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Health Technology Assessment Programme
National Institute for Health Research
Evaluation, Trials and Studies Coordinating Centre
University of Southampton, Alpha House
Enterprise Road, Southampton, SO16 7NS

tel: +44(0)23 8059 5586

fax: +44(0)23 8059 5639

email: hta@hta.ac.uk

web: www.nets.nihr.ac.uk

optima

personalised treatment of breast cancer

Chief Investigator

Rob Stein

Authorised Signature: 

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UCL

Warwick Medical School CLINICAL TRIALS UNIT

University College London Hospitals NHS Foundation Trust

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Contact Details

Sponsor	**University College London** David Wilson Joint Research Office University College London Gower Street London WC1E 6BT Tel: 020 7619 2000 ext 75199 Email: david.wilson@ucl.ac.uk	**Chief Investigator**	**Dr Rob Stein** Department of Oncology, UCL Hospitals 1st Floor Central, 250 Euston Road London NW1 2PG Tel: 020 3447 4430 Fax: 020 3447 9055 Email: r.stein@ucl.ac.uk
Co-Chief Investigator	**Dr Andreas Makris** Department of Clinical Oncology Mount Vernon Hospital Rickmansworth Road, Northwood HA6 2RN Tel: 01923 844723 Fax: 01923 844167 Email: amakris@nhs.net	**Co-Chief Investigator**	**Dr Luke Hughes-Davies** Department of Oncology Addenbrookes Hospital Cambridge CB1 7UA Tel: 01223 245151 Email: Lh205@cam.ac.uk
CTU Lead & Senior Trial Statistician	**Prof Janet Dunn, PhD** **Professor of Clinical Trials** Warwick Clinical Trials Unit Warwick Medical School University of Warwick Gibbet Hill Road Coventry CV4 7AL Tel: 024 7657 5847 Fax: 024 7652 8375 Email: j.a.dunn@warwick.ac.uk	**Senior Project Manager**	**Helen Higgins** Warwick Clinical Trials Unit Warwick Medical School University of Warwick Gibbet Hill Road Coventry CV4 7AL Tel: 024 76151178 Fax: 024 7652 8375 Email: helen.higgins@warwick.ac.uk
Trial Co-ordinator	**Amy Campbell** Warwick Clinical Trials Unit Warwick Medical School University of Warwick Gibbet Hill Road Coventry CV4 7AL Tel: 024 7615 1948 Fax: 024 765 1586 Email: a.f.campbell@warwick.ac.uk	**QA Advisor**	**Claire Daffern** **QA Manager** Warwick Clinical Trials Unit Warwick Medical School University of Warwick Gibbet Hill Road Coventry CV4 7AL Tel: 024 76150605 Fax: 024 76151586 Email: c.daffern@warwick.ac.uk
Statistical Advisor	**Prof Nigel Stallard** **Professor of Biostatistics** Warwick Medical School University of Warwick Gibbet Hill Road Coventry CV4 7AL	**Trial Statistician**	**Andrea Marshall** **Statisticians** Warwick Clinical Trials Unit Warwick Medical School University of Warwick Gibbet Hill Road Coventry CV4 7AL
Lead Investigator, Qualitative Research	**Prof. Jenny Donnovan** Head of School, Social and Community Medicine University of Bristol Canynge Hall, 39 Whatley Road Bristol BS8 2PS	**Patient Representative**	**Adrianne Morgan** Independent Cancer Patient Voices Email: Adrienne@icpv.org.uk
Health Economists	**Dr Claire Hulme & Peter Hall** Academic Unit of Health Economics Leeds Institute of Health Sciences University of Leeds 101 Clarendon Road Leeds LS2 9LJ	**Health Economic Advisor**	**Prof Chris McCabe** Health Economics Department of Emergency Medicine University of Alberta Canada
Oncology Advisor	**Prof David Cameron** Department of Medical Oncology Edinburgh University & NHS Lothian Crewe Road South Edinburgh EH4 2XU	**Oncology Advisor**	**Dr Iain MacPherson** Department of Oncology Beatson West of Scotland Cancer Centre 1053 Great Western Road Glasgow G12 0YN

Oncology Advisor	**Dr Helena Earl** Department of Oncology Addenbrookes Hospital Box 193-R4 Cambridge CB2 0QQ	**Oncology Advisor**	**Prof Chris Poole** Arden Cancer Centre University Hospitals Coventry and Warwickshire, Clifford Bridge Road Walsgrave Coventry CV2 2DX
Oncology Advisor	**Dr Dan Rea** School of Cancer Sciences University of Birmingham, Edgbaston Birmingham B15 2TT	**Breast Care Nurse**	**Victoria Harmer** Breast Care Unit Imperial College Healthcare NHS Trust Charing Cross Hospital London W6 8RF Tel: 0203 313 0659 Email: Victoria.harmer@imperial.nhs.uk
Surgical Advisor	**Miss Adele Francis** Consultant Surgeon Department of Breast Surgical Oncology University Hospitals Birmingham Ward West 2, Nuffield House Breast Secretaries Office Queen Elizabeth Hospital Edgbaston, Birmingham B15 2TH	**Pathology Advisor**	**Prof Sarah Pinder** Professor of Breast Pathology Division of Cancer Studies, Kings College London 3rd Floor Bermondsey Wing Guy's Hospital Great Maze Pond London WC2R 2LS
Pathology Advisor	**Dr Mary Falzon** Consultant Histo/Cytopathologist. Divisional Clinical Director. University College Hospital Rockefeller Building University Street London WC1 6JJ	**Scientific Advisor**	**Prof John Bartlett** Ontario Institute for Cancer Research MaRS Centre, South Tower 101 College Street, Suite 800 Toronto Ontario M5G 0A3 Canada
Diagnostics Advisor	**Keith Miller** UCL Advanced Diagnostics 1st floor Rockefeller Building 21 University Street London WC1E 6JJ Tel: 020 7679 6048 Fax: 020 7679 6275 Email: info@uclad.com		

ABBREVIATIONS

Abbreviation	Explanation
ASCO	American Society of Clinical Oncology
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CSG	Clinical Studies Group
DFS	Disease Free Survival
ER	Estrogen Receptor
FDA	Federal Drug Authority
FFPE	Formalin fixed paraffin embedded
FISH	Fluorescence in situ Hybridisation
GCP	Good Clinical Practice
GP	General Practitioner
HER2	Human Epidermal Growth Factor Receptor-homologue 2
HRT	Hormone Replacement Therapy
HTA	NIHR Health Technology Assessment
ICH	International Conference on Harmonisation
IDMEC	Independent Data Monitoring and Ethics Committee
IMHC	Immunohistochemistry
ISH	In-situ hybridisation
ITC	Isolated tumour cells
Main REC	Main Research Ethics Committee
MDT	Multidisciplinary Team
MRC	Medical Research Council
NCRI	National Cancer Research Institute
NCRN	National Cancer Research Network
NEQAS	National External Quality Assurance Service
NICE	National Institute for Clinical Excellence
NPI	Nottingham Prognostic Index
OPTIMA	**O**ptimal **P**ersonalised **T**reatment of early breast cancer using **M**ulti-parameter **A**nalysis
PI	Principal Investigator
PR	Progesterone Receptor
QA	Quality assurance
QC	Quality control

Abbreviation	Explanation
QoL	Quality of Life
QRS	Qualitative Research Study
qRT-PCR	Quantitative reverse transcriptase polymerase chain reaction
RCT	Randomised controlled trial
R&D	Research and Development
REC	Research Ethics Committee
RS	Recurrence score
SABCS	San Antonio Breast Cancer Symposium
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee
UCL	University College London
UCLH	University College London Hospitals NHS Foundation Trusts
WCTU	Warwick Clinical Trials Unit

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1. Trial Summary

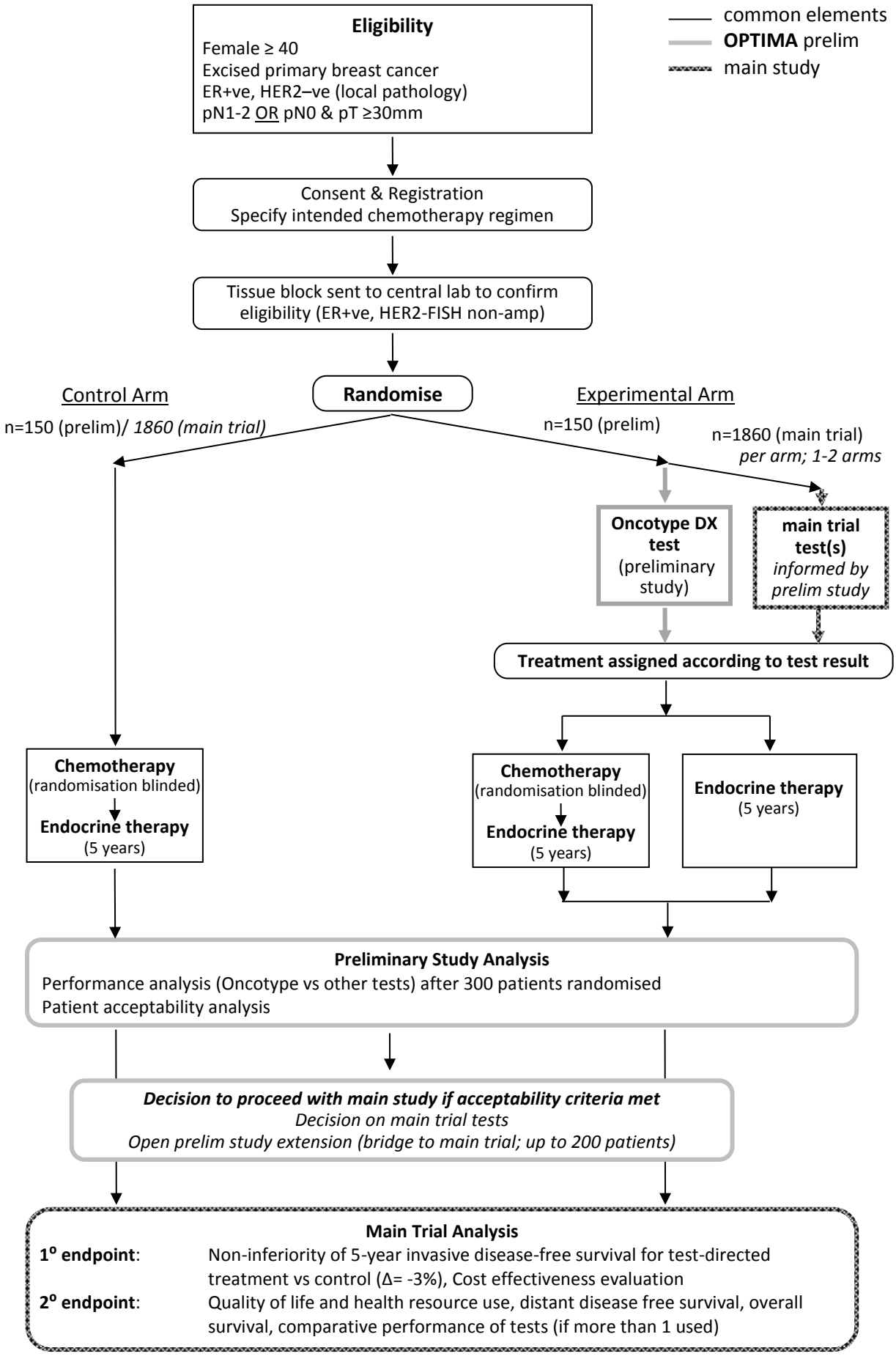
Title:	**O**ptimal **P**ersonalised **T**reatment of early breast cancer using **M**ulti-parameter **A**nalysis
Rationale:	It is normal clinical practice to offer several months of adjuvant chemotherapy to women with early breast cancer who have involved axillary lymph nodes. A recommendation for chemotherapy 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 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 such as Oncotype DX 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 medicine in breast cancer by using multi-parameter tests to identify those women who are likely to benefit from chemotherapy and sparing those who are unlikely to benefit from an unnecessary and unpleasant treatment. 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. OPTIMA *prelim* is the preliminary phase of the study which will select the testing technology to be used in the main trial and demonstrate whether the main trial is feasible.
Eligibility Criteria:	• Female, age ≥ 40 • Excised invasive breast cancer with local treatment either completed or planned according to trial guidelines. • ER +ve (Allred score ≥3 or H-score ≥10 or as otherwise established by the reporting pathologist) as determined by the referring centre and following central review. • HER2 negative – i.e. IHC 0-1+, or FISH or other ISH non-amplified (HER2 testing in lab meeting NEQAS EQA standards), as determined by the referring centre and following central review. • Axillary lymph node status: (i) 1-9 involved (macro metastases i.e. >2mm OR micro metastases i.e. >0.2-2mm) OR (ii) node negative AND tumour size ≥ 30mm. Nodes containing isolated tumour cell clusters (ITC) only, i.e. ≤0.2mm diameter will be considered to be uninvolved. • 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 and multiple ipsilateral cancers are permitted provided at least one tumour fulfils the entry criteria and none meet any of the exclusion criteria). Patients with bilateral tumours where both tumours fulfil all eligibility criteria including size and nodal status are excluded. *Note: For separate synchronous primary cancers, whether ipsilateral or bilateral, it is anticipated that laboratories will, as per standard good practise, assess ER and HER2 on the different lesions. Sites should send a block for each separately*

	reported tumour for central eligibility testing provided sufficient material is available. If there are multiple invasive foci which are deemed to derive from one main cancer (satellite foci), which have the same histological features including for example tumour type and grade, it is not required that every focus will have receptor status re-assessed. • Written informed consent for the study.
Exclusion Criteria:	• ≥10 involved axillary nodes or involved internal mammary node. • ER –ve OR HER2 amplified on central review. • 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 in situ ductal carcinoma (DCIS) of the breast treated with surgery only. • The use of estrogen 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:	***Preliminary study objectives*** 1. To evaluate the performance and health-economics of alternative multi-parameter tests to determine which technology(s) should be evaluated in the main trial. 2. To establish the acceptability to patients and clinicians of randomisation to test-directed treatment assignment. 3. To establish efficient and timely sample collection and analysis essential to the delivery of multi-parameter test driven treatment. ***Main Trial Objectives*** 1. To identify a method of selection that reduces chemotherapy use for patients with hormone sensitive primary breast cancer without detriment to invasive

	disease free survival and overall survival. 2. To establish the cost-effectiveness of test-guided treatment strategies compared to standard practice.
Trial Design:	OPTIMA is a multi-centre partially blind randomised clinical trial with a non-inferiority endpoint and an adaptive design. OPTIMA *prelim*, the preliminary or feasibility phase of the study, has the same structure as the main trial.
Trial arms:	**Experimental:** Test guided 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:	**Preliminary study:** Oncotype DX (Chemotherapy assigned according to Recurrence Score cut-off of >25 vs. ≤25) **Main trial:** test(s) to be used and their cut-offs selected according to outcome of the preliminary study
Trial Treatments:	**Chemotherapy** (permitted regimens): • FEC75-80 • FEC90-100 • FEC-T • TC • E-CMF • FEC-Pw **Endocrine therapy:** • Postmenopausal: aromatase inhibitor (any permitted) • Premenopausal at trial entry: ovarian suppression with GnRH agonist for 3 years + tamoxifen for 5 years
No. patients:	**Preliminary study:** 300 patients (plus 200 patient extension) **Main trial:** 1860 patients per arm; 2-3 arms
Stratification:	1. Chemotherapy regimen 2. Number of involved nodes 3. Menopausal status
Outcome measures:	**Preliminary study:** • 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 centre opening to recruitment. 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 85% or more of chemotherapy assigned patients. **Main trial:** • Invasive disease free survival (IDFS) non-inferiority of test-directed chemotherapy treatment and endocrine therapy compared to chemotherapy followed by endocrine treatment for all patients • Cost effectiveness evaluation of protocol specified multi-parametric assay

	driven treatment against standard clinical practice
Analysis:	The selection of the tests to be included in the main trial will be based on observations from the feasibility study. 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 (and combination of tests), whilst multivariate models will be used to determine factors influencing concordance. These analyses will determine if patients in the feasibility study will contribute to the main trial with appropriate adjustments. For the main trial 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. Three interim analyses of the primary outcome measure are planned for the main trial, equally spaced in terms of numbers of IDFS.

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 NHS could be spared unnecessary costs. Whilst estrogen receptors and 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 who have node-positive or large (pT ≥30mm) node-negative tumours which are ER positive and HER2 negative. These women 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 of 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 48,000 in 2008, 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 estrogen receptor (ER) status and HER2 status. These latter two also predict sensitivity to anti-estrogen 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 estrogen receptor positive and lower grade tumours (2)

Endocrine therapy with tamoxifen and more recently aromatase inhibitors is considered to be the mainstay of treatment for postmenopausal women with estrogen receptor (ER) positive disease, the commonest presentation of breast cancer. Aromatase inhibitors have been shown to be superior to tamoxifen in a number of large randomized clinical trials and current NICE guidance recommends that these drugs should be offered to the majority of post-menopausal patients (3).

In recent years there has been a large expansion in the use of adjuvant chemotherapy, especially for post-menopausal 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 women, 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. It is estimated that it costs over £8,500 to deliver a course of taxane chemotherapy to a patient with early stage breast cancer (4). 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 of more than £150m 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 tumour 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 – estrogen (ER) and progesterone (PgR) and HER2. ER and PgR expression are good prognostic markers and predict sensitivity to anti-estrogen drugs. HER2 gene amplification 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 (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
Estrogen 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). A robust assay, PAM50 (13), that involves measuring the expression of 50 genes in formalin-fixed paraffin-embedded (FFPE) material (which is the standard tissue handling protocol for routine laboratories) using qRT-PCR methods or the nanoString© system has recently been described but is not in routine clinical use.

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 academic groups and commercial organisations. Although many are poorly validated and remain experimental, a small number have significant evidence to support their clinical utility, particularly in ER positive tumours. Most of the better validated assays have been developed commercially and are either available or in the process of being developed for clinical use (table 2).

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

Assay (Investigators or Company)	Details of Multi-parametric assay	Test Material	Test Output	Ref.
Perou and Sorlie (academic)	The original description of the intrinsic classification using 495 genes (the most highly cited papers in breast cancer).	Fresh/ frozen	category	(10, 11)
Oncotype DX (Genomic Health Inc)	A 21 gene qRT-PCR expression assay (using 16 cancer related and 5 normalisation genes)	FFPE	risk score	(14)
MammaPrint (Agendia)	A 70 gene microarray based expression signature.	Fresh/ frozen FFPE ±	risk score	(15, 16)
Rotterdam signature (academic)	A 76 gene microarray based expression signature; not commercially available.	Fresh/ frozen	risk score	(17)
PAM50 (ARUP Laboratories & nanoString Technologies)	A 50 gene expression assay using RT-PCR or the nanoString system.	FFPE	subtyping & risk score	(13, 18)
Breast Cancer Index (bioTheranostics)	A 7 gene qRT-PCR expression assay	FFPE	risk score	(19)
Blueprint (Agendia)	A microarray based assay used in conjunction with MammaPrint	Fresh/ frozen FFPE ±	subtyping	N/A
Genomic Grade (Ipsogen)	A 97 gene microarray based expression signature.	Fresh/ frozen FFPE ±	risk score	(20)
Randox Breast Cancer Array (Randox laboratories)	A 23 gene assay using bio-chip technology	Fresh/ frozen FFPE ±	subtyping	N/A
IHC4 (HistoRx & non-proprietary)	Quantitative immunohistochemical assay for ER, PgR, Her2, Ki67	FFPE	risk score	(21)
Mammostrat (GE Healthcare)	A 5 gene immunohistochemical assay.	FFPE	risk score	(22, 23)
NPI plus	A 10 gene immunohistochemical assay.	FFPE	risk score	N/A

qRT-PCR=quantitative reverse transcriptase polymerase chain reaction. FFPE=formalin-fixed paraffin- embedded. FFPE±=FFPE method in development. ER=estrogen receptor, PgR=Progesterone receptor. Ki67 is a proliferation marker.

Many of these assays, particularly Oncotype DX (14), Mammostrat (22, 23) and MammaPrint (14,15), offer a simple numerical estimate of risk for all breast cancer rather than provide any information about a broad pathological classification. Most are strongly influenced by steroid hormone sensitivity, HER2 and proliferation.

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 almost no 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. It is certainly conceivable that fewer markers could be assayed with similar value and better cost-effectiveness. 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 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.

A more detailed description of selected tests follows:

1) Oncotype DX: The pivotal study deriving the 21 gene signature assay, "Oncotype DX" (14) selected 16 markers (*www.oncotypedx.com*) and 5 control genes derived from expression array analysis of tamoxifen treated cancers and translated into a multiplex PCR diagnostic assay with an associated "risk score" estimating the risk of disease recurrence following tamoxifen treatment in node negative breast cancers. Multiple additional studies, in retrospective phase III trials and in the context of aromatase inhibitors (24-28) confirm the value of Oncotype DX as a predictor of residual risk following endocrine therapy (25, 29-31). Oncotype DX has been demonstrated to provide superior prognostic information to Adjuvant! (32). It is now broadly accepted that Oncotype DX satisfies current criteria for validation as a diagnostic assay (33). An American Society of Clinical Oncology Expert Panel reviewed the evidence and recommended the use of Oncotype DX in routine care in 2007. As of September 2010, the test, which is performed in a single central laboratory, had been ordered by over 10,000 doctors in over 55 countries for more than 175,000 patients making this the current market lead both regarding levels of evidence and current clinical utility.

2) Mammostrat: Derived following expression array analysis identifying markers of residual risk in early breast cancer, the Mammostrat assay relies on immunohistochemical analysis of 5 markers (p53, NDRG1, SLC7A5, CEACAM5, and HTF9C) using a proscribed and validated scoring approach (23). First described in 2006, this assay was validated across multiple retrospective institutional and clinical trial cohorts, including the NSABP B-14 and NSABP B-20 trials (22, 23, 34). Recent evidence from the TEAM trial (Bartlett SABCS 2010 P3-10-33) suggests this assay also provides information on residual risk in patients treated with aromatase inhibitors. Following FDA approval of this test as a marker of residual risk in early breast cancer, the assay is available on a commercial basis within the US and from 2012 in Europe.

3) IHC4 and fluorescence IHC4: The "IHC4" and fluorescence IHC4 tests are extensions of long standing evidence on the ability of conventional IHC markers, ER, PgR, HER2 and Ki67 (35, 36) to select patients at increased residual risk following endocrine therapy. Two key advances have underpinned recent developments utilising these markers, namely the centralised *quantitative* analysis performed in a number of pivotal clinical trials of endocrine therapy (37-39) and the development of fluorescence IHC based methods with improved reproducibility and scalability (40, 41). These approaches cumulated in a number of reports of algorithms, such as that defined by Cuzick et al (21), which integrated this data into a predictor of residual risk, which provided information equivalent to that from the more complex and expensive Oncotype DX assay. Additional testing of this algorithm is ongoing using both conventional and fluorescence based IHC methods (Bartlett personal communication).

4) PAM50 Following the pivotal publication (10, 11) of molecular classifiers of breast cancer subtypes, the development of a simple molecular assay for clinical determination of these subtypes has been a key objective. The development of the PAM50 multiplex PCR assay parallels that of Oncotype DX in that it translates expression array data into a clinically viable diagnostic assay (13, 35, 36) using 50 genes to identify molecular sub-types of early breast cancer (Luminal A, Luminal B etc) (13). Studies validating the PAM50 signature have been performed, predominantly using *in silico* validation cohorts and expression array data (13). More recently the assay has been adopted by a commercial partner, NanoString Technologies and is currently being developed for clinical validation in a number of retrospective clinical trial cohorts. Therefore, rapid progress in the understanding of the utility of this approach is likely in the near future.

5) Randox Breast Cancer Array (BCA) is a cDNA based biochip assay which classifies breast tumours into intrinsic subtype by examining the expression signatures of 21 test genes with 4 controls. As such, Randox BCA and other multi-gene expression tests could be used as an alternative or in addition to immunohistochemical analysis for the sub-typing of breast cancer. It is also claimed that the gene expression signature of the tumour cell can be used to predict the risk of recurrence of breast cancer following surgery. It is thought that information on the subclass of the tumour and the risk of recurrence,

if available, could help to assist clinical decision making, including treatment planning and ongoing cancer management. This assay is currently in development.

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 a node positive post-menopausal 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 (42). 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 (43). 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, 44).

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.

5. Rationale

In 2007 the American Society of Clinical Oncology (ASCO) made a practice guideline recommendation for the use of Oncotype DX (45). This has led to its widespread adoption in North America where it has been performed on over 175,000 patients during the past three years at a cost of $500m. Economic evaluations conducted from US, Canadian and Japanese groups all conclude that Oncotype DX is cost-effective in those jurisdictions for women with node negative ER positive breast cancer (e.g. (46)). The cost of the test (currently $4,075 in the US) is covered by Medicare and many other health care provider groups. It is also increasingly supported by private UK health insurers who regard it as cost effective technology if it can identify patients who will not benefit from expensive (private sector) chemotherapy.

Although the evidence for Oncotype DX is persuasive, the supporting evidence defining the test threshold is entirely retrospective and is based on comparatively small numbers of patients. A North American prospective trial (TAILORx) assessing Oncotype DX guided treatment in a low risk population is expected to report initial results in 2014 or 2015 (47). A second Oncotype DX based trial (RxPONDER) for higher risk patients opened to recruitment in 2011 (48). Both studies test all consenting patients using Oncotype DX and randomise patients to chemotherapy in addition to endocrine therapy within a window of Oncotype DX Recurrence Scores. Patients enrolled in TAILORx do not have axillary node metastases and the majority would probably not routinely be offered chemotherapy in UK practice. In the case of RxPONDER,

patients have 1-3 involved nodes but the study also permits the inclusion of patients with very low RS for whom there is little evidence of benefit from chemotherapy based on the existing studies performed with Oncotype DX. In a third prospective study, MINDACT, all enrolled patients have a MammaPrint assay performed on tumour tissue and are randomised to chemotherapy or not where there is discordance between clinically and test assessed recurrence risk (49). The MammaPrint array technology used in MINDACT requires fresh tissue, which is widely considered to be unsuitable for general use in the NHS.

Currently Oncotype DX is the best validated predictive multi-parameter assay although the field is evolving rapidly. The lack of comparative data with other multi-parameter tests means that it is possible that other existing tests may allow more reliable identification of chemotherapy sensitive disease than Oncotype DX. The available evidence for instance suggests that both the IHC4 and PAM50 tests may also have predictive properties. The cost-effectiveness of Oncotype DX is clear in the North American health-care market but less so in the NHS where the existence of high-quality histopathology services offers the possibility of rolling out IHC4 across NHS at a fraction of the cost of Oncotype DX; i.e. Oncotype DX may not be the most cost effective platform for test-guided chemotherapy in the NHS.

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 women with ER-positive HER2-normal primary breast cancer who are likely to benefit or not benefit from chemotherapy. OPTIMA is an adaptive trial that allows more than one technology to be evaluated and will be run in 2 phases. The initial feasibility study (OPTIMA *prelim*) will compare the performance of technologies to establish which will be included in the main efficacy trial and to evaluate the acceptability of the approach to patients. The approach taken in OPTIMA is to randomise patients between standard therapy (chemotherapy and endocrine therapy) and test-directed treatment. OPTIMA will primarily test the validity of multi-parameter test directed therapy rather than study the performance of a specific assay in detail. The adaptive design of the study will facilitate this. As such it should be considered complementary to the 3 on-going international studies. An evaluation of the cost-effectiveness of the assay used in the main study is central to the OPTIMA design. The detailed comparative analysis of the performance of alternative multi-parameter assays to be undertaken as part of OPTIMA *prelim* will allow the selection of a technology that is likely to prove suitable for roll-out in the NHS in the main study. OPTIMA differs from the 3 on-going 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. 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 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 200 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

7. Trial Objectives

7.1 OPTIMA *PRELIM* 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.

7.2 MAIN TRIAL

- To establish a method of selecting patients with hormone sensitive primary breast cancer who are likely to benefit or not benefit from post-operative chemotherapy.
- To establish the cost-effectiveness of alternative test-guided treatment strategies compared to standard practice.

8. Outcome Measures

8.1 OPTIMA *PRELIM*

- 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 centre 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.

8.2 MAIN TRIAL

Primary outcomes

- Invasive disease free survival (IDFS) non-inferiority of test-assigned 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

- Quality of life and health resource use as measured by EQ-5D & FACT-B
- Distant disease free survival
- Comparative performance of multi-parameter assays (if more than one adopted)
- Patient compliance to long term endocrine therapy
- Overall survival (OS)

9. Patient Selection, Eligibility & Treatment

9.1 Inclusion Criteria

- Female, age ≥ 40
- Excised invasive breast cancer with local treatment either completed or planned according to trial guidelines.
- ER +ve (Allred score ≥3 or H-score ≥10 or as otherwise established by the reporting pathologist) as determined by the referring centre and centrally confirmed.
- HER2 negative – i.e. IHC 0-1+, or FISH or other ISH non-amplified (HER2 testing in lab meeting NEQAS EQA standards), as determined by the referring centre and centrally confirmed.
- Axillary lymph node status: (i) 1-9 involved (macro metastases i.e. >2mm OR micro metastases i.e. >0.2-2mm) OR (ii) node negative AND tumour size ≥ 30mm. Nodes containing isolated tumour cell clusters (ITC) only, i.e. ≤0.2mm diameter will be considered to be uninvolved.
- 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 and multiple ipsilateral cancers are permitted provided at least one tumour fulfils the entry criteria and none meet any of the exclusion criteria. Patients with bilateral tumours where both tumours fulfil all eligibility criteria including size and nodal status are excluded.
  Note: For separate synchronous primary cancers, whether ipsilateral or bilateral, it is anticipated that laboratories will, as per standard good practise, assess ER and HER2 on the different lesions. Sites should send a block for each separately reported tumour for central eligibility testing provided sufficient material is available. If there are multiple invasive foci which are deemed to derive from one main cancer (satellite foci), which have the same histological features including for example tumour type and grade, it is not required that every focus will have receptor status re-assessed.
- Written informed consent for the study.

9.2 Exclusion Criteria

- ≥10 involved axillary nodes or involved internal mammary node.
- ER –ve OR HER2 positive/amplified on central eligibility testing
- 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 in situ ductal carcinoma (DCIS) of the breast treated with surgery only.
- The use of estrogen 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 Responsibilities Form) 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 prelim Trial Office at 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 REGIMES

Chemotherapy chosen from a list of allowed regimens: intended regimen must be stated at registration

- FEC75-80:

  fluorouracil [F] 500-600 mg/m^2, i.v. q.3weeks x 6 cycles
  epirubicin [E] 75-80 mg/m^2,
  cyclophosphamide [C] 500-600 mg/m^2

- FEC90-100:

  fluorouracil [F] 500 mg/m^2, i.v. q.3weeks x 6 cycles
  epirubicin [E] 90-100mg/m^2,
  cyclophosphamide [C] 500mg/m^2

- TC:

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

- FEC-T:

  FEC100 (as above) i.v. q.3weeks x 3 cycles
  followed by
  Docetaxel [T] 100mg/m^2 i.v. q.3weeks x 3 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

- FEC-Pw:

  fluorouracil [F] 500 mg/m^2, i.v. q.3weeks x 3-4 cycles
  epirubicin [E] 90-100mg/m^2,
  cyclophosphamide [C] 500mg/m^2
  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 G-CSF should be given according to local guidelines.

9.5 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 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.

- Postmenopausal at trial entry: aromatase inhibitor (any permitted)
- Premenopausal at trial entry: ovarian suppression with either a licensed GnRH agonist for at least 3 years or bilateral surgical oophorectomy (radiation menopause is not permitted) AND tamoxifen for 5 years

Women who fulfil the following criteria will be considered post-menopausal:

- 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.

Although ovarian suppression (OS) is currently recommended in addition to tamoxifen for premenopausal women who decline chemotherapy, the additional benefit of OS for premenopausal women who have completed chemotherapy remains uncertain and is the subject of ongoing research. Ovarian Suppression is however 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 aromatase inhibitors in postmenopausal women are known to cause accelerated bone loss (50). 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 NCRN Bone Health Guideline (50) and the 2009 NICE CG80 Early Breast Cancer Guideline (3).

All patients should have a baseline DEXA study within 3 months of starting ovarian suppression or an aromatase inhibitor. 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 (50) (which will be circulated to all sites) for investigation and treatment of low bone density at baseline.

9.6 Surgery

Appropriate surgery should be performed according to local guidelines.

- Breast Conservation:
  If breast conservation is undertaken then margins should be clear. If re-excision is required to gain clear margins this further surgery can take place 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 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 at sentinel node biopsy (including micro metastases, macro metastases AND Isolated Tumour Cells Clusters [ITC]) should have further surgical management according to local protocol. All planned axillary surgery must be completed before trial entry.

  Centres may choose to avoid axillary clearance following a positive sentinel node biopsy for patients who have undergone breast conserving surgery and who fulfil the following criteria.
  - No palpable nodes
  - No more than two involved nodes.
  - Clinical tumour size T1-T2 (≤5cm)

9.7 RADIOTHERAPY

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 (at least two of the following factors: ER negative, grade 3, lympho-vascular invasion). 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 not be routinely irradiated.

- 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 at the time consent has been given ('trial entry'). Before contacting the OPTIMA Trial Office at Warwick Clinical Trials Unit (WCTU), a Registration Form and Eligibility Form must be completed.

To preserve the patient's anonymity, only their allocated trial number and initials will be required on the 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 by the Trial management team at registration on the registration form to allow flagging with the Office of National Statistics and to allow sample tracking. Patients should be assured that their confidentiality will be respected at all times.

These details can be phoned or faxed to the Trial Office:

Warwick Clinical Trials Unit
Telephone 024 7615 0402 (Mon-Fri, 9am-5pm)
Fax: 024 7615 1586

During registration, 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 registration.

Once eligibility on local criteria has been confirmed through the randomisation system, the patient will be allocated a unique registration number. The Trial Office will then send a confirmation fax containing the registration details. The research site will promptly send a tumour block to the Central Laboratory at UCL for confirmatory pathology testing of ER and HER2 status. The Central Laboratory will subsequently inform WCTU of the patient's ER and HER2 status eligibility. Patients confirmed to be eligible will then be randomised, by the Trial Office, to standard treatment (control arm) or to test-directed treatment. Randomisation will be by computer using a minimisation algorithm.

In order to minimise delay, the Central Laboratory will prepare samples for the multi-parameter assay provider in parallel with undertaking eligibility confirmation. Testing will proceed for patients confirmed as eligible by the Central Laboratory and randomised to test-directed treatment.

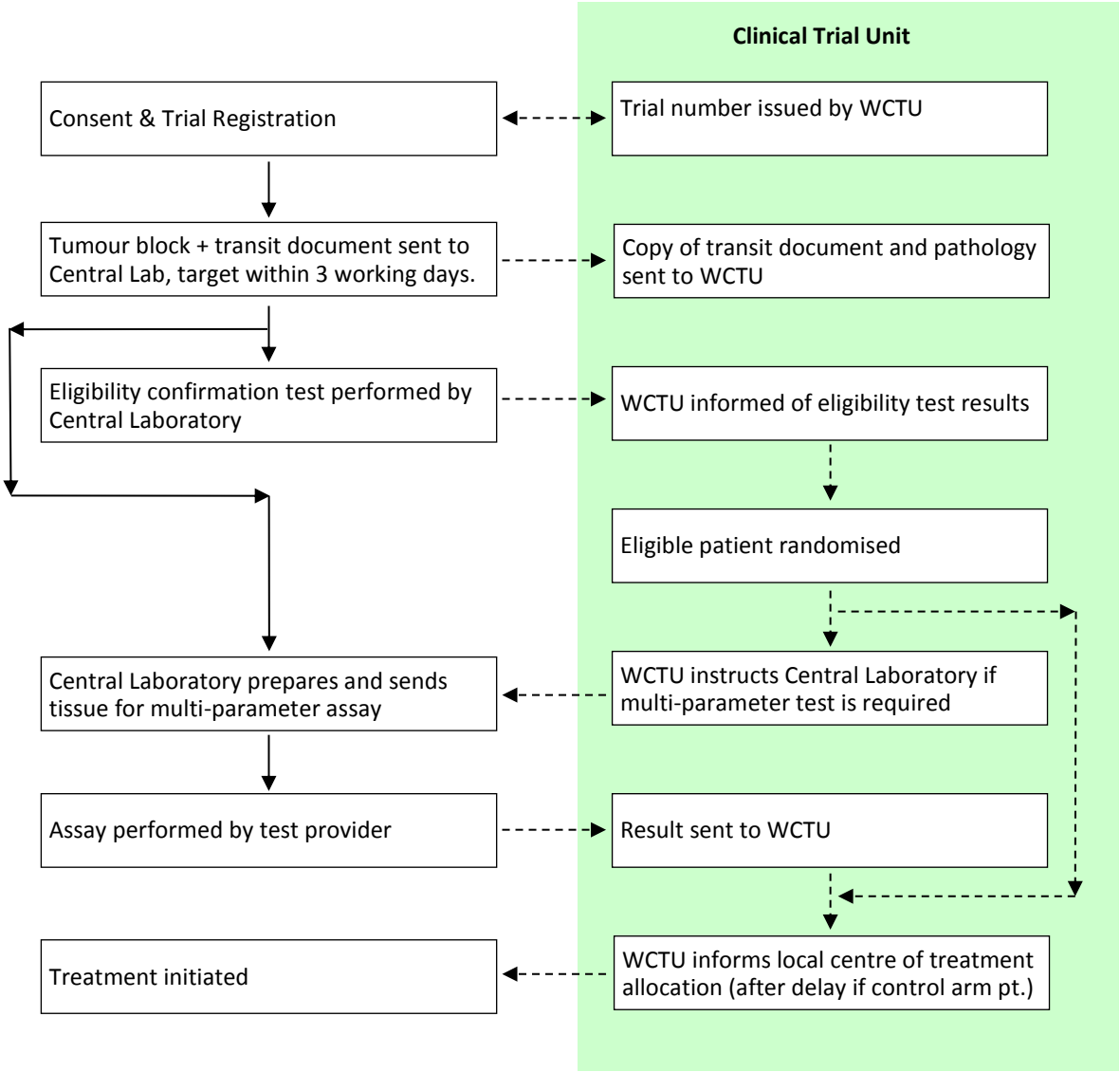
The provider of the multi-parameter assay, will return the assay result directly to WCTU. The trial office will subsequently inform the research site, by fax, whether the patient is to receive chemotherapy or not.

The research site will be blind to patient randomisation for patients allocated chemotherapy. For patients randomised to standard treatment, WCTU will delay informing the treating centre of the treatment allocation by a time period equivalent to that taken to perform the multi-parameter assay for those randomised to test-guided treatment.

Samples from patients randomised to standard treatment (control arm) may be sent to the multi-parameter assay provider for testing as part of the Pathology Research Programme at the time of central eligibility confirmation but in this case the results will not be used to determine treatment.

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.

Figure 2. Tissue handling Flow Diagram



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).

10.1 Randomisation Documentation

After patients have been registered, 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 (see Appendices).

The Registration Form and Eligibility Form must be sent to the OPTIMA Trial Office. 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

OPTIMA tissue sample collection: 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 registration, 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
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 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.

All patients in the OPTIMA trial will be asked to 'gift' their tissue for further research associated with the OPTIMA study as described below.

11.2 Pathology Research in the Preliminary Study

Oncotype DX testing will be performed by Genomic Health Inc. (Redwood City, California, USA) on tumour tissue samples for patients randomised to test-directed treatment. Additional research testing of tumour tissue will be performed on all confirmed eligible patients irrespective of randomisation to enable the performance of alternative multi-parameter assays to be evaluated. This includes patients who enter the extension phase of the preliminary study. Intended evaluations include the Oncotype DX, IHC4, Mammostrat, PAM50 and Randox BCA assays. Additional testing may be performed according to their availability. Tissue samples or sample extracts may be sent outside the UK for testing. Tumour tissues will be stored in the OPTIMA Tissue Bank at the University of Edinburgh. This research is integral to the preliminary study and in the event of a patient withholding consent, that patient will not be allowed to join the study.

Patients will be asked to consent for future (unspecified) research to be performed on their tissue samples. This research may include genetic testing performed on the tumour tissue. This part of the consent is optional. In the event of such permission being given, tumour samples will be retained in the OPTIMA Tissue Bank beyond the completion of the preliminary study. In the event of tissue being required by the treating centre for future diagnostic use then the remaining tissue block will be returned.

11.3 Pathology Research in the Main Study

Pathology research is integral to the OPTIMA study. Patients will be asked to consent for future (unspecified) research to be performed on their tissue samples. This research may include subjecting all tumour samples from eligible patients to testing using the assay(s) used to make treatment assignments in the trial. This research may also include genetic testing performed on the tumour tissue. Patients may also be asked to donate research blood samples. These consents are optional. When such permission is given, samples will be stored in the OPTIMA Tissue Bank. In the event of tissue being required by the treating centre for future diagnostic use then the remaining tissue block will be returned.

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.

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

12.1 Schedule of events

Table 3 summarises the schedule of events within OPTIMA.

12.2 Quality of Life & Health Resource Use Assessment

The first set of Quality of life and Health Resource Use forms should be given to patients after written consent is obtained *but prior to randomisation*. Further quality of life forms and Health Resource Use forms will be administered at baseline (must be before treatment allocation), 3, 6, 9, 12 and 24 months from end of date of consent.

Each participating site will be responsible for providing patients with Quality of Life booklets. The local researcher or their delegated staff member must explain the requirements, ensure the patient understands how to complete the questionnaires and the time-frames within which they are required, and (if the patient has completed them at home) ensure the booklets are returned to the local site which should then submit them to the Optima Trial Office at WCTU following completion. The member of staff responsible for this must be appropriately recorded on the Site Responsibilities Form.

12.3 Schedule of delivery of intervention and data collection

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 Office for National Statistics.

Patients will be asked to complete the OPTIMA patient questionnaire incorporating FACT-B and EQ-5D as well as health resource use. It is required that all questionnaires are completed at baseline (must be before treatment allocation), 3-monthly for the first 12 months and at month 24.

Table 3: Schedule of Events

	Pre-randomisation [a]	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 for central eligibility confirmation	X						
Medical history	X						
Staging scans (if indicated)	X[b]						
Chemotherapy treatment		X[c]		X			
Endocrine treatment and compliance		X[d]			X		
Breast imaging					X[e]	X[e]	
OPTIMA Patient Questionnaire Booklet (QoL & Health resource use)	X		X[f]	X[f]	X[f]	X[f] (at 24 months only)	
Follow-up						X[g]	X[g]

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

a. Patients who sign a consent form may have their eligibility confirmed by the OPTIMA central laboratory while waiting for other local test results to become available (e.g. staging results, confirmation of menopausal status).
b. Staging should be performed in line with normal clinical practice. Formal staging is recomended 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.
c. Chemotherapy, as pre-specified, to start within 2 weeks of treatment allocation. Monitoring during treatment is according to local guidelines.
d. Endocrine therapy to start within 2 weeks of treatment allocation or within 4 weeks of completing chemotherapy. Monitoring during treatment is according to local guidelines.
e. Nature and exact timing of breast imaging according to local policy.
f. 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.
g. 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[FEC75-80, FEC90-100, E-CMF] vs. taxane- non-anthracycline[TC] vs. combined anthracycline-taxane [FEC-T, FEC-Pw])
- Number of involved nodes (none vs. +ve sentinel node biopsy without axillary surgery vs. 1-3 nodes vs. 4-9 nodes)
- Menopausal status (pre/peri-menopausal vs. post-menopausal)

14.2 POWER AND SAMPLE SIZE

Preliminary study sample size

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-guided' 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 200 patients will allow recruitment to continue at an estimated 30 patients per month for 6 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-guided 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.

Main trial sample size

The baseline characteristics of the population to be studied are assumed to be 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 DFS for patients in the transATAC study, with ER +ve HER2 negative tumours with axillary lymph node involvement who were not treated with chemotherapy was 82% (Dowsett & Cuzick, unpublished). The results for patients in the TEAM pathology study were similar (Bartlett & Rea, unpublished).

The power calculations assume a 5-year invasive disease-free survival rate of 85% in the control arm and a 4 year recruitment period with a minimum of 5 years follow-up period. On this basis, with a 5% significance and 85% power, a trial randomising **1860 patients** in each treatment arm (3720 in a 2-arm study) will have the ability to demonstrate non-inferiority of the test arm, defining non-inferiority as 'no worse than 3%' below the control arm 5-year disease-free survival. This allows for a **5%** non-compliance rate (less than 3% non-compliance is anticipated based on experience in previous studies as these patients are willing to come for treatment and follow-up) and for the comparison of the secondary endpoints.

In addition the collection of prognostic and/or predictive factors within the pilot study of 300 (plus 200 roll on) patients will help in the identification of sub-groups for the main trial in terms of acceptability and compliance in patients and clinicians to the concept of test driven therapy. Within the scope and timeframe of the pilot study we will be unable to determine sub-groups who may or may not benefit from test driven therapy as this needs recurrence and survival data collected with adequate follow-up. However within the main trial it will be possible to detect the influence of these identified stratification variables (and other prognostic/predictive factors and molecular markers) on DFS and overall survival. Table 4 shows how the difference in prevalence and number of patients influences the ability to detect hazard ratios with changing power at the 5% alpha level.

Table 4: Statistical simulations: numbers of patients required for predictive markers

Number of patients	Marker prevalence	Interaction Ratio	Alpha	Power
1500	50%	1.5	0.05	42%
		2.0	0.05	85%
1500	20%	1.5	0.05	29%
		2.0	0.05	67%
2000	50%	1.5	0.05	52%
		2.0	0.05	93%
2000	20%	1.5	0.05	37%
		2.0	0.05	79%
3000	50%	1.5	0.05	70%
		2.0	0.05	98%
3000	20%	1.5	0.05	51%
		2.0	0.05	92%

14.3 ANALYSIS PLAN

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.

Data from both the preliminary study and the main trial will be used, with appropriate adjustment, and combining information from the two stages using a combination test as proposed by Bretz (51). In order for the results from the two stages to be independent, the 'first stage' analysis would be of long-term follow-up data from all women randomised in the preliminary stage and the 'second stage' analysis would be of all women randomised in the main study (52).

For the main trial 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 (53), 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. 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 secondary endpoint of overall survival will be calculated from the date of trial entry to the date of death, or the censor date. Distant disease free survival will be calculated from trial entry to the date of distant relapse or death, or the censor date. Quality of life will be carried out using longitudinal methods and appropriate statistical tests. These analyses will be carried out on an intention-to-treat basis.

Three interim analyses of the primary outcome measure are planned for the main trial, equally spaced in terms of numbers of IDFS. OPTIMA *prelim* will inform the type of patients selected for the main trial which will determine the analysis time-points in terms of event numbers. OPTIMA *prelim* will also inform the detailed analysis plan for the main trial outcome measures.

14.4 Independent Data Monitoring and Ethics Committee (IDMEC)

OPTIMA *prelim*

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 IDMEC will review progress 7 months after grant activation where reports containing recruitment, protocol compliance and delivery of test results will be reviewed by the IDMEC. The second IDMEC 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.

Main Trial

The IDMEC will continue to 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 IDMEC), annually or more frequent if requested. OPTIMA *prelim* will inform the detailed analysis plan for the main trial outcome measures to include timing of interim analyses for the primary outcome measure. The IDMEC 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.

14.5 Trial timetable and milestones for OPTIMA *prelim*

OPTIMA *prelim* will randomise 300 patients from 6-7 NCRN research networks in the UK. Up to 200 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 200 patients in the best case scenario.

May 2012	Grant activated
May-Oct 2012	Centre set-up and screening
Sept 2012	IDMEC and TSC joint meeting to review protocol & timelines

Oct 2012	1st patient randomised
April 2013	72 patients, IDMEC followed by TSC review
Oct 2013	210 patients, IDMEC followed by TSC review
Dec 2013	Discussion with HTA re application for main trial
Feb 2014	300 patients recruited
April 2014	IDMEC followed by TSC review

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

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 Preliminary study economic analysis plan

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.[1] 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.

15.2 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 (54). 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 (55). For a full description of the modelling methods upon which the analysis will be based see Hall et al (56).

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 Research Study

Participation in the Qualitative Research Study (QRS) is not mandatory. The OPTIMA trial is anticipated to be challenging for recruitment because women who would normally be offered immediate chemotherapy after surgery will be asked to consider being randomised to have a test that might lead to a recommendation not to have chemotherapy. Patient involvement is integral to the design of OPTIMA and the patient advocacy group ICPV (Independent Cancer Patient's Voice) has contributed to study design, patient information sheet and is represented on the TMG. Within OPTIMA *prelim*, an integrated qualitative study will be undertaken, based on a refinement of the methods developed for the ProtecT (Prostate testing for cancer and Treatment) study complex recruitment intervention (57). This will be undertaken in two phases under the aegis of the MRC ConDuCT (Collaboration and Innovation in Difficult and complex RCTs) methodology hub, which specialises in working with RCTs likely to be challenging for recruitment.

Phase I

The aim of the QRS is to work with trial staff to understand the recruitment process in the early stages, so that any difficulties related to design or conduct can be raised and changes put in place. The QRS will also be used to determine any staff training that needs to be developed or feedback given to staff. There are several distinct parts to Phase I that are intended to provide information about recruitment as it happens, and to provide the basis for the plan of action to improve it.

1. Patient pathway through eligibility and recruitment

A comprehensive process of logging of potential trial participants through screening and eligibility phases will be put in place in order to monitor recruitment. The logs and flow charts will be assessed for complexity and compliance with the protocol as well as variation between centres. In particular, the logs will give an indication of the numbers of eligible patients and particular points where they are 'lost' from the RCT. They will also indicate levels of equipoise – as evidenced by the numbers rejecting participation in the RCT. Flow charts will indicate the degree of complexity of participation and any variations between centres.

2. In-depth interviews and investigator meetings

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) Participants 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, based on those used in previous studies, but also encouraging the informants to express their own views about the RCT and any recruitment challenges expected or experienced.

Informants in group (a) will be asked about the background, development and purpose of the RCT, including their knowledge of the evidence and equipoise; their role in the trial and recruitment, including their expectation of the pathway through eligibility and recruitment. They will also be asked to provide a short verbal summary of the RCT for the interviewer, as if s/he were a patient.

Informants in group (b) who directly recruit to the trial will also be asked the questions about their knowledge of the evidence and personal views about equipoise; the recruitment pathway, how they feel the protocol fits their clinical setting and any adjustments they think are needed. They will also be asked how they explain the RCT, the tests, and the randomisation process. They will be asked to audio-record their appointments with patients, with a view to discussing any discomfort or perceived difficulty with this.

Informants in group (c) will include those who have agreed to randomisation and those who have rejected it but are willing to discuss their views. The following will be explored: perspectives of living with breast cancer, previous experiences with treatments, views about testing, and the acceptability of randomisation between the arms. Attempts will be made to obtain a variation sample that includes those who are younger/older, choosing to participate or not, and employed/unemployed.

It is likely in the early stages of the feasibility phase of the RCT that the CI, TMG and clinical investigators will meet several times. The QRS researcher will ask to observe these meetings and to audio-record them with permission. The QRS researcher will discuss the agenda with the CI, with the aim of fostering discussion, particularly about issues of eligibility and equipoise if these have emerged from the early findings. The meetings will also be a forum to discuss the findings of the QRS, and to deliver training or information about recruitment.

Interviews and meetings will be audio-recorded and transcribed with consent. Recordings may be transcribed verbatim whole or in selected parts, as necessary for comprehensive or targeted analysis. Transcripts and notes will be analysed thematically by the QRS researcher, using techniques of constant comparison and case-study approaches. Detailed descriptive accounts of the themes and cases will then be produced by the QRS researcher.

Interviews and meetings will provide data about: the perspectives of eligible patients, the evidence underlying the RCT, including the importance of the question and the commitment of staff to it, as well as individual clinical equipoise; the application of the protocol in clinical centres and any logistical issues; and suggestions about reasons for recruitment difficulties (if they emerge) and potential solutions from those working closely within the RCT.

3. Audio-recording of recruitment appointments

The importance of audio recording discussions about RCT recruitment will be emphasised to the CI and TMG, and methods of communicating this with recruiters will be explored. The CI and TMG will be asked to attempt to identify a 'recruitment appointment' suitable for recording. The QRS researcher will work 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.

One main point of contact (usually the lead research nurse) will be identified per centre and digital audio-recorders will be provided; the number of recorders required for the RCT will depend on the number of actively recruiting staff in the centre 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'.

The QRS researcher will listen to consultations, document relevant details and provide an account for the QRS PI. Issues to be fed back to the RCT CI/TMG, or to be used anonymously in training programmes will be discussed and defined. These data will form the basis for feedback to individuals and to determine the content of its information, and training programmes to be initiated in Phase II.

4. Study documentation

The CI/TMG will be working on the RCT protocol, ethical approval and governance documents during the early stages of the QRS. Patient information sheets (PIS) and consent forms will be scrutinized with potential RCT participants by the QRS researcher to identify aspects that are unclear or potentially open to misinterpretation, 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 II: Feedback to CI/TMG

The QRS researcher will present summaries of anonymised findings to the RCT CI and TMG, identifying any aspects of RCT design and conduct that could be hindering recruitment with the supporting evidence. There are likely to be several meetings regularly during the feasibility phase of the study to present these findings and discuss a plan of action to try to improve recruitment, if this proves necessary. The plan will be agreed by the RCT CI/TMG and QRS PI and researcher. No activities will be undertaken by the QRS researcher without the prior approval of, and collaboration with, the RCT CI and TMG. The plan for the RCT will be focussed on the issues emerging from the QRS. It is likely that some aspects will be generic, such as difficulties with the application of eligibility criteria or explaining randomisation. The plan is likely to include some or all of: reconsideration of study information, advice about presenting the study, discussions about equipoise or evidence, issues with patient pathways, and logistical issues in particular centres. These may be addressed by a new PIS, documents, changes to the protocol, or training for recruiters in the presentation of RCTs in general or the specific RCT.

Numbers of eligible patients, and the percentages of these that are approached about the RCT, consent to be randomised and immediately accept or reject the allocation will be assessed before the plan of action is implemented, and regularly afterwards to check whether rates are improving. Interviews with recruiters will ask about the acceptability of the QRS and any changes that occur.

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 Office of National Statistics, 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. Warwick Medical School Clinical Trials Unit 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)

The TMG includes a multidisciplinary team of clinicians, statisticians, a translational scientist and a patient advocate who have considerable expertise in all aspects of design, running, quality assurance and analysis of the trial.

18.2 TRIAL STEERING COMMITTEE (TSC)

The TSC will have an independent Chairperson. 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. Members of the TMG will be co-opted onto the TSC as appropriate.

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 IDMEC
- Informing and advising on all aspects of the trial

18.3 NCRI CLINICAL STUDIES GROUP

NCRI Breast CSG developed and approved the trial, and provided input into responses to reviewers of the outline application.

18.4 ADMINISTRATION

The Chief Investigator for the trial is Rob Stein, UCLH. The trial will be co-ordinated from the OPTIMA Trial Office at Warwick Clinical Trials Unit (WCTU), under the direction of Professor Janet Dunn. Clinical responsibility will be undertaken by the Lead Investigators of the Trial Management Group.

18.5 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, Warwick Clinical Trials Unit SOPs and the Protocol. GCP-trained personnel will conduct the trial. Free GCP training will be given, through the local National Cancer Research Networks (NCRN), to sites who do not have experience in conducting randomised, prospective, controlled, clinical trials.

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 Warwick Clinical Trials Unit.

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 [INSERT] Research Ethics Committee (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 prelim 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 IDMEC
- 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

Optima prelim has been funded by a grant from HTA.

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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