ISRCTN42400492 https://doi.org/10.1186/ISRCTN42400492

# Optimal personalised treatment of early breast cancer using multiparameter analysis

| Submission date | Recruitment status | [X] Prospectively registered |
|---|---|---|
| 26/06/2012 | No longer recruiting | [_] Protocol |
| **Registration date** | **Overall study status** | [_] Statistical analysis plan |
| 26/06/2012 | Ongoing | [X] Results |
| **Last Edited** | **Condition category** | [_] Individual participant data |
| 15/12/2025 | Cancer | |

**Plain English summary of protocol**
http://cancerhelp.cancerresearchuk.org/trials/a-trial-looking-predict-when-chemotherapy-needed-breast-cancer-optima

## Contact information

**Type(s)**
Public

**Contact name**
Ms Georgina Dotchin

**Contact details**
Warwick Clinical Trials Unit
Division of Health Sciences
The University of Warwick
Coventry
United Kingdom
CV4 7AL
+44 (0)2476 151 057
OPTIMA@warwick.ac.uk

## Additional identifiers

**Protocol serial number**
Protocol number: 11/0479; UKCRN ID: 12255; funder project numbers: HTA 10/34/01, HTA 10/34/501

## Study information

**Scientific Title**

Optimal Personalised Treatment of early breast cancer using Multiparameter Analysis: a randomised study

## Acronym
OPTIMA

## Study objectives
Current study hypothesis as of 14/02/2024:
Tumour multi-parameter assays predict chemotherapy sensitivity. Patients with hormone-sensitive primary breast cancers that have a low multi-parameter assay score do not have a meaningful chance of benefiting from adjuvant chemotherapy despite other factors that may predict a high risk of disease recurrence.
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 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 selected the testing technology to be used in the main trial and demonstrated that the main trial is feasible.

Preliminary study objectives:
1. To evaluate the performance and health economics of alternative multiparameter 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 recurrence and survival.
2. To establish the cost-effectiveness of test-directed treatment strategies compared to standard practice.

More details can be found at https://fundingawards.nihr.ac.uk/award/10/34/501#/

Previous study hypothesis:
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.

Preliminary study objectives:
1. To evaluate the performance and health-economics of alternative multiparameter 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 recurrence and survival.
2. To establish the cost-effectiveness of test-directed treatment strategies compared to standard practice.

More details can be found at http://www.nets.nihr.ac.uk/projects/hta/103401 and http://www.nets.nihr.ac.uk/projects/hta/1034501

## Ethics approval required
Ethics approval required

## Ethics approval(s)
approved 08/05/2012, NHS Health Research Authority London Surrey (formerly South East Coast - Surrey) (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 (0)20 7972 2545; iras.queries@hra.nhs.uk), ref: 12/LO/0515

## Study design
Randomized; Interventional; Design type: Diagnosis

## Primary study design
Interventional

## Study type(s)
Treatment

## Health condition(s) or problem(s) studied
Breast cancer

## Interventions
Control: Chemotherapy followed by endocrine therapy
Experimental: Test directed assignment of chemotherapy or not, followed by endocrine therapy
Follow up length: 10 years

## Intervention Type
Other

## Primary outcome(s)
Current primary outcome measures amended 30/03/2023 and added 14/02/2024:
Main trial:
1. Invasive Breast Cancer Survival (IBCFS) non-inferiority of test-directed chemotherapy treatment and endocrine therapy compared to chemotherapy followed by endocrine treatment
2. Cost-effectiveness evaluation of protocol-specified multi-parameter assay-driven treatment against standard clinical practice

Previous primary outcome measures amended 17/01/2023 and added 14/02/2024:
Main trial:

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

Previous primary outcome measures:
OPTIMA prelim:
1. Identification of a multi-parameter test technology that is suitable for validation in the main study.
2. Recruitment of 300 patients in not more than 2 years from the first centre opening to recruitment, and, for the final 150 patients:
2.1. Patient acceptance rate will be at least 40%
2.2. Recruitment will take no longer than 6 months
2.3. Chemotherapy will start within 6 weeks of signing the OPTIMA consent form for no less than 85% of chemotherapy-assigned patients

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

## Key secondary outcome(s))

Current secondary outcome measures amended 30/03/2023 and added 14/02/2024:
1. Invasive Breast Cancer Free Survival and other outcome measures for patients with low-score tumours for patients with low-score tumours (defined as tumours for which the Prosigna score is below the cut-off [≤60] for chemotherapy use) [key secondary endpoint]
2. Recurrence Free Interval (RFI), Invasive Breast Cancer Free Survival (IDFS) and Distant Recurrence Free Interval (DRFI)
3. Breast Cancer Specific Survival (BCSS) and Overall Survival (OS)
4. Health Resource Use and Quality of Life as measured by EQ-5D and FACT-B
5. Patient compliance with long-term endocrine therapy

Previous secondary outcome measures amended 17/01/2017 and added 14/02/2024:
Main trial
1. Distant recurrence-free survival (DRFS)
2. Breast cancer-specific survival (BCSS) and Overall survival (OS)
3. IDFS for patients with low-risk patients with low-risk tumours (low-risk tumours are tumours for which the Prosigna score is below the cut-off [≤60] for chemotherapy use)
4. Health resource use and Quality of life measured by EQ-5D & FACT-B
5. Patient compliance with long-term endocrine therapy

Previous secondary outcome measures as of 29/09/2015; the title was amended to include "OPTIMA prelim at recruitment start (05/09/2012)" on 14/02/2024:
Main trial:
1. Quality of life and health resource use as measured by EQ-5D & FACT-B
2. Distant disease-free survival
3. Comparative performance of multi-parameter assays (if more than one is adopted)
4. Patient compliance with long-term endocrine therapy
5. Overall survival (OS)

## Completion date

31/12/2035

# Eligibility

### Key inclusion criteria

Current participant inclusion criteria (amended 20/10/2020) and added 14/02/2024:
1. Female or male, age ≥40 years
2. Excised invasive breast cancer with local treatment either completed or planned according to trial guidelines.
3. ER positive (>10% of tumour cells stained positive) as determined by the referring site in a laboratory meeting national external quality assurance standards and in accordance with national or ASCO-CAP guidelines (83).
4. HER2 negative (IHC 0-1+, or ISH negative/non-amplified) as determined by the referring site in a laboratory meeting national external quality assurance standards and in accordance with national or ASCO-CAP guidelines (84).
5. Tumour size and axillary lymph node status; one of the following must apply:
1.1. 4-9 lymph nodes involved AND any invasive tumour size.
1.2. 1-3 nodes involved, with at least 1 node containing a macrometastasis (i.e. deposit >2mm diameter) AND any invasive tumour size.
1.3. 1-3 lymph nodes involved with micrometastases only (i.e. deposit >0.2-2mm diameter) AND invasive tumour size ≥ 20mm.
1.4. Node negative AND invasive tumour size ≥ 30mm.
2. Considered appropriate for adjuvant chemotherapy by the treating physician.
3. 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.
4. Multiple ipsilateral cancers are permitted provided at least one tumour fulfils the tumour size and axillary lymph node entry criteria, and none meet any of the exclusion criteria.
5. Bilateral cancers are permitted provided the tumour(s) in one breast meets the eligibility criteria and the other, contralateral tumour is not ER negative and/or HER2 positive and not clinically significant.
6. Short term pre-surgical treatment with endocrine therapy including in combination with non-cytotoxic agents is allowed providing that the duration of treatment does not exceed 8 weeks.
7. Informed consent for the study.

Previous Inclusion criteria at recruitment start (17/01/2017) added 14/02/2024:
Main trial:
1. Female or male, age >= 40 years
2. Excised invasive breast cancer with local treatment either completed or planned according to trial guidelines.
3. ER positive (Allred score >=3 or H-score >=10 or >1% of tumour cells stained positive) as determined by the referring site (in a laboratory meeting NEQAS standards).
4. HER2 negative (IHC 0-1+, or ISH negative/non-amplified (ratio of HER2/chromosome 17 <2.00 and copy number <6)) as determined by the referring site (in a laboratory meeting NEQAS standards).
5. Tumour size and axillary lymph node status; one of the following must apply:
5.1. 4-9 lymph nodes involved AND any invasive tumour size.
5.2 1-3 nodes involved, with at least 1 node containing a macrometastasis (i.e. deposit >2mm diameter) AND any invasive tumour size.
5.3. 1-3 lymph nodes involved with micrometastases only (i.e. deposit >0.2-2mm diameter) AND invasive tumour size ≥ 20mm.

5.4 node negative AND invasive tumour size ≥ 30mm.:
6. Considered appropriate for adjuvant chemotherapy by treating physician.
7. 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.
8. Bilateral cancers are permitted provided at least one tumour fulfils the entry criteria and none meet any of the exclusion criteria.
9. Multiple ipsilateral cancers are permitted provided at least one tumour fulfils the entry criteria and none meet any of the exclusion criteria.
10. Written informed consent for the study.

Previous inclusion criteria as of 29/09/2015:
1. Female or male, age >= 40 years
2. Excised invasive breast cancer with local treatment either completed or planned according to trial guidelines.
3. ER positive (Allred score >=3 or H-score >=10 or >1% of tumour cells stained positive) as determined by the referring site (in a laboratory meeting NEQAS standards).
4. HER2 negative (IHC 0-1+, or ISH negative/non-amplified (ratio of HER2/chromosome 17 <2.00 and copy number <6)) as determined by the referring site (in a laboratory meeting NEQAS standards).
5. Axillary lymph node status:
5.1. 1-9 involved (macrometastases i.e. >2mm) OR
5.2. Node negative AND tumour size >= 30mm.
Nodes containing micrometastases (i.e. >0.2-2mm) or isolated tumour cell clusters (ITC) only (i.e. <=0.2mm) will be considered to be uninvolved.
6. Considered appropriate for adjuvant chemotherapy by treating physician.
7. 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.
8. Bilateral cancers are permitted provided at least one tumour fulfils the entry criteria and none meet any of the exclusion criteria.
9. Multiple ipsilateral cancers are permitted provided at least one tumour fulfils the entry criteria and none meet any of the exclusion criteria.
10. Written informed consent for the study.

Previous inclusion criteria; the title was amended to include "OPTIMA prelim at recruitment start (05/09/2012)" on 14/02/2024:
1. Female, age >= 40 years
2. Excised invasive breast cancer with local treatment either completed or planned according to trial guidelines.
3. Estrogen Receptor (ER) +ve (Allred score >=3 or Hscore >=10 or as otherwise established by the reporting pathologist) as determined by the referring centre and centrally confirmed.
4. Human epidermal growth factor receptor 2 (HER2) negative - i.e. IHC 0-1+, or FISH or other ISH nonamplified (HER2 testing in lab meeting NEQAS EQA standards), as determined by the referring centre and centrally confirmed.
5. Axillary lymph node status:
5.1. 1-9 involved (macro metastases i.e. >2mm OR micro metastases i.e. >0.22mm) OR
5.2. 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.
6. Considered appropriate for adjuvant chemotherapy by treating physician
7. 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
8. Bilateral and multifocal cancers are permitted provided at least one tumour fulfils the entry criteria and none meet any of the exclusion criteria (pathology information must be available for at least 2 tumours).
9. Negative staging if either clinical suspicion of metastatic disease or high risk (pT >50mm or >=4 involved nodes)
10. Written informed consent for the study

## Participant type(s)
Patient

## Healthy volunteers allowed
No

## Age group
Mixed

## Lower age limit
40 years

## Upper age limit
100 years

## Sex
All

## Total final enrolment
0

## Key exclusion criteria
Current participant exclusion criteria (amended 17/09/2022) and added 14/02/2024:
1. ≥10 involved axillary lymph nodes (with either macrometastases and/ or micrometastases) or involvement of any of internal mammary, supraclavicular and infraclavicular nodes.
1.1. NOTE: Internal mammary lymph nodes identified by anatomical imaging studies alone will be considered uninvolved where the diameter is <10mm.
2. ER negative/low OR HER2 positive/amplified tumour (as determined by the referring site).
3. Metastatic disease.
4. Previous diagnosis of malignancy unless:
4.1 managed by local treatment only AND disease-free for 10 years.
4.2 ductal carcinoma in situ (DCIS) or pleomorphic lobular carcinoma in situ (pleomorphic LCIS) of the breast managed by local treatment only; treatment with anti-oestrogens is not permitted.
4.3 any other in situ carcinoma as defined by the International Classification of Diseases for Oncology (ICD-O) including basal cell carcinoma of skin and cervical intraepithelial neoplasia.
5. Pre-operative anti-cancer treatments except short-term endocrine therapy administered as per the inclusion criteria.
6. Adjuvant systemic treatment commenced prior to trial entry* except endocrine therapy, which must be discontinued prior to starting trial-allocated chemotherapy.
7. Treatment with agents, including ovarian suppression, known to influence breast cancer growth but prescribed for other indications within one year of trial entry* except as follows:
8. Use of oestrogen replacement therapy (HRT) provided this is stopped before surgery.
9. Drugs administered for in vitro fertilization or fertility preservation.

10. Use of hormonal contraception.
11. Trial entry* and randomisation more than 12 weeks after completion of breast cancer surgery. Trial entry should ordinarily be within 8 weeks of final surgery.
12. Planned further surgery for breast cancer, including axillary surgery, to take place after trial entry*, except either re-excision or completion mastectomy for close or positive/involved margins which may be undertaken following completion of chemotherapy if given.

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

Previous participant exclusion criteria at recruitment start (17/01/2017), added on 14/02/2024:
Main trial
1. >=10 involved axillary nodes (with either macrometastases and/ or micrometastases) or evidence for internal mammary node involvement.
2. ER negative OR HER2 positive/amplified (as determined by the referring site).
3. Metastatic disease.
4. Previous diagnosis of malignancy unless:
4.1. managed by surgical treatment only and disease free for 10 years
4.2. basal cell carcinoma of skin or cervical intraepithelial neoplasia or
4.3. ductal carcinoma in situ (DCIS) of the breast treated with surgery only
4.4. lobular carcinoma in situ (LCIS) or lobular neoplasia of the breast.
5. The use of oestrogen replacement therapy (HRT) at the time of surgery. Patients who are taking HRT at the time of diagnosis are eligible provided the HRT is stopped before surgery.
6. 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.
7. 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.
8. Trial entry more than 8 weeks after completion of breast cancer surgery.
9. 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.

Previous participant exclusion criteria as of 29/09/2015:
1. >=10 involved axillary nodes (as defined in the inclusion criteria) or involved internal mammary node.
2. ER negative OR HER2 positive/amplified (as determined by the referring site).
3. Metastatic disease.
4. Previous diagnosis of malignancy unless:
4.1. Managed by surgical treatment only and disease free for 10 years
4.2. Previous basal cell carcinoma of skin, cervical intraepithelial neoplasia or ductal carcinoma in situ (DCIS) of the breast treated with surgery only or previous diagnosis of lobular carcinoma in situ (LCIS).
5. The use of oestrogen replacement therapy (HRT) at the time of surgery. Patients who are taking HRT at the time of diagnosis are eligible provided the HRT is stopped before surgery.
6. 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.
7. 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.

8. Trial entry more than 8 weeks after completion of breast cancer surgery.
9. 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.
10. 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.

Previous participant exclusion criteria; the title was amended to include "OPTIMA prelim at recruitment start (05/09/2012)" on 14/02/2024:
1. >=10 involved axillary nodes or involved internal mammary node
2. ER -ve OR HER2 positive/amplified on central eligibility testing
3. Previous diagnosis of malignancy unless:
3.1. Managed by surgical treatment only and disease free for 10 years or
3.2. Previous basal cell carcinoma of skin, cervical intraepithelial neoplasia or in situ ductal carcinoma of the breast treated with surgery only
4. 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 the day of surgery
5. Previous 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
6. Planned further surgery for breast cancer other than either re-excision or completion mastectomy for close margins this may be undertaken following completion of chemotherapy
7. Patients with more than two involved axillary nodes (as defined in the inclusion criteria) identified by sentinel node biopsy or by axillary sampling who have not undergone further axillary surgery

### Date of first enrolment
05/09/2012

### Date of final enrolment
31/12/2025

## Locations

### Countries of recruitment
United Kingdom

England

Australia

New Zealand

Norway

Sweden

Thailand

**Study participating centre**
**Warwick Clinical Trials Unit**
Warwick Medical School
The University of Warwick
Coventry
England
CV4 7AL

# Sponsor information

**Organisation**
University College London

**ROR**
https://ror.org/02jx3x895

# Funder(s)

**Funder type**
Government

**Funder Name**
Health Technology Assessment Programme

**Alternative Name(s)**
NIHR Health Technology Assessment Programme, Health Technology Assessment (HTA), HTA

**Funding Body Type**
Government organisation

**Funding Body Subtype**
National government

**Location**
United Kingdom

# Results and Publications

**Individual participant data (IPD) sharing plan**
De-identified individual participant datasets generated during the current study will be available upon request from the OPTIMA Trial Management Group (optima@warwick.ac.uk) 6 months

after publication of the HTA final report for 10 years. All data sharing will be governed by a contract between the Sponsor (University College London) and all stakeholders.

## IPD sharing plan summary

Available on request

## Study outputs

| Output type | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|---|---|---|---|---|
| Results article | results | 01/02/2016 | | Yes | No |
| Participant information sheet | Participant information sheet | 11/11/2025 | 11/11/2025 | No | Yes |
| Study website | Study website | 11/11/2025 | 11/11/2025 | No | Yes |