optima

personalised treatment of breast cancer

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ABBREVIATIONS

Abbreviation	Explanation
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
DCIS	Ductal carcinoma in situ
DDFS	Distant disease free survival
DEXA	Dual energy X-ray absorptiometry
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
GnRH	Gonadotropin-releasing hormone
GP	General Practitioner
HER2	Human Epidermal Growth Factor Receptor 2
HRT	Hormone Replacement Therapy
HSCIC	Health and Social Care Information Centre
ICH	International Conference on Harmonisation
ICPV	Independent Cancer Patient's Voices
IDFS	Invasive disease free survival
IDMC	Independent Data Monitoring Committee
IHC	Immunohistochemistry
ISH	In-situ hybridisation

Abbreviation	Explanation
ITC	Isolated tumour cells
i.v.	Intravenous
LCIS	Lobular carcinoma in situ
LH	Luteinizing hormone
M	Methotrexate
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 Clinical 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
Pw	Paclitaxel
q.	Every
QA	Quality assurance
QRS	Qualitative Recruitment Study
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
SOP	Standard Operating Procedure
T	Docetaxel

Abbreviation	Explanation
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

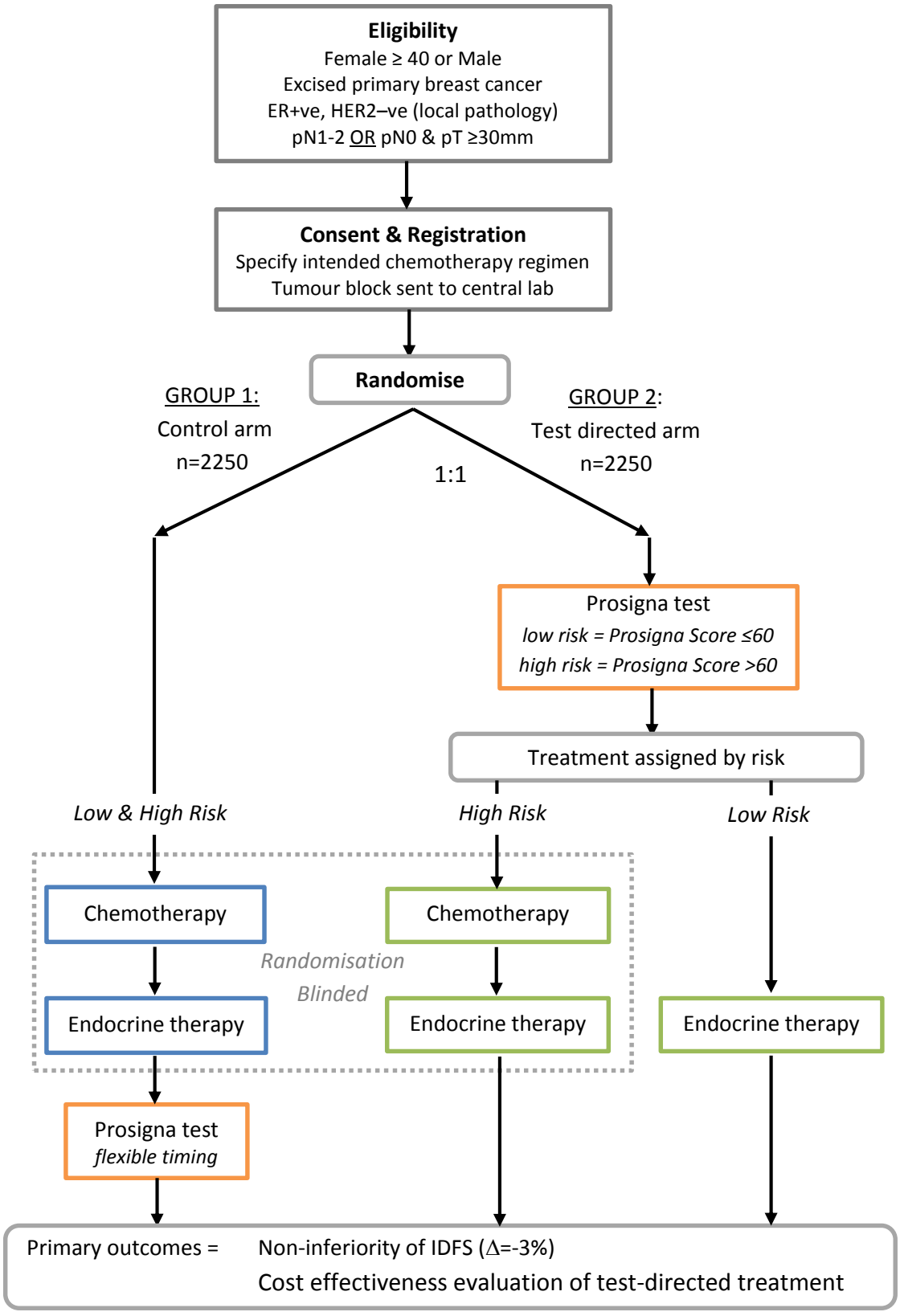
Title:	**O**ptimal **P**ersonalised **T**reatment of early breast cancer using **M**ulti-parameter **A**nalysis
Rationale:	It is normal clinical practice to offer several months of adjuvant chemotherapy to patients with early breast cancer who have involved axillary lymph nodes. A recommendation for chemotherapy is incorporated into a number of guidelines. Recently however it has been argued that chemotherapy may have little effect on some subtypes of breast cancer, which broadly are identified as being hormonally responsive tumours without HER2 gene amplification/HER2 protein overexpression and with a low or intermediate grade. These patients already benefit substantially from hormonal therapies and the addition of chemotherapy is thought to confer no significant additional survival advantage. There is also evidence that multi-parameter genomic tests may identify a population of patients who do not significantly benefit from chemotherapy despite being at risk of relapse as a result of tumour size or nodal involvement. 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 who are likely to benefit from chemotherapy and sparing those who are unlikely to benefit from an unnecessary and unpleasant treatment, and to establish the cost-effectiveness of this approach. The OPTIMA study population would ordinarily be treated with a combination of chemotherapy and endocrine therapy. The trial compares the management of patients using test-directed assignment to chemotherapy 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.
Eligibility Criteria:	• Female or male, age ≥ 40 • Excised invasive breast cancer with local treatment either completed or planned according to trial guidelines. • ER positive (Allred score ≥3 or H-score ≥10 or >1% of tumour cells stained positive) as determined by the referring site (in a laboratory meeting NEQAS standards). • HER2 negative (IHC 0-1+, or ISH negative/non-amplified (ratio of HER2/chromosome 17 <2.00 and copy number <6)) as determined by the referring site (in a laboratory meeting NEQAS standards). • Axillary lymph node status: (i) 1-9 involved (macrometastases i.e. >2mm) OR (ii) node negative AND tumour size ≥ 30mm. Nodes containing micrometastases (i.e. >0.2-2mm) or isolated tumour cell clusters (ITC) only (i.e. ≤0.2mm) will be considered to be uninvolved. *Note: Although it is anticipated that the majority of patients with node positive disease will be identified by histological examination, those diagnosed as macrometastases by OSNA (or equivalent PCR-based assay) are considered eligible.* • Considered appropriate for adjuvant chemotherapy by 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. • Bilateral cancers are permitted provided at least one tumour fulfils the entry criteria and none meet any of the exclusion criteria.

	Note: If the patient is regarded as eligible with regard to both cancers, blocks from both lesions will be submitted for Prosigna testing. Clinical management will be based on the higher Prosigna score for patients randomised to test-directed treatment. • Multiple ipsilateral cancers are permitted provided at least one tumour fulfils the entry criteria and none meet any of the exclusion criteria. *Note: Blocks from more than one lesion should be submitted for Prosigna testing 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.* • Written informed consent for the study.
Exclusion Criteria:	• ≥10 involved axillary nodes (as defined in the inclusion criteria) or involved internal mammary node. • ER negative OR HER2 positive/amplified (as determined by the referring site). *Note: Patients with non-luminal tumour subtypes identified by Prosigna testing will have central retesting of receptor status. If they are subsequently identified as having ER negative or HER2 positive/amplified tumours on re-testing they will be treated appropriately for the tumour characteristics and will continue to be followed-up as part of the OPTIMA trial.* • 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: o managed by surgical treatment only and disease-free for 10 years o previous basal cell carcinoma of skin, cervical intraepithelial neoplasia or ductal carcinoma in situ (DCIS) of the breast treated with surgery only or previous diagnosis of lobular carcinoma in situ (LCIS). • The use of oestrogen replacement therapy (HRT) at the time of surgery. Patients who are taking HRT at the time of diagnosis are eligible provided the HRT is stopped before surgery. • Pre-surgical chemotherapy, endocrine therapy or radiotherapy for breast cancer. Treatment with endocrine agents known to be active in breast cancer including ovarian suppression is permitted provided this was completed >1 year prior to study entry. • Commencement of adjuvant treatment prior to trial entry. Short-term endocrine therapy initiated because of, for instance, prolonged recovery from surgery is permitted but must be discontinued at trial entry. • Trial entry more than 8 weeks after completion of breast cancer surgery. • Planned further surgery for breast cancer, including axillary surgery, to take place after randomisation, except either re-excision or completion mastectomy for close or positive/involved margins which may be undertaken following completion of chemotherapy.

	• Patients with more than two involved axillary nodes (as defined in the inclusion criteria) identified by sentinel node biopsy or by axillary sampling where further axillary surgery is not planned.
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-centre partially blinded randomised 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)
Trial Treatments:	**Chemotherapy** (permitted regimens): • (F)EC75-80 • (F)EC90-100 • (F)EC-T • TC • E-CMF • (F)EC-Pw **Endocrine therapy** (permitted treatment)**:** • Postmenopausal at trial entry: aromatase inhibitor for 5-10 years • Premenopausal at trial entry: tamoxifen or an aromatase inhibitor for 5-10 years; plus ovarian suppression with GnRH agonist for at least 3 years OR bilateral oophorectomy. • Male: tamoxifen for 5-10 years
No. patients:	4500 patients (2250 patients per arm) *(Sample size does not include patients recruited into OPTIMA prelim)*
Stratification:	1. Chemotherapy regimen 2. Number of involved nodes 3. Histological grade 4. Tumour size 5. 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: • Distant disease free survival (DDFS) • Breast cancer specific survival (BCSS) and Overall survival (OS) • IDFS for patients with low-risk tumours • Quality of Life and Health Resource Use as measured by EQ-5D & FACT-B • Patient compliance to 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 event or the censor date. The primary outcome of IDFS will be assessed using the Kaplan-Meier survival curves and compared using Cox models after adjustment for stratification variables. The final analysis of the primary outcome measure will be undertaken when all patients have a minimum of 3 years follow-up.

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. Data from the Oxford Overview has suggested 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 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 the National Health Service (NHS) 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 using molecular techniques, mostly applied to paraffin-embedded tissue. The most mature test is the Oncotype DX Recurrence Score (RS), which measures the expression of 21 genes. Retrospective analyses of two clinical trials of tamoxifen, with or without chemotherapy, have suggested that the RS is predictive of chemotherapy benefit. A number of other less well-characterised multi-parameter assays may also fulfil the same role.

OPTIMA aims to assess the value of multi-parameter tests in women aged 40 or older and in men who have node-positive or large (pT ≥30mm) node-negative tumours that are ER positive and HER2 negative. These patients are currently offered adjuvant chemotherapy in addition to endocrine therapy. In this study they would be randomised either to receive standard treatment (chemotherapy) or to "test directed treatment". In the latter the recommendation for chemotherapy will be based on risk category as defined by the test: high-risk patients will be offered chemotherapy, low risk 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 50,000 in 2011, and with about 12,000 deaths in the same year, 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.

The treatment of primary breast cancer, which is undertaken with curative intent, is divided into local (surgery and radiotherapy) and systemic (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) status 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; later relapse is a 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

randomized clinical trials and current National Institute for Clinical Excellence (NICE) guidance recommends that these drugs should be offered to the majority of postmenopausal patients (3).

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 ((4) 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 (5). As a result, adjuvant chemotherapy treatment for breast cancer imposes a financial burden in the order of £80m a year 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 is then used to predict individual patient treatment benefit. The best known of these tools is Adjuvant! (6), which is recommended in NICE guidance (3). However, Adjuvant! and similar tools 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 pathology-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) (7). 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-targetted drugs such as trastuzumab (Herceptin). The value of Ki67, a marker of proliferation which is not routinely measured, is more controversial (8) and is subject to difficulties in assay standardisation (9).

Since 2000 with the invention of the technology of microarray profiling, a new molecular classification of breast cancer has been developed (10, 11). This classification divides breast cancers into four main "intrinsic subtypes": luminal A, luminal B, HER2 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 sub-types. 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 of the intrinsic classification

	Luminal A	Luminal B	HER2	Basal
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. Recently, progress has been made in mapping the original microarray based system onto immunohistochemical markers that can be used in routine pathology laboratories (2, 12) although correlation is imperfect (13). Considerable progress has also been made with developing RNA-based assays (e.g. Prosigna (PAM50) and MammaPrint/ Blue Print – 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 would 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. The main focus of this development has been in ER positive HER2 negative and mostly node-negative tumours. There is good quality evidence to support the use of many of these assays, which are either currently available or in the process of being developed for clinical use (table 2).

Many of these assays, particularly Oncotype DX (14), Mammostrat (15, 16) and MammaPrint (14, 17), 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 exoression.

The majority of the assays have been developed primarily as prognostic tests. The best validated assays have been retrospectively tested on archival material from historical trials; to date no prospective evaluation of any multi-parameter assay has been reported. Additionally there is little data on the cross-comparison between the assays and it is significant to note that there is considerable overlap between the markers included in many of these tests. Most critically, there is very little data that allows the performance of the assays to be compared with best routine pathological practice. Nevertheless the available comparisons suggest that all assays classify tumours with 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 (Investigators or Company)	Details of Multi-parametric assay	Test Output	Availability	Ref.
Perou and Sorlie (academic)	The original description of the intrinsic classification using 495 genes (the most highly cited papers in breast cancer).	subtype		(10, 11)
Oncotype DX (Genomic Health Inc)	A 16 (+5 normalisation) gene qRT-PCR expression assay for ER	risk score & category	Central lab (US)	(14)
MammaPrint + BluePrint (Agendia)	A 70 + 80 gene microarray based expression signature.	risk category, subtype	Central lab (NL)	(17, 18)
PAM50 (nanoString Technologies)	A 50 (+5 normalisation) gene expression assay using the nanoString platform.	Subtype and risk score & category	Regional labs	(13, 19)
Breast Cancer Index (BCI) (bioTheranostics)	A 7 gene qRT-PCR expression assay for ER positive breast cancer	risk score & category	Central lab (US)	(20, 21)
Mammostrat (Clarient/ GE Healthcare)	A 5 gene immunohistochemical assay.	risk score	Central lab (US)	(15, 16)
IHC4 (non-proprietary, Genoptix)	Quantitative immunohistochemical assay for ER, PgR, Her2, Ki67; conventional immunohistochemistry, AQUA ™ fluorescence IHC	risk score & category	Local labs, Central lab (US)	(22)
MapQuant (Genomic Grade Index) (Bordet Institute)	A 97 gene microarray based expression assay.	risk score & category	Not currently available.	(23, 24)
EndoPredict (Sividon)	A 7 gene qRT-PCR expression assay.	risk score & category (includes clinical data)	Regional labs	(25)
NPI plus	A 10 gene immunohistochemical assay.	risk score	In development	(26)
MammaTyper (BioNTech Diagnostics GmbH)	A 4-gene qRT-PCR assay for ER, PgR, HER2 & Ki67.	subtype	In development	(27)

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 (14). 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 the 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 Genomic Health Inc. in a single US laboratory.

Multiple studies (reviewed in (28-31)) have confirmed the value of Oncotype DX as a predictor of residual risk following endocrine therapy. Oncotype DX reclassifies risk defined by Adjuvant!, a widely used risk prediction nomogram that utilises conventional histopathology parameters. Oncotype DX has also been shown to predict chemotherapy sensitivity in the neoadjuvant setting (32, 33) as well as risk of local recurrence with a possible interplay with radiotherapy (34).

Analysis of individual patient Oncotype DX Recurrence Scores in the NSABP B-20 trial in women without axillary nodal involvement (35) and in the SWOG88-14/ INT0010 trial in women with node-positive disease (36) has shown 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 (31, 37).

Limitations of Oncotype DX, as highlighted by 4 systematic reviews (28-30) 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 (30). Additionally, Oncotype DX is only able to predict risk of recurrence within 5 years of diagnosis (38). No prospective studies reporting the impact of Oncotype DX on long-term outcomes such as overall survival have been identified, nor has the test been prospectively trialled against alternatives. There is no evidence that the Oncotype DX assay is any more informative than other gene expression assays (19, 39).

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 (13). 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 Inc. as Prosigna, an assay that can be performed in suitable local laboratories using hardware and reagents provided by the company. The analytical validity of the assay has been demonstrated in this distributed environment (40) and the company was granted the necessary FDA (Federal Drug Authority) approval for its marketing as a prognostic assay in postmenopausal patients in September 2013. The FDA-approved signature (Prosigna Score or ROR_PT) includes a parameter derived from expression of the proliferation-related genes in PAM50 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 2 studies (13, 41) and has been shown to reclassify risk defined by Adjuvant! using conventional pathology. Similarly, Prosigna has been demonstrated to predict residual risk and to reclassify risk using the large transATAC cohort and approximately 1500 mostly node negative patients treated with endocrine therapy alone in the ABSCG08 study (42, 43). Prosigna, in contrast to Oncotype DX and IHC4, is also able to predict late (beyond 5 years) recurrence in these 2 patient cohorts (38, 44). Both of these patient cohorts were postmenopausal and the terms of the FDA approval of Prosigna reflects this. PAM50 but as yet not Prosigna has been validated in a premenopausal patient cohort (45). PAM50 has also been shown to predict response to neoadjuvant chemotherapy and to distinguish response rates between higher and lower risk groups with ER positive disease (13, 46). Three studies have explored the ability of PAM50 to predict long-term outcome in trials comparing 2 chemotherapy regimens, two of which were conducted in early breast cancer (47, 48) and one in advanced disease (49). None of the 3 studies selected patients by receptor expression, so the numbers of patients analysed with luminal disease was comparatively small. Two of the 3 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 (48), which is a counterintuitive finding. There are no published studies exploring the effect of using either version of the assay in clinical practice.

NICE has reviewed the evidence supporting the use of Prosigna and its likely cost to the NHS as part of the Medtech innovation-briefing programme (50).

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 (51). 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 (28-30)). Several studies have shown that MammaPrint is able to predict response to neoadjuvant chemotherapy including differentiating between high and low risk ER positive disease (46, 52, 53). 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 (31, 54), 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 (28-30). The limitations of the evidence in support of Oncotype DX also apply to MammaPrint.

IHC4 and fluorescence IHC4: There is evidence that 4 conventional immunohistochemistry (IHC) markers, ER, PgR, HER2 and Ki67 (12) 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 (22). 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 (55). Both methods of detection provided significant prediction of residual risk following endocrine therapy with reasonable correlation.

The low estimated cost (£150) of performing IHC4 using conventional IHC (30) 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 (56). It is possible that performing the assay using quantitative immunofluorescence established in local laboratories will prove more reproducible, but this is yet to be established.

MammaTyper: This is a 4-gene qRT-PCR expression assay being developed commercially by BioNTech Diagnostics GmbH. The assay measures ER, PgR, HER2 and Ki67 mRNA (27). 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 (41). Formal validation studies of the assay are ongoing.

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 steroid hormone sensitive breast cancer treated with tamoxifen, the Overview suggests that 10-year mortality is reduced from about 31% to 25% by anthracycline chemotherapy (57). Whilst this is highly significant, 17 patients need to be treated for one life to be saved.

All 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 (58). 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 (13, 46).

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 the first test developed that is able to predict whether or not tumours are likely to be sensitive to chemotherapy.

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 (59). 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 (60). Two trials, BIG 1-98 (61) and TEAM (62) 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 (63) or for a switch from tamoxifen to AI (compared to no further endocrine treatment) after 5 years (64). To date there is no information about the effectiveness of AI therapy beyond 5 years although by inference this too should be beneficial. 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 both ovarian suppression or oophorectomy and chemotherapy-induced ovarian failure also reduce relapse risk. Chemotherapy induced ovarian failure is common in the over 40's.

The only randomised trials to investigate the benefit of ovarian suppression in the era of contemporary breast cancer treatment are the companion SOFT and TEXT trials (65, 66). 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 SOFT patients.

The SOFT trial showed no overall benefit for the addition of ovarian suppression to tamoxifen. However for the approximately 50% of participants whose cancers were judged to be of sufficiently high risk to require initial chemotherapy by their oncologist, there was a clear and substantial benefit for ovarian suppression, especially when combined with an AI. The majority of patients with node-positive disease enrolled in SOFT were treated with chemotherapy. TEXT confirmed the overall superiority of ovarian suppression + AI over ovarian suppression + tamoxifen.

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 September 2013 (67). 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 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 at this time. Five additional technologies, including PAM50, were removed from the scope in November 2011 on the grounds that at that time there was insufficient evidence for them to be included in the analysis. Oncotype DX testing as approved recommended by DG10 was made available to English NHS patients in April 2015; negotiations are underway in the remainder of the UK (July 2015).

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 trial 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 taken out of the body of the protocol and moved 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 (68).

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 centres 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 DG10 guidance recommends that Oncotype DX testing be 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 this test provides superior prognostic information to conventionally assessed histological grade. The economic analysis conducted for DG10 showed Oncotype DX was not cost-effective when applied to the entire potentially eligible population of patients with node negative disease. The recommendation for its use was therefore as a prognostic test, restricted to patients with larger or higher grade tumours but even so its use is predicted to result in a net cost to the NHS that could only be brought within the NICE thresholds were the provider to offer 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 not influenced by the use of adjuvant chemotherapy (57). The predefined risk categories for the assay 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 provider offers no 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 much more likely to benefit from multi-parameter tests used as predictors of chemotherapy sensitivity, to direct treatment decisions as these can only reduce chemotherapy use in this population. Comparatively little evidence currently exists for the value of multi-parameter tests in this population. OPTIMA, by studying a largely node positive population will provide this evidence. Evidence that Oncotype DX and other tests are able to predict chemotherapy sensitivity above and beyond providing prognostic information is suggestive but is based on a very limited number of patients evaluated retrospectively. If correct then multi-parameter assays would be far more powerful tools than simple prognostic indicators. NICE recommended that further research be performed on this topic: OPTIMA will answer this important question.

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

• **TAILORx** (69): 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 primary analysis is expected in 2017. 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.

• **MINDACT - EORTC 1004** (70): This pan-European trial compared adjuvant chemotherapy treatment decisions based on the MammaPrint test with decisions based on clinical risk calculated using "Adjuvant!". 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 primary analysis is expected to take place in late 2015.

• **RxPonder** (71): 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 (68). Although evidence to support the use of Prosigna was not available in 2011 for inclusion in the NICE DG10 evaluation, 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. 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-centre partially blinded randomised 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 400 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). OPTIMA is an adaptive trial to allow additional multi-parameter test technology to be evaluated in the future.

7. Trial 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 disease free survival (DDFS)
- Breast cancer specific survival (BCSS) and Overall survival (OS)
- IDFS for patients with low-risk tumours
- Quality of life and health resource use as measured by EQ-5D & FACT-B
- Patient compliance with long term endocrine therapy

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 (Allred score ≥3 or H-score ≥10 or >1% of tumour cells stained positive) as determined by the referring site (in a laboratory meeting NEQAS standards).
- HER2 negative (IHC 0-1+, or ISH negative/non-amplified (ratio of HER2/chromosome 17 <2.00 and copy number <6)) as determined by the referring site (in a laboratory meeting NEQAS standards).
- Axillary lymph node status: (i) 1-9 involved (macrometastases i.e. >2mm) OR (ii) node negative AND tumour size ≥ 30mm. Nodes containing micrometastases (i.e. >0.2-2mm) or isolated tumour cell clusters (ITC) only (i.e. ≤0.2mm) will be considered to be uninvolved.

  Note: Although it is anticipated that the majority of patients with node positive disease will be identified by histological examination, those diagnosed as macrometastases by OSNA (or equivalent PCR-based assay) are considered eligible.
- Considered appropriate for adjuvant chemotherapy by 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.
- Bilateral cancers are permitted provided at least one tumour fulfils the entry criteria and none meet any of the exclusion criteria.
  Note: If the patient is regarded as eligible with regard to both cancers, blocks from both lesions will be submitted for Prosigna testing. Clinical management will be based on the higher Prosigna score for patients randomised to test-directed treatment.

- Multiple ipsilateral cancers are permitted provided at least one tumour fulfils the entry criteria and none meet any of the exclusion criteria.

  Note: Blocks from more than one lesion should be submitted for Prosigna testing 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.
- Written informed consent for the study.

9.2 EXCLUSION CRITERIA

- ≥10 involved axillary nodes (as defined in the inclusion criteria) or involved internal mammary node.
- ER negative OR HER2 positive/amplified (as determined by the referring site).

  Note: Patients with non-luminal tumour subtypes identified by Prosigna testing will have central re-testing of receptor status. If they are subsequently identified as having ER negative or HER2 positive/amplified tumours on re-testing they will be treated appropriately for the tumour characteristics and will continue to be followed-up as part of the OPTIMA trial.
- 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:
  - managed by surgical treatment only and disease-free for 10 years
  - previous basal cell carcinoma of skin, cervical intraepithelial neoplasia or ductal carcinoma in situ (DCIS) of the breast treated with surgery only or previous diagnosis of lobular carcinoma in situ (LCIS).
- The use of oestrogen replacement therapy (HRT) at the time of surgery. Patients who are taking HRT at the time of diagnosis are eligible provided the HRT is stopped before surgery.
- Pre-surgical chemotherapy, endocrine therapy or radiotherapy for breast cancer. Treatment with endocrine agents known to be active in breast cancer including ovarian suppression is permitted provided this was completed >1 year prior to study entry.
- Commencement of adjuvant treatment prior to trial entry. Short-term endocrine therapy initiated because of, for instance, prolonged recovery from surgery is permitted but must be discontinued at trial entry.
- Trial entry more than 8 weeks after completion of breast cancer surgery.
- Planned further surgery for breast cancer, including axillary surgery, to take place after randomisation, except either re-excision or completion mastectomy for close or positive/involved margins which may be undertaken following completion of chemotherapy.
- Patients with more than two involved axillary nodes (as defined in the inclusion criteria) identified by sentinel node biopsy or by axillary sampling where further axillary surgery is not planned.

9.3 INFORMED CONSENT

It is the responsibility of the local Principal Investigator (or designee as listed on the Site Signature and Delegation Log) to obtain written informed consent in compliance with national requirements from each patient prior to entry into the trial. 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 written consent being given.

A copy of the signed Consent Form(s) must be given to the patient. The documents are available in electronic format to facilitate printing onto local headed paper. Original Consent Forms must be retained on site (it is recommended that the original is retained in the trial site file, with a copy filed in the relevant patient's hospital notes). Completed Consent Forms must not be sent to the OPTIMA Trial Office at Warwick Clinical Trials Unit (WCTU).

If the Patient Information Sheet and/or Consent Form are modified during the course of the trial, sites will be notified of the procedure to follow for patients already consented and for prospective patients.

9.4 CHEMOTHERAPY REGIMENS

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

- (F)EC75-80:
  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
  note – fluorouracil may be omitted from this regimen
- (F)EC90-100:
  fluorouracil [F] 500 mg/m^2, i.v. q.3weeks x 6 cycles
  epirubicin [E] 90-100mg/m^2,
  cyclophosphamide [C] 500mg/m^2
  note – fluorouracil may be omitted from this regimen
- TC:
  docetaxel [T] 75mg/m^2 i.v. q.3weeks x 4-6 cycles
  cyclophosphamide [C] 600mg/m^2
- (F)EC-T:
  FEC100 (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
- 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.4 weeks x 4 cycles
  OR 100mg/m^2 p.o. daily x14 days
  methotrexate [M] 40mg/m^2
  fluorouracil [F] 600mg/m^2
- (F)EC-Pw:
  FEC100 (as above) i.v. q.3weeks x 3-4 cycles
  followed by
  Paclitaxel 80-90mg/ m^2 i.v. q.1 week x 9-12 cycles

Anti-emetics and other supportive care including the use of Granulocyte - Colony Stimulating Factor (G-CSF) should be given according to local guidelines.

9.5 ADJUVANT ENDOCRINE THERAPY

Endocrine therapy is to be started no later than 2 weeks from treatment allocation in patients assigned to no chemotherapy or 4 weeks after the final dose of chemotherapy for all other patients. Concomitant endocrine therapy and chemotherapy is not allowed. Endocrine therapy should not be delayed until after radiotherapy.

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

Women who fulfil the following criteria will be considered postmenopausal:

- Age ≥ 60
- Bilateral surgical oophorectomy
- Age 45-59 years and > 1 year natural amenorrhoea
- Age < 45 years and amenorrhoea > 5 years
- For amenorrhoea not fulfilling the above criteria including hysterectomy without bilateral surgical oophorectomy age <60, then FSH, LH and oestradiol must be assayed to confirm postmenopausal status.

Women who do not fulfil the above criteria and who develop post-chemotherapy amenorrhoea should be considered to be premenopausal.

- Postmenopausal at trial entry:
  All postmenopausal women should be treated with an aromatase inhibitor (anastrozole, exemestane or letrozole) for 5-10 years, unless there is a contraindication.
- 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 for at least 3 years or by bilateral oophorectomy.

  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.

  Patients should be considered for a further 5 years of adjuvant endocrine therapy with either tamoxifen or an aromatase inhibitor. If switching from tamoxifen to an aromatase inhibitor at 5 years, then menopausal status needs to be confirmed at this stage as post-menopausal.
- Male:
  Tamoxifen for 5-10 years.

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.

Ovarian suppression in premenopausal women and AIs in postmenopausal women are known to cause accelerated bone loss (72). For this reason, careful attention should be paid to bone health for all patients randomised into the OPTIMA protocol. Bone density monitoring should be performed according to local protocol, informed by the 2008 National Cancer Research Network (NCRN) Bone Health Guideline (72) and the 2009 NICE CG80 Early Breast Cancer Guideline (3).

It is recommended that all patients have a baseline Dual energy X-ray absorptiometry (DEXA) study within 3 months of starting ovarian suppression or an AI. If the T score is >-1.0 no further monitoring is required. If the T score is <-1.0, repeat DEXA should be performed after approximately 2 years. Clinicians are encouraged to follow the recommendations contained in the NCRN Bone Health Guideline (72) for maintenance of bone health.

9.6 ADJUVANT BISPHOSPHONATES

A recent meta-analysis has demonstrated a survival benefit for women with early breast cancer receiving adjuvant bisphosphonates (73). 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 if they were premenopausal at diagnosis they will have received ovarian suppression.

It is recommended that patients in the OPTIMA trial receive a bisphosphonate (oral or intravenous) for 3-5 years.

9.7 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 before or after chemotherapy.

- Mastectomy:

  If mastectomy is performed, immediate reconstruction should be offered according to local protocol 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 protocol.

- Axillary Surgery:

  All patients should undergo pre-operative axillary staging with an ultrasound scan and needle biopsy or fine needed aspiration (FNA) of any suspicious or indeterminate nodes.

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

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

9.8 RADIOTHERAPY GUIDELINES

Radiotherapy will be given in accordance with local guidelines. CT-based treatment planning is recommended. Centres may enter patients into clinical trials of post-operative radiotherapy.

- Breast Conserving Surgery

  Breast radiotherapy is required 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 required for patients with ≥4 positive axillary nodes, T3 tumours with any node positivity and is recommended for tumours with a positive deep margin.

  Chest wall radiotherapy may be considered for patients with 1-3 positive axillary nodes, or high-risk node negative disease. The chest wall is the target volume.

- Regional lymph node radiotherapy

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

  Axillary radiotherapy in addition to breast radiotherapy may be given using a 4-field technique when patients with up to two involved sentinel nodes do not undergo clearance. The axilla should not otherwise be routinely irradiated.

  Internal mammary nodes should be treated according to local protocol.

- 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

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

10. Randomisation Procedure

The randomisation procedure will commence after written informed consent has been given ('trial entry'). During randomisation, eligibility will be confirmed using the results of local pathology testing. Patients will be stratified according to intended chemotherapy regimen, number of involved nodes, 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.

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

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

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 treatment allocation between 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.

To preserve the patient's anonymity, only their allocated trial number and initials will be required on the Case Report Forms (CRFs). With the patient's permission, their name and date of birth, address and health service (NHS) number/Community Health Index (CHI) number will be collected at randomisation on the Randomisation Form to allow flagging with the Health and Social Care Information Centre (HSCIC), Office of National Statistics (ONS) and other relevant bodies, and to allow sample tracking. Patients should be assured that their confidentiality will be respected at all times.

Following randomisation the research site will promptly send a tumour block to the trial's Central Laboratory. The Central Laboratory will inform the OPTIMA Trial Office upon receipt of the tumour block.

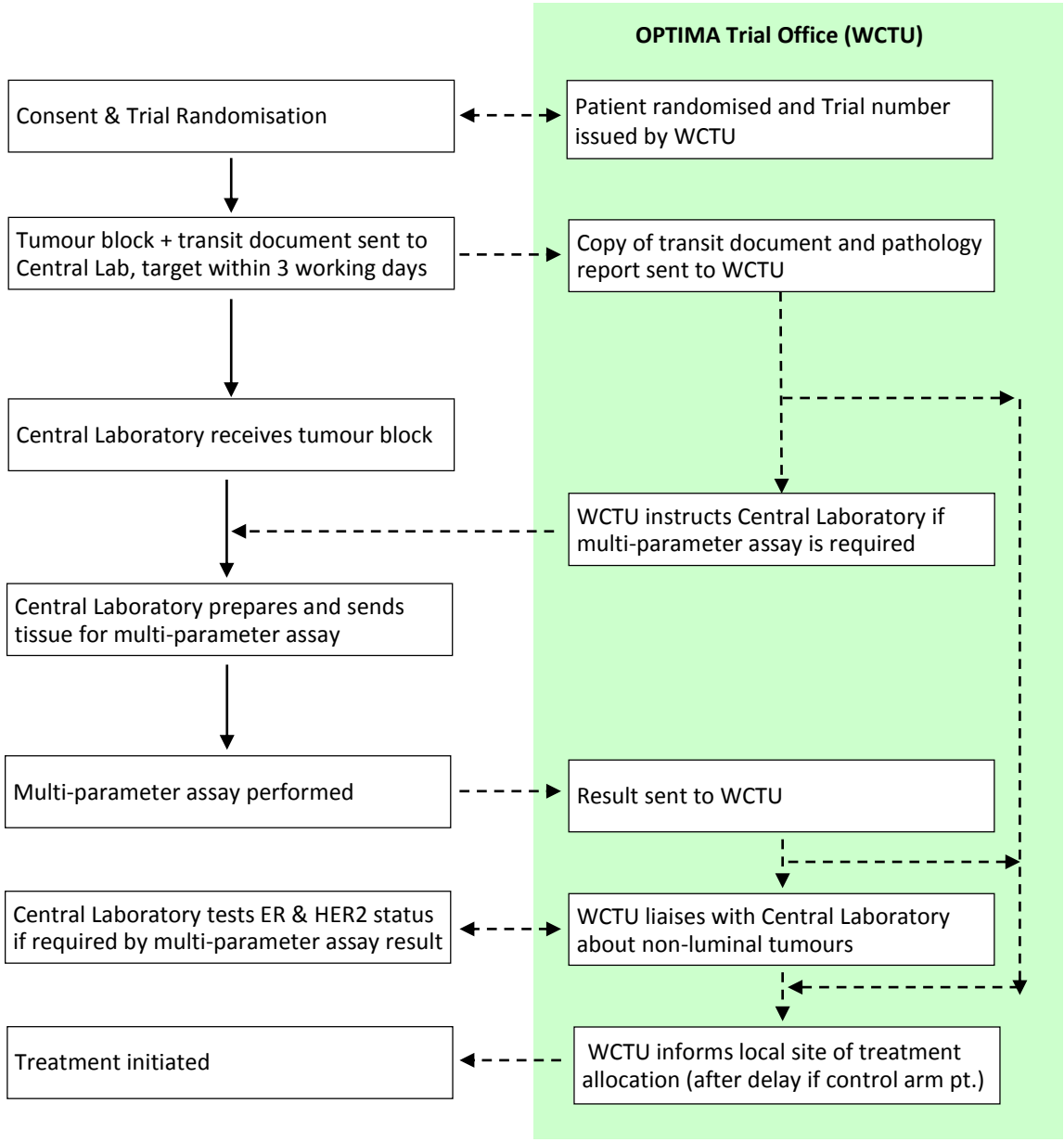
For patients randomised to test-directed treatment, the Central Laboratory will prepare and despatch tissue for multi-parameter testing. The multi-parameter assay result will be returned to the OPTIMA Trial Office. The trial office will subsequently inform the research site, by fax/email, whether the patient is to receive chemotherapy or not.

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 multi-parameter assay for those randomised to test-directed treatment.

The randomisation process from date of patient registration to treatment assignment will take approximately 3-4 weeks. The information flow and tissue handling necessary for randomisation and treatment assignment is summarised in the flowchart (figure 2).

A small (estimated as approximately 4%, from OPTIMA *prelim*) proportion of patients may require confirmation of tumour ER and HER2 status because of the multi-parameter assay result, most commonly because the tumour has a non-luminal phenotype. The Central Laboratory will perform receptor re-testing. If the patient is found to have an ER negative or HER2 positive/amplified tumour as a result, 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.

Figure 2. Tissue handling Flow Diagram



10.1 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 also be included.

A Screening Log must be maintained to document all patients considered for the trial but subsequently excluded. Where possible, the reason for non-entry to the trial must be documented. This must 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).

11. Laboratory Investigations

11.1 Central Trial Laboratory Investigations

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

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

UCL Advanced Diagnostics
1st Floor, Rockefeller Building
21 University Street
London, WC1E 6JJ

Tel: 020 7679 6039
Fax: 020 7679 6275
Email: info@uclad.com
Web: www.uclad.com

Details regarding the processing and delivery of tissue blocks to the Central laboratory service including the transit document to accompany the sample and the packaging and shipping instructions are provided in the sample collection standard operating procedure (SOP). The transit document will be completed by research staff at the treating site and will record permissions agreed by the patient for future research. This document will constitute evidence of consent to the receiving laboratory.

11.2 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 future diagnostic use then the remaining tissue block will be returned.

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-risk 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.

Patients will additionally be asked to "gift" their tumour samples for unspecified future research. This donation is optional. The research may include genetic testing performed on the tumour tissue. Patients may also be asked to donate research blood samples. 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.

12. Data Collection

Each site will be provided with an Investigator File containing Case Report Forms (CRFs). Data collected on each patient must be recorded by the local Principal Investigator, or his/her designee, as accurately and completely as possible. 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. Original CRFs should be sent to the Trial Office, with a copy retained at site.

Completed CRFs should be returned to
OPTIMA Trial Office
Warwick Clinical Trials Unit
Division of Health Sciences, Warwick Medical School
University of Warwick, Gibbet Hill Road
Coventry CV4 8UW

12.1 Schedule of events

Table 3 summarises the schedule of events within OPTIMA.

12.2 Quality of Life & Health Resource Use Assessment

Patients will be asked to complete the OPTIMA patient questionnaire incorporating FACT-B and EQ-5D as well as health resource use information. The first OPTIMA patient questionnaire should be given to patients after written consent is obtained *but prior to randomisation*. Further OPTIMA patient questionnaires will be administered at 3, 6, 12 and 24 months from the date of consent.

Each participating site will be responsible for providing patients with Quality of Life 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.

12.3 Follow-up

Follow-up will be for 10 years from trial entry. Telephone follow-up is permitted for patients who have been discharged from clinical review. Information will also be obtained where possible from Hospital Episode Statistics in conjunction with the National Cancer Intelligence Network. Patients will also be flagged with the ONS.

Table 3: Schedule of Events

	Pre-randomisation	Following treatment allocation	3-monthly from trial entry	6 months from trial entry	12 months from trial entry	Annually to 5 years from trial entry	Annually from 5 to 10 years
Local inclusion criteria satisfied	X						
Informed trial consent taken	X						
Chemotherapy planned	X						
Archival tissue block sent to central laboratory	X						
Medical history	X						
Staging scans (if indicated)	X[a]						
Chemotherapy treatment		X[b]					
Endocrine treatment and compliance		X[c]			X	X	X
Breast imaging					X[d]	X[d]	
OPTIMA Patient Questionnaire Booklet (Quality of Life & Health Resource Use)	X		X[e]	X[e]	X[e]	X[e] (at 24 months only)	
Follow-up						X[f]	X[f]

Notes: Trial entry will be defined as the date the trial consent form is signed.

a. Staging should be performed in line with normal clinical practice. Formal staging is recommended for patients with symptoms or abnormal biochemistry consistent with metastatic disease or with stage III disease (tumours > 5cms with any nodal involvement OR any tumour size with 4 or more involved nodes). CT scan of thorax, abdomen & pelvis (or chest X-ray & liver ultrasound) AND isotope bone scan are preferred.
b. Chemotherapy, as pre-specified, to start within 2 weeks of treatment allocation. Monitoring during treatment is according to local guidelines.
c. Endocrine therapy to start within 2 weeks of treatment allocation or within 4 weeks of the final dose of chemotherapy. Monitoring during treatment is according to local guidelines.
d. Nature and exact timing of breast imaging according to local policy.
e. At all time-points except baseline, the Patient Questionnaire Booklet can be completed in clinic, 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.
f. Telephone follow-up is permitted for patients who have been discharged from clinical review.

13. 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 may be withdrawn from trial treatment at the discretion of the Investigator and/or Trials Steering 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.

14. Statistical Considerations

14.1 Stratification

- 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])
- Number of involved nodes (node negative [includes isolated tumour cells] vs. micrometastases only vs. positive sentinel node biopsy without axillary surgery 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

Sample size

OPTIMA *prelim* informed the type of patients that would be entered into OPTIMA. The baseline 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 distant DDFS was 84% (Dowsett, Cuzick & Sestak, unpublished).

The power calculations assume a 4 year recruitment period with a minimum of 3 years 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 control arm 5-year invasive disease-free survival (IDFS) of at least 85% with a 5% significance level and 85% power. However, this sample size is sufficient to consider a variety of scenarios if the population or treatment changes, as well as satisfying the assumptions for the analysis of the secondary outcomes (Table 4). The addition of up to 500 patients in total (250 in each arm) from OPTIMA *prelim* will allow non-inferiority to be assessed with a 2.5% significance level.

Table 4: Power calculations assuming 4 years recruitment, minimum of 3 years follow-up and non-inferiority defined as no worse than 3% below the control arm.

			Sample size in each arm with:			
Control 5 year IDFS	**Test-directed 5 year IDFS**	**HR**	**80% power; 5%significance**	**85% power; 5%significance**	**80% power; 2.5%significance**	**85% power; 2.5%significance**
82%	79%	1.19	2200	2550	2850	3150
83%	80%	1.20	2100	2500	2800	3100
84%	81%	1.21	2100	2450	2750	3050
85%	82%	1.22	1950	**2250**	2600	2700
87%	84%	1.25	1750	2000	2400	2650
90%	87%	1.32	1500	1800	2100	2500
92%	89%	1.40	1300	1400	1750	1950
95%	92%	1.63	950	1100	1350	1500

Key: IDFS = Invasive disease free interval

A 4500 patient sample size would have at least 80% power to demonstrate non-inferiority of IDFS for patients with tumours categorised as low risk using the multi-parameter test (estimated at 65% of patients, based on OPTIMA *prelim*) at 3.5% with a 5% significance level and a 5 year IDFS in the control arm of at least 86.5%.

In addition, it will also be possible to detect modest interaction effects between trial arms and markers on IDFS with reasonable power (Table 5).

Table 5: Power to detect an interaction between marker and trial arm under different marker prevalence and interaction effects

Marker prevalence	Interaction Ratio	Significance level	Power
50%	1.4	5%	55%
	1.5	5%	70%
	2.0	5%	99%
40%	1.4	5%	53%
	1.5	5%	69%
	2.0	5%	98%
30%	1.4	5%	48%
	1.5	5%	63%
	2.0	5%	97%
20%	1.4	5%	38%
	1.5	5%	51%
	2.0	5%	92%

OPTIMA is designed as an adaptive trial to allow the inclusion of another multi-parameter test or tests, if 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 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 (74). All time to event outcomes will be calculated from the date of trial entry to the date of first event, or the censor date. 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 1.22 assuming the control IDFS rate is 85% at 5 years.

The quality of life FACT-B scale will be scored and analysed using longitudinal methods and appropriate statistical tests. Compliance to 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 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 from the *prelim*inary study will be included in the analysis of the test-directed therapy versus control as a sensitivity analysis using a Cox proportional hazards model as described above but with non-inferiority assessed using the 97.5% quantile of the estimated hazard ratio, without inflating the error rate (75).

Two interim analyses of the primary outcome measure are planned, equally spaced in terms of numbers of IDFS 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). With at least 3 years follow-up available for each patient, it is estimated that there will be 624 events. The analysis time-points in terms of event numbers are at approximately 208, 416 and at least 624 events. 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.

14.4 TRIAL TIMETABLE AND MILESTONES

OPTIMA will randomise 4500 patients from at least 100 sites in the UK over a 4- year period. The primary outcome analysis will be performed when all patients will have at least 3 years, median 5 years follow-up.

A 24 month feasibility phase has been incorporated into OPTIMA where we aim to have 100 centres open, 1165 patients recruited, and reach an average recruitment rate of 0.8 patients or more per site per month during the last 6 months of this phase (months 18 to 24).

Prior to grant activation:	Finalisation of main trial protocol. Gain relevant approvals. Contracts for trial staff. Preparation of trial documentation, including site initiation documents and case report forms for new centres.
Months 0-6:	Grant activation and new site set up. Purchasing new computers. Main Trial launch meeting.
Month 1:	First patient randomised into Main trial
Month 12:	74 sites open; 300 patients randomised; IDMC followed by Trial Steering Committee (TSC) to monitor recruitment and progress
Month 18	100 sites open; 655 patients randomised.
Month 24:	100 sites; 1165 patients randomised. IDMC followed by TSC to monitor recruitment and progress.
Month 36:	120 sites; 2605 patients randomised. IDMC/TSC meetings
Month 48:	120 sites; 4500 patients randomised. IDMC/TSC meetings
Month 48-84:	Follow-up of patients, data collection & data cleaning and start analysis
Months 84-96:	Final analysis with 3 years minimum follow-up on all patients, preparation of HTA report and manuscript, presentation at Clinical National and International conferences, dissemination through patient and consumer groups.

15. 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.

15.1 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) at 5-years using data collected within the trial only. Methods recommended at the time of analysis will be followed to account for missing data and censoring (76). 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 (77). For a full description of the modelling methods upon which the analysis will be based see Hall et al (4).

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

16. Qualitative Recruitment Study

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 centres, 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 (78). The QRS will proceed in two iterative phases:

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 centres experiencing recruitment difficulties, with some high recruiting centres 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 centres, 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 centres 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 centres 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.

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 recruitment consultations is an important component of the QRS. The QRS researcher will work closely with the CI/TMG to identify centres 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 centres 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 centres 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 Recruiter 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 transferring of the recording to the computer and then to the QRS researcher will be provided to centres 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.

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 centres, 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.

17. Data Management & Patient Confidentiality

17.1 Data Acquisition

Personal data collected during the trial will be handled and stored in accordance with the 1998 Data Protection Act. The Case Report Forms (CRFs) will be designed by the Trial Co-ordinator in conjunction with the Chief Investigator and Statistician. Original CRFs must be sent to the coordinating team at WCTU and copies retained on site.

17.2 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 quality 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.

17.3 Confidentiality

The personal data recorded on all documents will be regarded as strictly confidential. To preserve the patient's anonymity, only their allocated trial number and initials will be recorded on the CRFs. Date of birth will be used as an initial identifier for pathology samples and pathology forms. With the patient's permission, their name and date of birth, address and health service (NHS) number/Community Health Index (CHI) number will be collected by the OPTIMA Trial Office on the registration form to allow flagging with the HSCIC, ONS and other relevant bodies, sample tracking and postage of questionnaires for those who do not complete them in clinic. In addition, with the patient's permission, they may be contacted to be interviewed about their decision to enter the trial (or not). Interviews may be audio recorded and will be stored electronically and identified by trial number only. Patients should be assured that their confidentiality will be respected at all times.

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 governmental queries, it will be necessary to have access to the complete trial records, provided that patient confidentiality is protected. 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.

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 co-ordinator.

17.4 Data Storage & 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 five years after completion of the trial in accordance with WCTU SOPs.

18. Trial Organisation

18.1 Trial Management Group (TMG) and core Trial Management Group (cTMG)

The TMG are the OPTIMA investigators and are responsible for trial design and monitoring trial progress. The TMG includes a multidisciplinary team of 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 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.

18.2 Trial Administration

The Chief Investigator for the trial is Rob Stein, University College London Hospitals NHS Foundation Trust (UCLH). 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).

18.3 Trial Steering Committee (TSC)

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 Steering Committee, in the development of this protocol and throughout the trial will take responsibility for:

- Major decisions such as a need to change the protocol for any reason
- 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

18.4 Independent Data Monitoring Committee (IDMC)

An independent Data Monitoring Committee (IDMC) will be established for this trial. Their main objective will be to advise the Trial Steering Committee. The IDMC will review the main trial for trial progress, recruitment, protocol compliance and interim analysis of outcomes (not formally tested outside of the trial statistical analysis plan to be agreed with the IDMC), annually or more frequent 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.

18.5 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 outline application.

18.6 Patient Involvement

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

18.7 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 conference or by site initiation visit.

An accreditation checklist will be completed for all sites to confirm that pre-activation activities have been completed and all relevant staff members are able to participate.

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. Patient Protection & Ethical Conduct

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.

Before enrolling patients into the trial, each trial site must ensure that the local conduct of the trial has the approval of the relevant trust Research & Development (R&D) department. Sites will not be permitted to enrol patients into the trial until written confirmation of R&D approval, or equivalent, is received by WCTU.

Patients' participation in the trial must be documented in the patient notes and must be communicated to the patient's GP.

19.1 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.

19.2 Ethical & Regulatory Review

OPTIMA Trial has obtained ethics approval from National Research Ethics Committee South East Coast - Surrey (main REC) in the UK. The local Principal Investigator must submit this protocol, any supporting documentation and any amendments, to the R&D Office at the Trust (e.g. R&D), as appropriate in accordance with local requirements and recommendations made by the main REC.

19.3 Annual Report

OPTIMA Trial staff will send an annual trial update report to the main REC, which will be distributed to all sites. It is the responsibility of each site to send a copy of this report to the R&D Office in accordance with local requirements and recommendations made by the main 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.

19.4 Protocol Amendments

All agreed protocol amendments will be documented by the OPTIMA Trial Office and will be submitted to the main REC for approval prior to submission to local parties as appropriate. 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.

20. Research Governance

20.1 Sponsor

UCL will act as Sponsor for the OPTIMA trial.

20.2 Essential Documentation

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

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

20.4 Financial Support

The OPTIMA trial has been funded by a grant from the NIHR HTA programme.

21. Dissemination & Publication

The results of the trial will be reported first to trial collaborators. The main report will be drafted by the trial co-ordinating team at the WCTU, and the final version will be agreed by the TSC before submission for publication, on behalf of the collaboration.

The success of the trial depends on the collaboration of researchers from across the UK. Equal credit will be given to those who have wholeheartedly collaborated in the trial.

The trial will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines (www.consort-statement.org).

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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 (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 (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 (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 (SECTION 14)

Preliminary study sample size (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 (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) (Section 14.4)

An independent data monitoring and ethics committee will be established for this trial. Their main objective will be to advise the Trial Steering Committee as to whether there is evidence or 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 where 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* (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) who 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 (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 (79). 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	Date Submitted to REC	Submission	REC opinion	Comments
V1.0	08 Mar 2012	14 Mar 2012	Initial application	Provisional favourable opinion issued 08 May 2012 reliant on specified changes.	n/a
V1.2	22 May 2012	22 May 2012	Re-submission of initial application	Approved 22 Jun 2012	Addressed REC comments on V1.0

Version 2:

Version	Version date	Date Submitted to REC	Submission	REC opinion	Comments
V2.0	23 Jul 2013	09 Aug 2013	SA#1/ Modified SA#1	Approved 16 Oct 2013	n/a
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	Date Submitted to REC	Submission	REC opinion	Comments
V3.0	18 Jul 2014	21 Jul 2014	SA#2	Unfavourable opinion 11 Aug 2014	Unfavourable opinion due to safety concern identified between submission of amendment and REC review.
V3.0	18 Jul 2014	20 Feb 2015	SA#4	Approved 26 Mar 2015	Version not implemented 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	Date Submitted to REC	Submission	REC opinion	Comments
V4.0	09 Sep 2015	11 Sep 2015	SA#5	18 Sep 2015	

Summary of changes made in V4.0:

- Features of the protocol specific to OPTIMA *prelim* removed from the main body into Appendix 1.
- Replacement of Oncotype DX by Prosigna as the primary test used to allocate treatment.
- 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.
- Eligibility criteria extended to include men.
- Lymph nodes containing micrometastases now considered as uninvolved for eligibility purpose.
- Clarification of eligibility rules for patients with bilateral and multiple ipsilateral cancers and allowing multi-parameter testing of more than one lesion.
- Fluorouracil made optional component of anthracycline combination chemotherapy (FEC) regimens.
- 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 pre-menopausal patients and recommendation for tamoxifen for men.
- Recommendation for use of adjuvant bisphosphate therapy for all patients (no recommendation for specific drug and schedule made).
- Update to surgery and radiotherapy guidance made to changes in “best practice” arising from new evidence.
- Update of Section 4 (Background) with addition of updated information and addition of sections 4.5 (The contribution of endocrine therapy to outcome) 4.6 (Availability of Multi-parameter Testing in the UK) and section 4.7 (Results of OPTIMA *prelim*) and to Section 5 (Rationale)
- 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