Welcome to...

optima
personalised treatment of breast cancer

'Lunch with OPTIMA'

- Please mute your microphone
- Please turn off your camera
- "Raise your hand" for attention **or** type any questions in the conversation window

The meeting will start at 12 o'clock

UCL | University of BRISTOL | NIHR National Institute for Health Research | WARWICK CLINICAL TRIALS UNIT

optimabreaststudy.com

Optimal Personalised Treatment of early breast cancer using Multi-parameter Analysis

Chief Investigator: Professor Rob Stein (UCL Hospitals)

OPTIMA trial organisation

Funder: National Institute for Health Research (NIHR) Health Technology Assessment Programme Health Technology Assessment (HTA) Programme

Sponsor: University College London

Trial Coordination: Warwick Clinical Trials Unit, University of Warwick

Qualitative Recruitment Study: University of Bristol

Why do the OPTIMA trial?

WARWICK
CLINICAL TRIALS UNIT

- Adjuvant chemotherapy is currently standard practice for patients with ER+ve HER2-ve node positive early breast cancer.
- Many of these patients may gain little extra benefit from chemotherapy in addition to hormonal treatment.
- These patients cannot be reliably identified by conventional pathology.
- Multi-parameter tests may be able predict which patients are likely to benefit from chemotherapy.
- Current evidence is not good enough to safely change clinical practise.
- OPTIMA aims to prove this and hence allow many patients to avoid chemotherapy safely.

OPTIMA prelim

Feasibility study

Before embarking on the main OPTIMA study we successfully completed a feasibility study.

- 412 patients were randomised into OPTIMA prelim.
- Chemotherapy decisions were made using Oncotype DX.
  - The test was performed by (Exact Sciences/) Genomic Health Inc. in California.

OPTIMA prelim:

- Demonstrated that the main OPTIMA study was acceptable to patients and clinicians.
- Informed the choice of Prosigna as the main trial test technology for chemotherapy decisions.

About multi-parameter assays

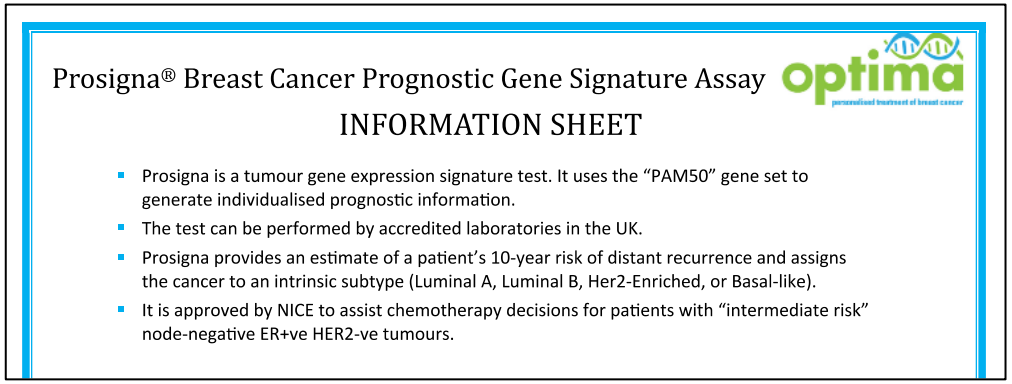
WARWICK
CLINICAL TRIALS UNIT

- Multi-parameter assays provide information about tumour biology that is more reliable than tumour grade.
  - Think of as providing a molecular grade.
- Six different tests are widely available in Europe & N. America – there is no gold standard!
- Tests provide information about risk of recurrence:
  - Superior to tumour grade for node-negative breast cancer.
  - Work best when combined with clinical data – tumour size & nodal status.
- NICE approved the Prosigna, EndoPredict and Oncotype DX tests to assist chemotherapy decisions for patients without lymph node involvement (DG34 guidelines, December 2018)
  - **The main OPTIMA trial uses Prosigna.**
- The tests may also predict chemotherapy sensitivity. This is the OPTIMA hypothesis.

What is Prosigna?

WARWICK
CLINICAL TRIALS UNIT

- Test measures expression of 50 genes (PAM50 gene set)
- Uses specialised equipment – highly reliable and reproducible – can be performed in any suitably qualified pathology laboratory.
- Prosigna provides:
  - A numerical "Risk of Recurrence" (ROR) score – predicts 10 year risk of metastatic relapse.
  - Intrinsic subtype (luminal A, luminal B, Her2-enriched or basal-like).
- Subtype adds information to ROR score.
  - Almost all ER+ve HER2-ve breast cancers are luminal A/B.
  - About 3-5% are non-luminal – these may be less sensitive to hormone therapy



Prosigna® Breast Cancer Prognostic Gene Signature Assay

optima

INFORMATION SHEET

- Prosigna is a tumour gene expression signature test. It uses the "PAM50" gene set to generate individualised prognostic information.
- The test can be performed by accredited laboratories in the UK.
- Prosigna provides an estimate of a patient's 10-year risk of distant recurrence and assigns the cancer to an intrinsic subtype (Luminal A, Luminal B, Her2-Enriched, or Basal-like).
- It is approved by NICE to assist chemotherapy decisions for patients with "intermediate risk" node-negative ER+ve HER2-ve tumours.

There is a trial information sheet on Prosigna which gives more detail about the test. You can find this in your Investigator Site File.

Why Prosigna?

WARWICK
CLINICAL TRIALS UNIT

Evaluation of alternative multi-parameter tests

- OPTIMA prelim used Oncotype DX to make chemotherapy decisions
  - 6 tests (including Oncotype) were compared in OPTIMA prelim
  - All the tests were shown to provide broadly equivalent risk information for the population
- Prosigna was chosen for the OPTIMA main trial because:
  - Very well validated as prognostic test
  - Can be performed in NHS labs (no overseas samples)
  - Health economics analysis suggests modestly more cost effective than others
- In OPTIMA prelim 18% of tumours had a “high score” (>25) by Oncotype DX vs. 34% by Prosigna
  - Patients with high-score tumours are allocated chemotherapy
  - Prosigna is the more conservative test
  - This may be important in node-positive breast cancer

OPTIMA Trial hypothesis

WARWICK
CLINICAL TRIALS UNIT

Tumour multi-parameter assays predict chemotherapy sensitivity.

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

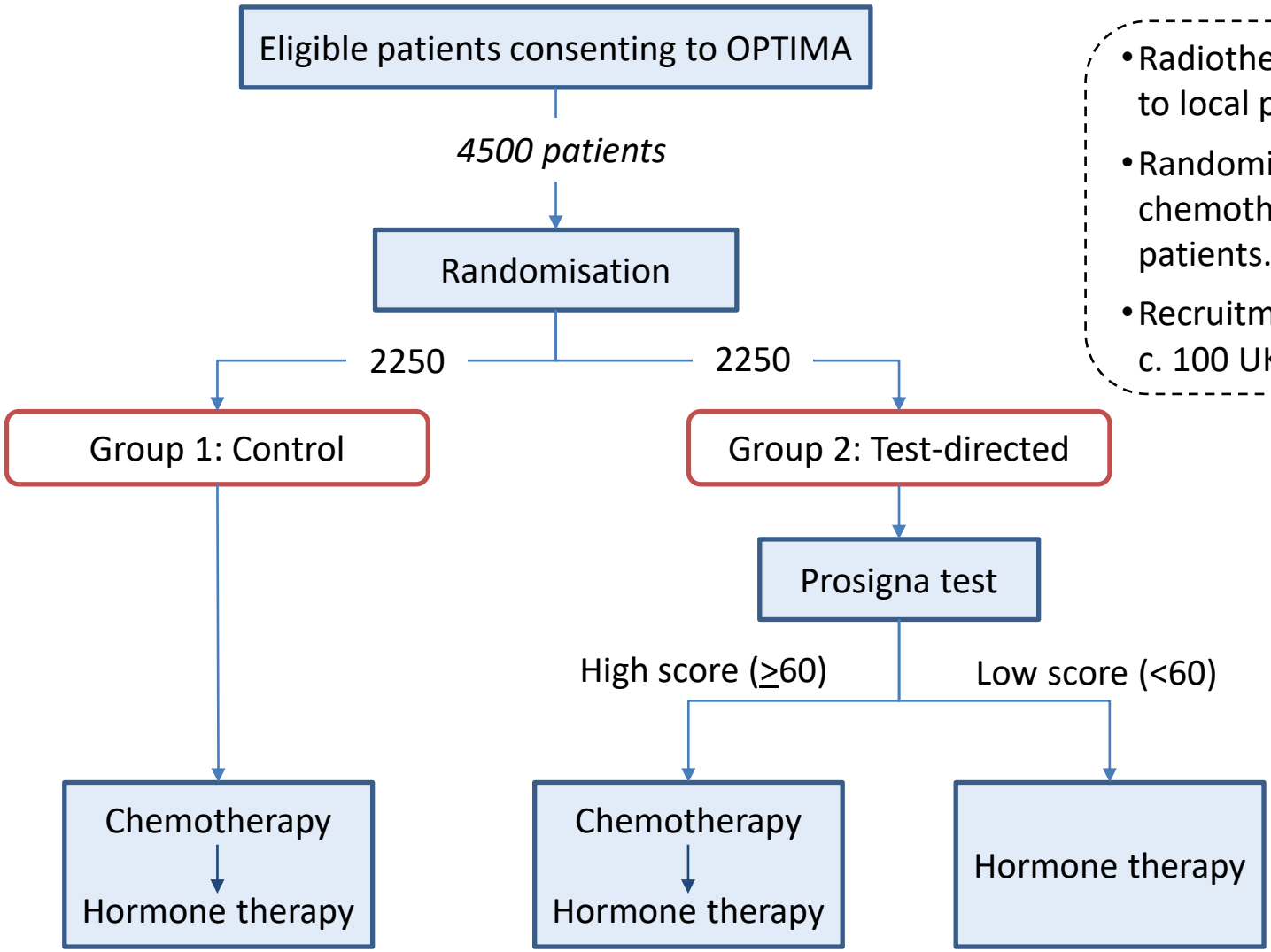
Trial objectives

WARWICK
CLINICAL TRIALS UNIT

- To identify a method of selection that reduces chemotherapy use for patients with hormone sensitive primary breast cancer without detriment to recurrence and survival.

- To establish the cost-effectiveness of test-directed treatment strategies compared to standard practice

Trial design



- Radiotherapy given according to local practice in both groups.
- Randomisation blinded for chemotherapy assigned patients.
- Recruitment over 5 years from c. 100 UK sites.

Primary outcome measures

WARWICK
CLINICAL TRIALS UNIT

- Invasive Disease Free Survival (IDFS): non-inferiority of test-directed chemotherapy treatment and endocrine therapy compared to chemotherapy followed by endocrine treatment

  IDFS includes all loco-regional recurrence of invasive breast cancer, contralateral new invasive breast cancer, metastatic disease, death from breast cancer, death from all other causes & new non-breast cancer

- Cost effectiveness evaluation of protocol specified multi-parametric assay driven treatment against standard clinical practice

Secondary outcome measures

WARWICK
CLINICAL TRIALS UNIT

- Invasive Disease Free Survival for patients with low-score tumours
- Distant Recurrence Free Interval (DRFI) and Distant Recurrence Free Survival (DRFS)
- Breast Cancer Specific Survival (BCSS) and Overall Survival (OS)
- Health Resource Use and Quality of Life as measured by EQ-5D and FACT-B
- Patient compliance with long-term endocrine therapy

Inclusion criteria

WARWICK
CLINICAL TRIALS UNIT

- ✓ Female or male age ≥ 40
- ✓ Excised invasive breast cancer
- ✓ ER positive with >10% staining and HER2 negative
- ✓ Tumour size and axillary lymph node status of either:
  - ✓ 4-9 lymph nodes involved AND with any invasive tumour size
  - ✓ 1-3 nodes involved, at least 1 nodes containing a macrometastasis (i.e. deposit >2mm diameter) AND with any invasive tumour size
  - ✓ 1-3 lymph nodes involved with micrometastases only (i.e. deposit >0.2-2mm diameter) AND invasive tumour size ≥20mm
  - ✓ Node negative AND tumour size ≥ 30mm

Note: Nodes containing isolated tumour cell clusters (ITC) only (i.e. deposit ≤0.2mm diameter) will be considered to be uninvolved.

Note: Involvement of lymph nodes with macrometastases or micrometastases may be determined either by histological examination or by OSNA or equivalent PCR-based assay.

Inclusion criteria

WARWICK
CLINICAL TRIALS UNIT

- ✓ Considered appropriate for adjuvant chemotherapy by the treating physician.
- ✓ Patient must be fit to receive chemotherapy and other trial-specified treatments with no concomitant medical, psychiatric or social problems that might interfere with informed consent, treatment compliance or follow up.
- ✓ Multiple ipsilateral cancers are permitted provided at least one tumour fulfils the tumour size and axillary node entry criteria and none meet any of the exclusion criteria.

NOTE: refer to section 10.2 of the protocol for guidance on selection of tumour blocks to be sent to the Central Laboratory

Inclusion criteria

WARWICK
CLINICAL TRIALS UNIT

- ✓ Bilateral cancers are permitted provided the tumour(s) in one breast meets the eligibility criteria and the contralateral tumour is not ER negative/ low-positive (≤10% staining) and/or HER2 positive and is not clinically significant, defined by both of the following:
  - i. The contralateral tumour does not meet the tumour size and lymph node eligibility criteria for trial entry, i.e. the following are not acceptable: presence of lymph node macro-metastases; presence of lymph node micrometastases if tumour size ≥20mm; tumour size ≥30mm if no lymph node involvement.
  - ii. The treating physician does not consider that the characteristics of the contralateral tumour alone justify consideration of adjuvant chemotherapy.
- ✓ Short term pre-surgical treatment with endocrine therapy including in combination with non-cytotoxic agents is allowed providing that the duration of treatment does not exceed 8 weeks.

  NOTE: a pre-treatment core biopsy should be sent to the Central Laboratory; a sample from a surgical excision or other on-treatment biopsy is not acceptable. Further guidance in section 10.2 of the protocol
- ✓ Informed consent for the study

Exclusion criteria

WARWICK
CLINICAL TRIALS UNIT

X ≥10 involved axillary nodes or evidence for internal mammary node involvement.

NOTE - Internal mammary lymph nodes identified by anatomical imaging studies alone will be considered uninvolved where the diameter is <10mm.

X ER negative / low-positive OR HER2 positive/amplified.

X 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).*

X Previous diagnosis of malignancy unless:

- Managed only by surgical treatment with or without local radiotherapy AND disease-free for 10 years
- basal cell carcinoma of skin or cervical intraepithelial neoplasia
- ductal carcinoma in situ (DCIS) or pleomorphic lobular carcinoma in situ (pleomorphic LCIS) of the breast treated with surgery with or without breast radiotherapy; treatment with anti-oestrogens is not permitted.

  NOTE: Isolated classical type lobular carcinoma in situ (LCIS) is not considered in this context to be a diagnosis of malignancy.

Exclusion criteria

WARWICK
CLINICAL TRIALS UNIT

- X Pre-operative anti-cancer treatments except short-term endocrine therapy administered as per the inclusion criteria.
- X Adjuvant systemic treatment commenced prior to trial entry* except endocrine therapy, which must be discontinued prior to starting trial-allocated chemotherapy.
- X Treatment with agents, including ovarian suppression, known to influence breast cancer growth but prescribed for other indications within one year of trial entry* except as follows
  i. Use of oestrogen replacement therapy (HRT) provided this is stopped before surgery.
  ii. Drugs administered for *in vitro* fertilization or fertility preservation.
  iii. Use of hormonal contraception.

*Trial entry is defined as the date of informed consent.

Exclusion criteria

WARWICK
CLINICAL TRIALS UNIT

X 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.

*Trial entry is defined as the date of informed consent.

X 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 if given.

NOTE: The timing of radiotherapy to the axilla for lymph-node involvement is not restricted.

Understanding the ER eligibility criteria

WARWICK CLINICAL TRIALS UNIT

- OPTIMA excludes ER low-positive tumours, defined as having 1-10% +ve staining.
- There are several methods of reporting ER status. Allred (or Quick) Score and H-Score combine %staining and staining intensity

Understanding Allred score

% staining	0.1%-1%	>1%-10%	>10%-33%	>33%-67%	>67%-100%
score	1	2	3	4	5

Add

Staining intensity	weak	moderate	strong
score	1	2	3

Result = 0 or 2-8

- All tumours with an Allred Score of 3 or less are ineligible. All tumours with scores 6-8 are eligible but for scores 4 or 5, you need to know %staining for eligibility.
- We are now asking sites to report %staining for all tumours

Patient pathway

WARWICK
CLINICAL TRIALS UNIT

Informed consent process

↓

Activities prior to randomising

↓

Randomise participant

↓

Send tissue sample(s) to central lab

↓

Prosigna testing
(for those randomised to test-directed treatment)

↓

Notification of treatment allocation

↓

Commence adjuvant treatment

- Patients usually approached at first oncology consultation.
- Avoid giving patients pre-conceptions about their adjuvant treatment, as these perceptions can be difficult to overcome once made.
- Promote awareness amongst local team that site participating in OPTIMA.
- Preliminary information sources for potential participants
  - Patient Flyer & Clinic Poster
  - OPTIMA website: optimabreaststudy.com

Informed consent – information phase

WARWICK
CLINICAL TRIALS UNIT

- Informed consent process
- Activities prior to randomising
- Randomise participant
- Send tissue sample to central lab
- Prosigna testing (for those randomised to test-directed treatment)
- Notification of treatment allocation
- Commence adjuvant treatment

Information Phase

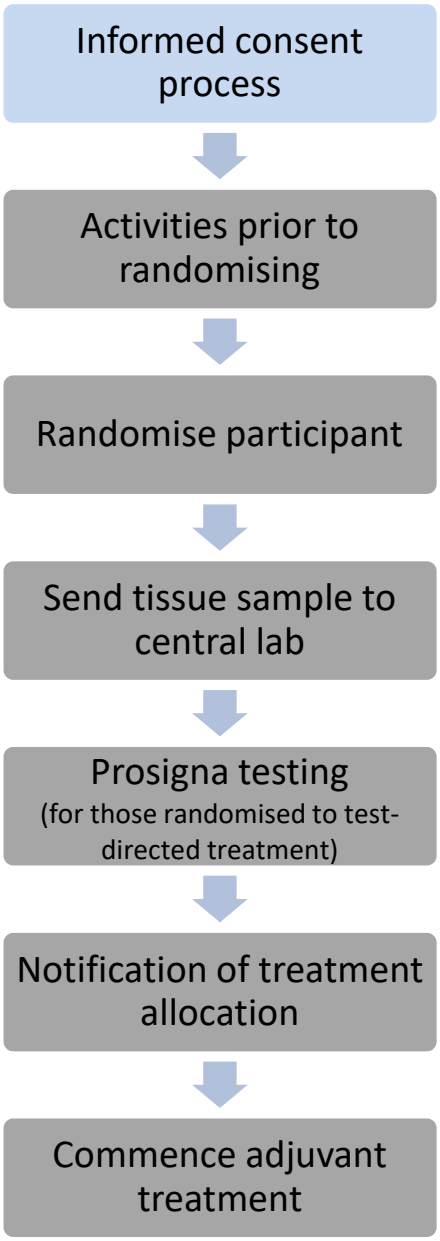
- Confirm eligibility
- Approach potential participant in clinic or during telephone or video consultation
- Discuss study in detail
- Provide patient with **Patient Information Sheet** (PIS) in person or by post / email
  - PIS may be sent out in advance of consultation.
- Opportunity for questions

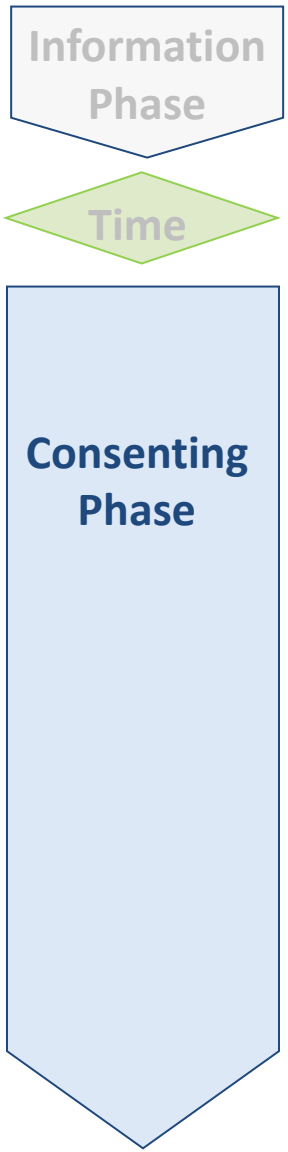
Time

TIME FOR CONSIDERATION
(Recommendation is at least 24hrs)

Consenting Phase

Consenting phase





- **OPTION 1: Consent in person**

- **OPTION 2: Remote Verbal Consent**

  This allows a participant to give initial verbal consent during telephone or video consultation for convenience, e.g. to avoid delays.

  - **It has limited scope**: allows randomisation and completion of pre-treatment allocation processes only.

Consent in person

Informed consent process

Activities prior to randomising

Randomise participant

Send tissue sample to central lab

Prosigna testing
(for those randomised to test-directed treatment)

Notification of treatment allocation

Commence adjuvant treatment

Information Phase

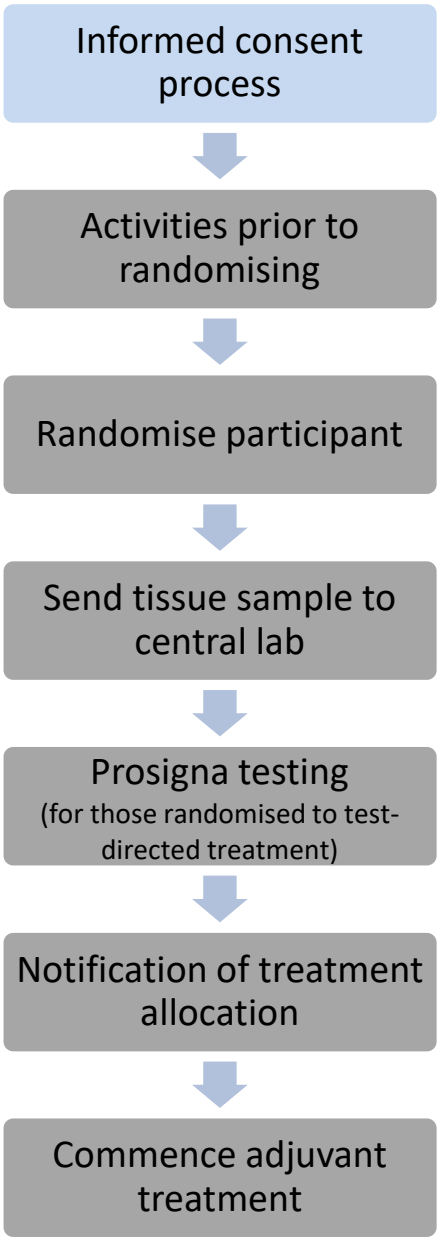
Time

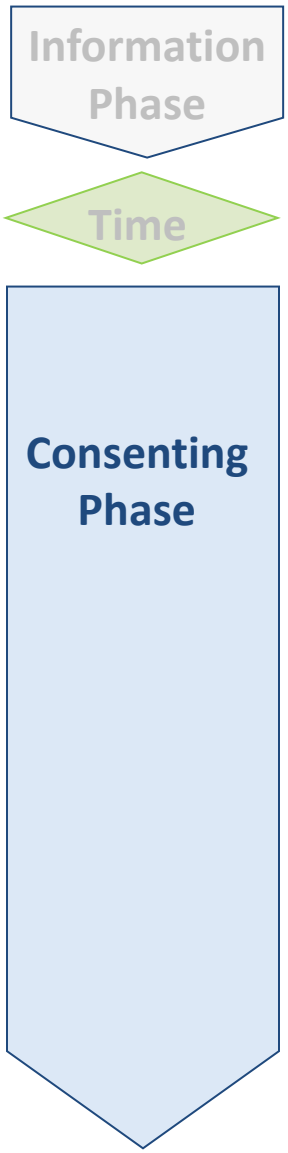
Consenting Phase

- Answer any further questions
- Participant initials each item on the **consent form** (CF), signs & date.
- Participant may complete the CF in clinic **OR** remotely.
  - If CF is completed remotely, participant takes original to clinic or sends by post to named individual.
  - Alternatively participant may scan / photograph CF and send electronically e.g. to approved email.
- Investigator* countersigns & dates the **consent form.**
  - Specific procedure for countersigning a photographic copy of consent form – refer to protocol.

*PI/or designee with *consent role assigned in the Delegation Log*

Remote verbal consent



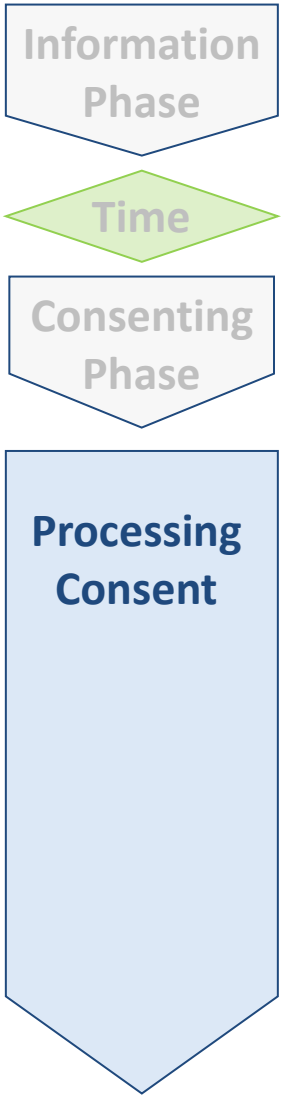


- Answer any further questions.
- Participant states intention to join study.
- Investigator* identifies likely delay in completion of written consent process and offers verbal consent; participant agrees.
- Investigator* completes the **Documentation of Remote Verbal Consent form.**
- Participant completes the **consent form** (CF), ASAP (as per previous slide)
- Once a signed **consent form** has been received, this should be countersigned whenever possible by the investigator who received verbal consent.

*PI/or designee with *consent role assigned in the Delegation Log*

Processing consent

- Informed consent process
- Activities prior to randomising
- Randomise participant
- Send tissue sample to central lab
- Prosigna testing (for those randomised to test-directed treatment)
- Notification of treatment allocation
- Commence adjuvant treatment



In all cases, investigator who countersigns the consent form must be satisfied that consent is genuine.

- The original signed & dated **Consent Form** should be filed in the Investigator Site File.
- The **Documentation of Remote Verbal Consent form** (if used) should also be filed in the Investigator Site File if relevant.
- Copies (paper or electronic) of all consent documents must be given / sent to patient.
- Patient participation must be recorded in medical notes.
- Send GP letter.
- **Consent forms must not be sent to Trial Office**

Before randomisation

- Informed consent process
- Activities prior to randomising
- Randomise participant
- Send tissue sample to central lab
- Prosigna testing (for those randomised to test-directed treatment)
- Notification of treatment allocation
- Commence adjuvant treatment

✓ Confirm eligibility	Complete *Eligibility Form (CRF 1)*
✓ Obtain Informed Consent	Complete the appropriate *Consent Form* (as per previous slides)
✓ Confirm stratification information	Complete *Randomisation Form (CRF 2)*
✓ Plan Chemotherapy	From permitted chemotherapy regimens
✓ Plan endocrine therapy (if pre-menopausal)	Do you intend to treat with AI or tamoxifen?
✓ Administer OPTIMA Patient Questionnaire Booklet	Quality of Life Health Resource Use questions
✓ Take medical history	Complete *Baseline Details Form (CRF 3)*

Randomisation process

- Informed consent process
- Activities prior to randomising
- Randomise participant
- Send tissue sample to central lab
- Prosigna testing (for those randomised to test-directed treatment)
- Notification of treatment allocation
- Commence adjuvant treatment

- Telephone Warwick Clinical Trials Unit Randomisation Service.
  - *Telephone number found on the form and in the protocol*
- The Randomisation officer will ask you to confirm the information documented on the *Randomisation Form (CRF 2)*
- At the end of the call you will be given a 4 digit Participant Trial Number
  - *This is often referred to as a 'TNO'*

- Informed consent process
- Activities prior to randomising
- Randomise participant
- Send tissue sample to central lab
- Prosigna testing (for those randomised to test-directed treatment)
- Notification of treatment allocation
- Commence adjuvant treatment

Randomisation form

WARWICK CLINICAL TRIALS UNIT

Information required at randomisation:

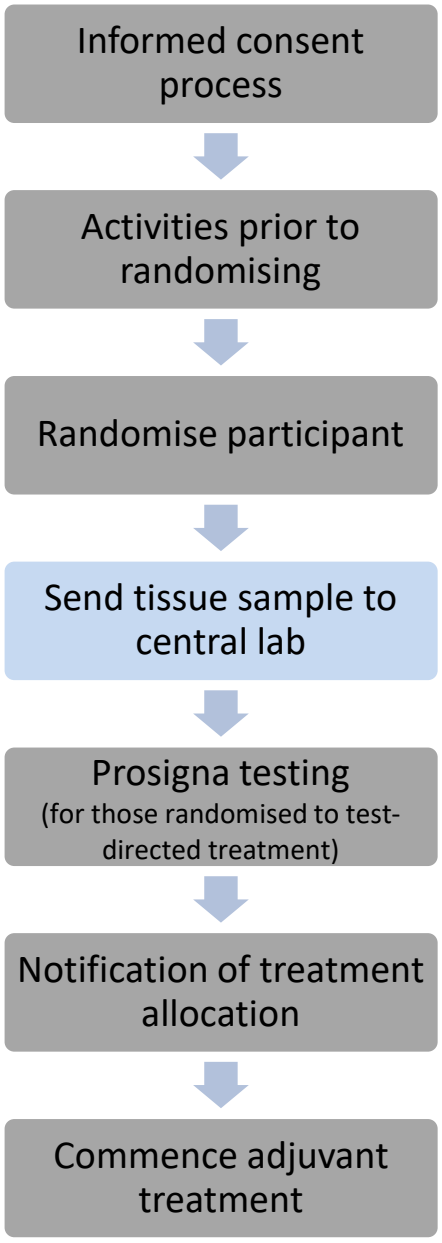
- Site + participant details and confirmation of eligibility
- Type of consent given (Written vs Remote Verbal Consent)
  - When participant has given Remote Verbal Consent , CRF 2a must be completed prior to treatment allocation.
- Whether approached & consented for the Qualitative Recruitment Study
- Stratification variables
  - Tumour size
  - Number of involved nodes
  - Histological grade
  - Menopausal status
- Planned treatment
  - Intended chemotherapy regimen (a stratification variable)
  - If pre-menopausal, intent to treat with AI or tamoxifen

Diagnostic tissue blocks

WARWICK
CLINICAL TRIALS UNIT

- Informed consent process
- Activities prior to randomising
- Randomise participant
- Send tissue sample to central lab
- Prosigna testing (for those randomised to test-directed treatment)
- Notification of treatment allocation
- Commence adjuvant treatment

- Following randomisation a **tissue block should be sent within 3 working days.**
- Site pathologist selects a representative tissue block from the appropriate surgical resection (SOP provided).
- Site completes the **Tissue Transit Form**
  - Includes details of invasive tumour size and number of involved nodes; information included in Prosigna test result.
  - Must be completed by a trial investigator or pathologist who is a member of the breast MDT.
- Site emails WCTU:
  - Site transmits the Tissue Transit Form, and copies of all anonymised histology reports, to the OPTIMA trial office via email.
- Site posts the sample to HSL-AD:
  - Site packages tumour sample, include the Tissue Transit Form (retain a copy for site file), copies of all anonymised histology reports and send to the Central Laboratory. (Packaging provided and postage paid for by trial.)
- WCTU will email site to confirm arrival of tissue block at central lab.



Redaction

WARWICK
CLINICAL TRIALS UNIT

All pathology reports which are sent to the OPTIMA trial office and the central lab **must be fully redacted** of patient identifiable data (PID).

- Please make sure participant TNO and initials are written on each page
- Check there is no PID within the body of the report as well as header
- Un-redacted reports will be recorded as a protocol violation

Permitted data items

- Date of Birth – This is PID but required as source data for sample tracking and matching pathology reports and tissue transit forms to the correct patient
- Lab number – not PID

Must be redacted

- Participant Name, Address, Hospital Number, NHS Number

- Informed consent process
- Activities prior to randomising
- Randomise participant
- Send tissue sample to central lab
- Prosigna testing (for those randomised to test-directed treatment)
- Notification of treatment allocation
- Commence adjuvant treatment

Tumour Block Selection

WARWICK CLINICAL TRIALS UNIT

Patients who have received **pre-operative endocrine treatment**

- a pre-treatment **core biopsy** should be selected.

NOTE: A tumour block from a surgical excision or other on-treatment biopsy is <u>not</u> acceptable: treated tumours are likely to have a lower Prosigna Score which could affect treatment allocation.

Patients with a **unifocal tumour**

- one representative tumour block should be selected

Patients with **multiple ipsilateral tumours**

- Blocks from more than one lesion should be submitted when they are
  - Considered clinically significant by the referring site and
  - Interpreted as synchronous primary cancers

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

If in doubt ask!

Non-luminal tumours

WARWICK
CLINICAL TRIALS UNIT

- Informed consent process
- Activities prior to randomising
- Randomise participant
- Send tissue sample to central lab
- Prosigna testing (for those randomised to test-directed treatment)
- Notification of treatment allocation
- Commence adjuvant treatment

- Patients with non-luminal tumour subtypes identified by Prosigna testing will have central confirmation of receptor status.
- Most of these are expected to be high-score tumours correctly identified as ER positive & HER2 negative
- A few tumours will be ER negative/ low-positive or HER2 positive/amplified on re-testing.
- These tumours are ineligible - sites will be notified.
- Patients with ineligible tumours should be treated appropriately for the tumour characteristics.
- Patients remain in OPTIMA and will continue with trial follow-up.

Testing & treatment allocation

WARWICK
CLINICAL TRIALS UNIT

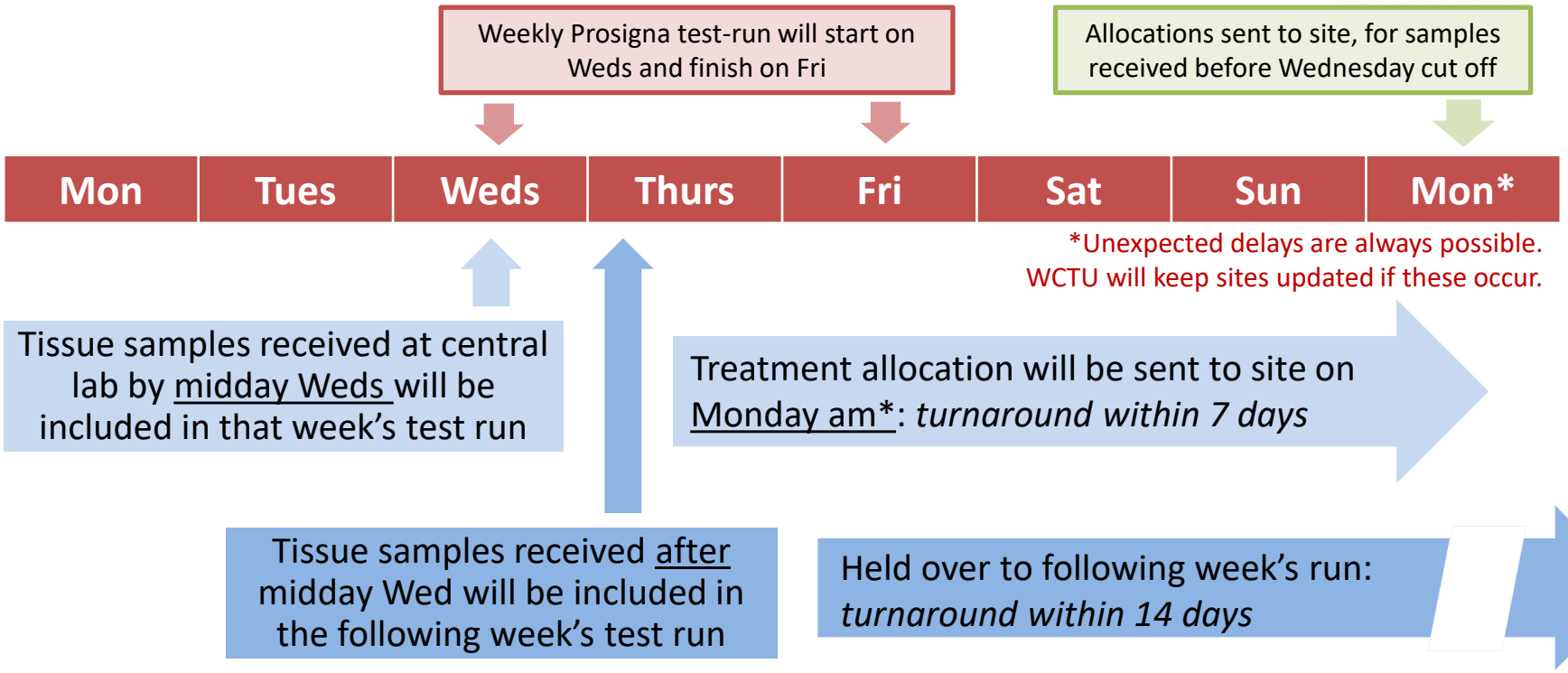
- Informed consent process
- Activities prior to randomising
- Randomise participant
- Send tissue sample to central lab
- Prosigna testing (for those randomised to test-directed treatment)
- Notification of treatment allocation
- Commence adjuvant treatment

TEST-DIRECTED ARM	STANDARD/CONTROL ARM
• Central lab receives sample	• Central lab receives sample
• Sample assessed for invasive tumour content	• Sample assessed for invasive tumour content
• Prosigna test performed	• Sample stored
• Prosigna test results reported to OPTIMA trial office	
• OPTIMA trial office notify site of participant's treatment allocation	• OPTIMA trial office notify site of participant's treatment allocation

TIME FROM RANDOMISATION TO NOTIFICATION OF TREATMENT ALLOCATION IS 2-3 WEEKS

For patients allocated to chemotherapy, randomisation is blinded from sites

Understanding the lab timetable



- Other factors that may impact the timeline:
  - Test failure (estimate 2%): repeat following week
  - Additional tests required (ER, HER2 confirmation for tumours with non-luminal Prosigna subtype, estimate 4%)
- Trial office will introduce balanced delays to notification of treatment allocation for control arm patients: you cannot assume a delay means that the patient is in the test-directed arm

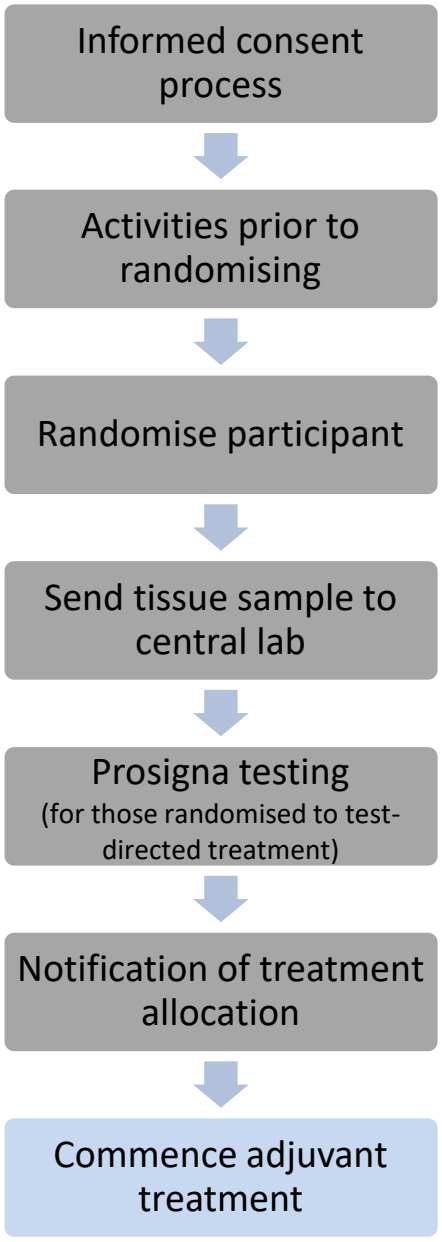
- Informed consent process
- Activities prior to randomising
- Randomise participant
- Send tissue sample to central lab
- Prosigna testing (for those randomised to test-directed treatment)
- Notification of treatment allocation
- Commence adjuvant treatment

Before treatment allocation

WARWICK CLINICAL TRIALS UNIT

✓ Eligibility check	WCTU will check all paperwork and ensure that the patient meets the eligibility based on their tumour
✓ Block processing	HSL-AD will process the tumour block(s) and check all paperwork to ensure that the tumour is acceptable for OPTIMA
✓ Confirm consent	WCTU will confirm the type of consent received. Full written consent must be received before allocation can be released. Site should complete *Confirmation of Written Consent Form (CRF 2a)* prior to allocation, if required.

After treatment allocation



Once all check have been completed, and all queries resolved, allocation will be processed by WCTU.

Allocations are automatically emailed to Site and can be sent to anyone on the Delegation log as required.

Allocations are always sent to:

- Randomising Investigator
- Person who made the Randomisation phone call
- Main Site Contact (as per the delegation log)

Tissue banking

WARWICK
CLINICAL TRIALS UNIT

Informed consent process

Activities prior to randomising

Randomise participant

Send tissue sample to central lab

Prosigna testing
(for those randomised to test-directed treatment)

Notification of treatment allocation

Commence adjuvant treatment

- The OPTIMA team is committed to further research to develop and improve multi-parameter assays.
- Tissue blocks for all patients will be stored in the OPTIMA Tissue Bank.
- The stored tissue block will be returned on request in the event that the treating site needs it for diagnostic use.
- Prosigna testing on stored tumour samples from patients randomised to the control arm is planned to allow outcome analysis for patients with low-score tumours. This is very important information for clinicians.
- Intended research includes undertaking additional multi-parameter testing on stored samples to allow evaluation of these tests in predicting outcome.

- Informed consent process
- Activities prior to randomising
- Randomise participant
- Send tissue sample to central lab
- Prosigna testing (for those randomised to test-directed treatment)
- Notification of treatment allocation
- Commence adjuvant treatment

Surgery

WARWICK CLINICAL TRIALS UNIT

Before Trial Entry:

- Before trial entry appropriate surgery should be performed according to local guidelines
- All planned axillary surgery must be completed before trial entry

Following Trial Entry:

- Re-excision of margins or completion mastectomy permitted following trial entry

Informed consent process

Activities prior to randomising

Randomise participant

Send tissue sample to central lab

Prosigna testing
(for those randomised to test-directed treatment)

Notification of treatment allocation

Commence adjuvant treatment

Chemotherapy

WARWICK
CLINICAL TRIALS UNIT

- Chosen from a list of permitted regimens.
- Intended regimen must be stated at randomisation.
- Chemotherapy is recommended to be started within 2 weeks of treatment allocation.
- Important to reassure the patient that waiting this amount of time will not have any detrimental effects on their health or outcome.
- Treatment and monitoring according to local guidelines.

PERMITTED REGIMENS	
✓ FEC75-80	✓ TC
✓ FEC90-100	✓ TAC
✓ EC90-100	✓ (F)EC-T
✓ E-CMF	✓ (F)EC-Pw/P2w
	✓ Dose dense AC/EC-P

Informed consent process

Activities prior to randomising

Randomise participant

Send tissue sample to central lab

Prosigna testing
(for those randomised to test-directed treatment)

Notification of treatment allocation

Commence adjuvant treatment

Endocrine therapy

WARWICK
CLINICAL TRIALS UNIT

- Endocrine therapy is recommended to be started no later than:
  - 2 weeks from treatment allocation in patients assigned to no chemo
  - 4 weeks after day 1 of the final cycle of chemo for all other patients
- The endocrine therapy a participant is given is based on the patient's gender and for women their menopausal status at the time of trial entry (i.e. consent), not when hormone therapy is initiated.
- The recommended duration of endocrine therapy is 10 years for all patients.

Informed consent process

Activities prior to randomising

Randomise participant

Send tissue sample to central lab

Prosigna testing
(for those randomised to test-directed treatment)

Notification of treatment allocation

Commence adjuvant treatment

Endocrine therapy

WARWICK
CLINICAL TRIALS UNIT

Initial treatment period (years 0-5)

Male:

- Tamoxifen

Postmenopausal at trial entry:

- Aromatase inhibitor. Tamoxifen may be given where there is a contraindication to aromatase inhibitor therapy.

Premenopausal at trial entry:

- Tamoxifen or an aromatase inhibitor. (Investigators must declare treatment intent at randomisation.)
- Participants should also undergo ovarian suppression e.g. with a Gonadotropin-releasing hormone (GnRH) agonist.

Informed consent process

Activities prior to randomising

Randomise participant

Send tissue sample to central lab

Prosigna testing
(for those randomised to test-directed treatment)

Notification of treatment allocation

Commence adjuvant treatment

Ovarian Suppression

WARWICK
CLINICAL TRIALS UNIT

All women who are pre-menopausal at trial entry should be treated with ovarian suppression for at least 3 years

- Optimal treatment
- Ensures balance between trial arms.

Treatment options:

- Licensed GnRH agonist, such as goserelin 3.6mg s.c. monthly or leuprorelin acetate 11.25mg s.c. 3-monthly for at least 3 years.
  N.B. refer to protocol guidance for monitoring GnRH agonist & AI combination
- Bilateral surgical oophorectomy
  Radiation menopause is not permitted.

Deferred initiation of GnRH agonists:

- Post chemotherapy amenorrhoea is common in older women. In many but not all cases this will be permanent.
- GnRH agonist treatment may be deferred for patients with amenorrhoea but should be initiated in the event of resumption of menses up to 2 years from trial entry

Informed consent process

Activities prior to randomising

Randomise participant

Send tissue sample to central lab

Prosigna testing
(for those randomised to test-directed treatment)

Notification of treatment allocation

Commence adjuvant treatment

Endocrine therapy

WARWICK
CLINICAL TRIALS UNIT

Extended treatment period (years 6-10)

As the OPTIMA population is considered to be at high risk of late relapse, all patients are advised extended adjuvant endocrine therapy for a further 5 years to a total of 10 years as follows:

Male: Tamoxifen

Female: Aromatase inhibitor or tamoxifen

For women who were deemed premenopausal at trial entry, if considering switching from tamoxifen to an aromatase inhibitor at 5 years, the patient's menopausal status needs to be confirmed at this stage as postmenopausal.

There is detailed guidance in the protocol regarding the determination of menopausal status in women receiving anti-oestrogen treatment.

Informed consent process

Activities prior to randomising

Randomise participant

Send tissue sample to central lab

Prosigna testing
(for those randomised to test-directed treatment)

Notification of treatment allocation

Commence adjuvant treatment

Adjuvant bisphosphonates

WARWICK
CLINICAL TRIALS UNIT

- Adjuvant bisphosphonate treatment is associated with a survival benefit.
- Benefit seen in postmenopausal women and those who become postmenopausal as a result of their treatment.
- All OPTIMA patients are eligible for treatment with a bisphosphonate (*either postmenopausal at trial entry or treated with ovarian suppression if pre-menopausal).*
- It is recommended that patients in the OPTIMA trial receive bisphosphonate treatment (oral or intravenous) for 2-5 years according to NICE guidelines.
- To avoid potential treatment imbalance, sites should ensure bisphosphonate treatment is the same for all patients irrespective of treatment allocation (i.e. whether the patient is receiving chemotherapy or not).

Follow-up

WARWICK
CLINICAL TRIALS UNIT

- Annual follow-up to 10 years
- Annual Follow-up Case Report Form to be completed
- Follow-up can be carried out in clinic.
- Telephone follow-up is permitted for patients who have been discharged from clinical review.
- Follow-up by e-mail is permitted if this is permitted by site's local information governance policies.
- At 12 and 24 months administer OPTIMA Patient Questionnaire Booklet.



QoL and health resource use

WARWICK
CLINICAL TRIALS UNIT

- Patient Questionnaire data is key to the outcomes of OPTIMA in terms of patient acceptability (QoL data) and cost effectiveness (health resource use)
- QoL and health resource use data is collected via Patient Questionnaire Booklets which are completed at the following time-points:
  - Baseline
  - 3 months after trial entry
  - 6 months after trial entry
  - 12 months after trial entry
  - 24 months after trial entry

At all time-points except baseline can be completed either in clinic, by post or telephone if not standard practice to see patient in clinic at this time point.

**Trial entry defined as date of informed consent*

Patient withdrawal

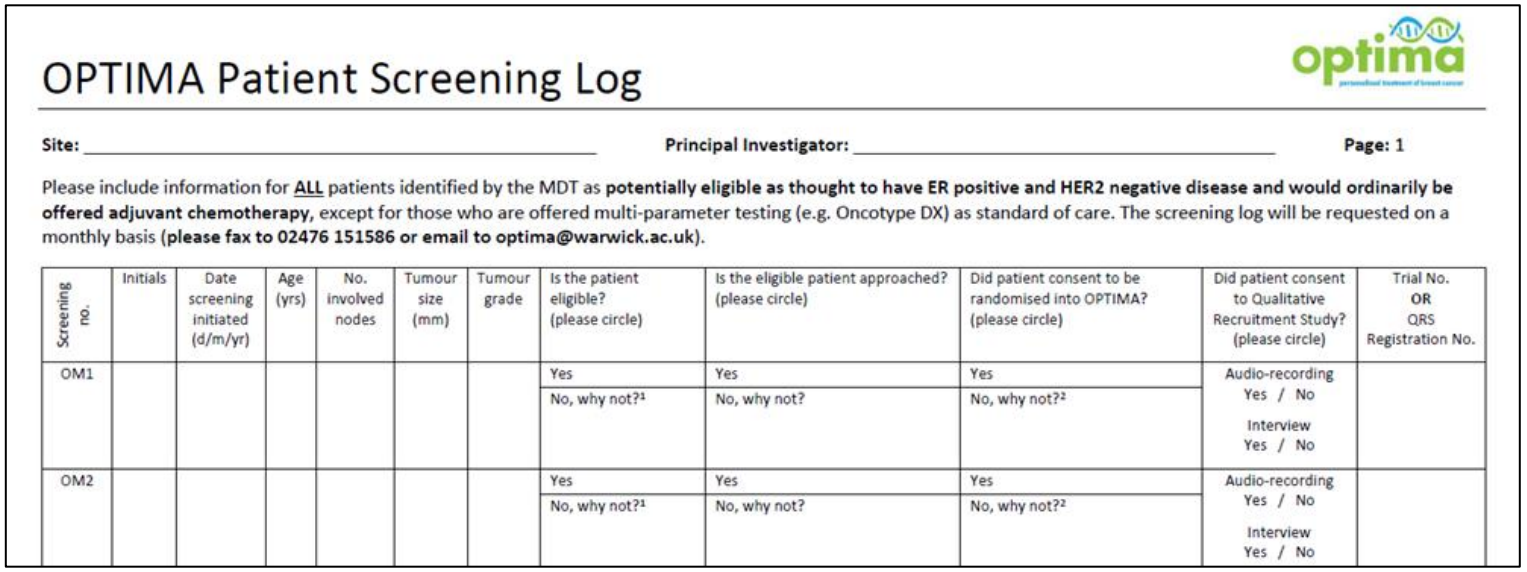
WARWICK
CLINICAL TRIALS UNIT

- Patients can withdraw from the trial at any time
- Withdrawal of patients should be communicated to the OPTIMA Trial Office as soon as possible and a Withdrawal CRF completed.
- Patients who move away from the area should not automatically be withdrawn from the trial. Transfer to another site or telephone follow-up is permitted.
- If a patient declines to follow their trial allocated treatment or ceases treatment early, this patient should not be withdrawn. Treatment, follow-up and quality of life data should be collected unless patient explicitly forbids further data from being collected.

Screening log

WARWICK
CLINICAL TRIALS UNIT

- Include all patients identified as potentially eligible (ER+ve, HER2 –ve, suitable for adjuvant chemotherapy)
- Do not include those offered multi-parameter testing as standard of care
- Provides valuable insight into recruitment process and can highlight potential obstacles
- Requirement of reporting randomised controlled trials and part of GCP
- Requested monthly



OPTIMA Patient Screening Log

optima

Site: _____ **Principal Investigator:** _____ **Page:** 1

Please include information for **ALL** patients identified by the MDT as **potentially eligible as thought to have ER positive and HER2 negative disease and would ordinarily be offered adjuvant chemotherapy**, except for those who are offered multi-parameter testing (e.g. Oncotype DX) as standard of care. The screening log will be requested on a monthly basis (**please fax to 02476 151586 or email to optima@warwick.ac.uk**).

Screening no.	Initials	Date screening initiated (d/m/yr)	Age (yrs)	No. involved nodes	Tumour size (mm)	Tumour grade	Is the patient eligible? (please circle)	Is the eligible patient approached? (please circle)	Did patient consent to be randomised into OPTIMA? (please circle)	Did patient consent to Qualitative Recruitment Study? (please circle)	Trial No. OR QRS Registration No.
OM1							Yes No, why not?[1]	Yes No, why not?	Yes No, why not?[2]	Audio-recording Yes / No Interview Yes / No	
OM2							Yes No, why not?[1]	Yes No, why not?	Yes No, why not?[2]	Audio-recording Yes / No Interview Yes / No	

Data collection

WARWICK
CLINICAL TRIALS UNIT

CRF completion

- ALL questions should be completed unless the question directs you not to.
- If data is missing please explain by means of a statement such as “not done”, “not applicable” or “unknown” so we do not query it as missing data.
- Please send original forms to be sent to the trial office and retain a copy for the site file.
- If you are not sure how to fill in any element of the form, we are very happy to help – call us anytime and we will be able to point you in the right direction.

Schedule of CRF return

- We ask for most of the CRFs to be sent to us within 4 weeks of completion.
- E.g. Baseline Forms to be sent within 4 weeks of randomisation.

Surgery CRF

- Asks you to attach the histology reports from surgery. Please obscure any identifiers and add participant’s trial ID.

Data collection

WARWICK
CLINICAL TRIALS UNIT

Data clarification process & CRF return

- Once a month send report to nominated person(s) by email.
- These list CRFs we would have expected to receive & any data queries.
- If treatment has been delayed or data manager on leave etc. please just let us know.
- We usually request a response to data queries within 2-3 weeks.

Self Evident Corrections

- We operate a system of self evident corrections on CRFs to limit the number of queries.
- All PI's and sites will be supplied with a list for approval
- All self evident corrections will be approved initially by the Trial Coordinator, all corrections will be made on the trial office copy of the CRF in green pen, and initialled and dated. We will not go back to site with these queries as the resolutions are self evident.
- *Example: Question asks if the patient has any previous or current diseases other than breast cancer and you have not ticked 'Yes' but there are diseases listed – we will tick 'Yes' with our initial and date. We will not go back to site with these queries as they are self evident.*

Compatible Trials

WARWICK
CLINICAL TRIALS UNIT

Patients randomised into OPTIMA can also take part in the following trials:

- POETIC-A (patients treated with pre-operative AI in the registration phase who do not proceed to randomisation are eligible)
- Add-Aspirin
- POSNOC (N.B. all planned axillary surgery must be completed prior to randomisation into OPTIMA)
- Radiotherapy trials
- Non-randomised trials

- Please check with the trial office if you are in doubt. In general anything that does not involve drug treatment is allowed

Preparing the team

The OPTIMA Guide for Surgeons

Surgeons and the OPTIMA study

Surgical support for OPTIMA at the multi-disciplinary team meeting is key for identifying potentially eligible patients. Whilst oncologists discuss OPTIMA in detail and consent patients, what a surgeon says to a patient about adjuvant chemotherapy is extremely important as it creates expectations. As such, surgeons set the scene for OPTIMA recruitment.

This guide summarises the study and its surgical considerations and offers tips for preparing eligible patients for a discussion about OPTIMA.

The study

OPTIMA is a randomised clinical trial designed to validate the use of tumour gene multi-parameter tests to guide chemotherapy use for patients with ER-positive HER2-negative early breast cancer. OPTIMA uses the Prosigna (PAM50) test but the design allows other tests to be evaluated.

The trial has two underlying assumptions

1. Multi-parameter tests all predict chemotherapy sensitivity
2. Tumour stage is prognostic for all patients regardless of multi-parameter test score

Patients with more advanced stage are therefore unlikely to benefit from chemotherapy if the tumour has a low test score despite an unfavourable prognosis.

The trial population are patients who would ordinarily be treated with chemotherapy. OPTIMA randomises eligible participants between standard treatment (chemotherapy followed by endocrine therapy) or to have a Prosigna test performed on the tumour. If the tumour has a high Prosigna Score (>60) then the patient will be assigned to standard treatment whilst those with a lower score receive endocrine therapy only. Patients receiving chemotherapy are blinded to the reason (randomised to control arm or high Prosigna test score). An estimated two thirds of patients whose tumours are tested will avoid chemotherapy.

The Prosigna test is performed on fixed tissue in a UK-based lab. The test takes less than 2 weeks from consent for the majority of patients. See the diagram overleaf for more information on study design.

OPTIMA is a pragmatic study that tries to accommodate local practice and not dictate treatment. In principle OPTIMA participants can join other clinical studies. This includes POSNOC.

OPTIMA expects to recruit mostly patients with node-positive (including micrometastatic) disease but does allow node-negative patients if for any reason multiparameter testing (e.g. with Oncotype DX) is not used as standard of care.

Surgical considerations*

OPTIMA is an adjuvant trial; neoadjuvant treatment is not permitted. This includes endocrine therapy as this reduces the score of all multi-parameter tests.

Secondary breast surgery such as re-excision of margins or secondary mastectomy is permitted following treatment initiation including chemotherapy but all planned axillary surgery must be completed prior to trial entry. This is because axillary node status is a trial stratification factor. Axillary radiotherapy as an alternative to clearance is allowed and should take place following chemotherapy (if the patient is allocated to this).

Short term adjuvant endocrine therapy may be given pre-randomisation but the time limit for patients to join OPTIMA is 8 weeks following their final surgery.

** Rules on neoadjuvant endocrine therapy and time limit for joining the study will be relaxed in protocol version 6.*

Talking with patients about OPTIMA

When preparing patients for an oncology appointment it would be helpful to flag up that part of that conversation will include a discussion about a clinical study – OPTIMA. Here is a suggestion for how you might do this:

"The oncologist will talk with you about further treatment. This will include a conversation about a study (called OPTIMA) to see whether you're likely to benefit from chemotherapy, as not all patients do. "

The OPTIMA Guide for Breast Nurse Specialists

Breast Nurse Specialists and OPTIMA

OPTIMA is a randomised controlled trial designed to find out if a multi-parameter test can effectively and safely identify if a patient is likely to benefit from adjuvant chemotherapy or not. OPTIMA uses the Prosigna test.

Recruitment to OPTIMA is a team activity relying on: surgeons, breast nurse specialists, pathologists, oncologists, research nurses and trial co-ordinators.

Breast nurse specialists build trusting relationships with patients and often patients will look to them for guidance about what will happen following surgery. What you and your surgical colleagues say to a patient about adjuvant treatment, can shape patient expectations and in turn, recruitment to OPTIMA.

This guide summarises the study and offers tips for preparing eligible patients for a discussion about OPTIMA.

The Study

OPTIMA aims to identify patients most likely to benefit from chemotherapy and those who may be better treated by moving directly to hormone therapy.

OPTIMA expects to recruit mostly patients with node-positive (including micrometastatic) disease because this is where there is greatest uncertainty. Node-negative patients can participate if Oncotype DX or other tests are not used.

Multi-Disciplinary Teams will identify patients with ER-positive HER2-negative early breast cancer that would ordinarily be treated with chemotherapy and who meet the eligibility criteria. Oncologists will explain the study to eligible patients and invite them to join OPTIMA.

OPTIMA randomises eligible participants between standard treatment (chemotherapy followed by endocrine therapy) or to have a Prosigna test performed on the tumour. If the tumour has a high Prosigna Score (>60) then the patient will be assigned to standard treatment whilst those with a lower score receive endocrine therapy only. Patients receiving chemotherapy are blinded to the reason (randomised to control arm or high Prosigna test score). An estimated two thirds of patients whose tumours are tested will avoid chemotherapy.

The Prosigna test is performed on fixed tissue in a UK-based lab. The test takes less than 2 weeks from consent for the majority of patients. See the diagram overleaf for more information on study design.

Introducing OPTIMA to Patients

When preparing patients for an oncology appointment it would be helpful to flag up that part of that conversation will include a discussion about a clinical study – OPTIMA. Here is a suggestion for how you might do this:

"The oncologist will talk with you about further treatment. This will include a conversation about a study (called OPTIMA) to see whether you're likely to benefit from chemotherapy, as not all patients do. "

Please avoid presenting chemotherapy as a definite as this can create an expectation of treatment. It may then be difficult for the oncologist to introduce the study concept and the idea that they may not get chemotherapy.

OPTIMA Patient Information Flyer

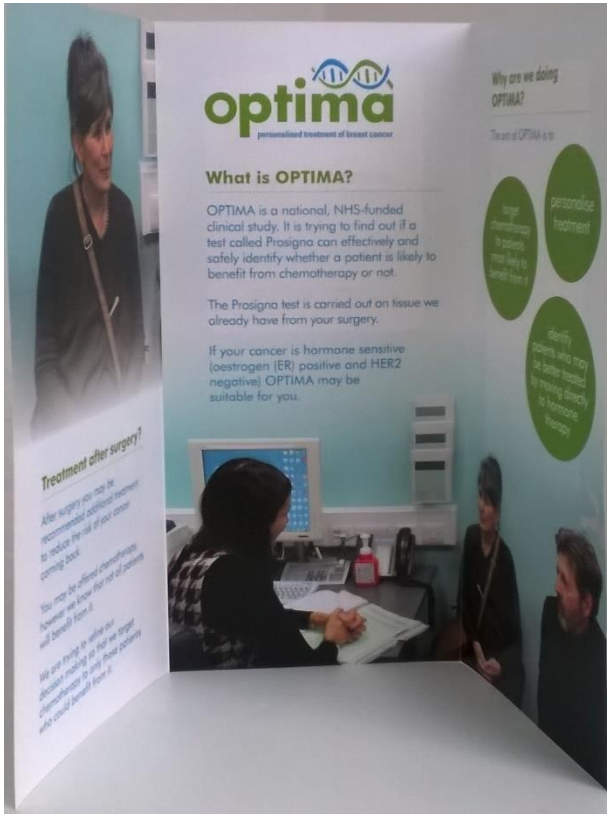
Have you just had surgery for breast cancer?

You might be suitable for OPTIMA

Working with patients, the OPTIMA team have produced a patient information flyer to introduce and prepare patients for a fuller discussion with an oncologist about OPTIMA. The flyer is in addition to the patient information sheet.

We ask that you hand it out at post-surgical appointments to patients flagged by the MDT as potentially eligible for OPTIMA.

Preparing the Patient



OPTIMA Patient Animation

[OPTIMA website]

OPTIMA team contacts

Please do not hesitate to contact us with any queries:

optima@warwick.ac.uk

WARWICK
CLINICAL TRIALS UNIT

Georgi Dotchin
OPTIMA Trial Manager
Tel: 02476 151 057

Katie McGuinness
OPTIMA Trial Manager
Tel: 02476 151 057

Amy Broadfield
OPTIMA Trial Co-ordinator

Caroline Jevons
OPTIMA Recruitment Facilitator

Michelle Davitt
OPTIMA Data Entry Clerk

Sam Careless
OPTIMA Data Entry Clerk

Carmel Conefrey
OPTIMA Qualitative Researcher
Tel: 0117 9287296
Email: carmel.conefrey@bristol.ac.uk