprorelin acetate 11.25mg (Prostap®) at time of amendment).
- Add 26Gy in 5 fractions over 5 days to permitted radiotherapy fractionation schedules (section 9.5).
- Allow Intra-operative radiotherapy use provided external beam RT is subsequently given (section 9.5).
- Introduce procedure for "remote consent" including remote verbal consent from patients wishing to join the study but who are unable to attend a clinic appointment in person (sections 1, 10.1).
- Additional detail of the intended statistical analysis procedure (sections 1, 14.3)
- Update to trial personnel and contact details, correction of typographical errors and rephrasing to improve ease of comprehension.

Activation date = 10 Oct 2020; number of patients randomised when V7.0 activated: xxx

Appendix 3: Country Specific Protocol Arrangements for non-UK sites

Appendix 3 contains the details of the local arrangements for trial management outside the UK where these differ from the main protocol either because of different legislative or regulatory requirements or because of local arrangements related to data and sample handling.