Persephone

Duration of Trastuzumab with Chemotherapy in Patients with Early Breast Cancer: Six Months versus Twelve

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WARWICK CLINICAL TRIALS UNIT

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List of abbreviations

ABPI	Association of the British Pharmaceutial Industry
AE	Adverse Event
ALT	ALanine Transaminase
ASCO	American Society of Clinical Oncology
AST	ASpartate Transaminase
BIG	Breast International Group
BNP	Brain Natriuretic Peptide
CHF	Congestive Heart Failure
CI	Chief Investigator
CI	Confidence Interval
CMF	Cyclophosphomide Methotrexate 5-Fluorouracil
CRF	Case Report Form
CT	Computed tomography scan
CTCAE	Common Terminology Criteria for Adverse Events
CTCR-BR03	Cambridge Translational Cancer Research - Breast Study numero 3
CXR	Chest X-Ray
DFS	Disease Free Survival
DNA	DeoxyriboNucleic Acid
DSMC	Data and Safety Monitoring Committee
ECD	Epirubicin Cyclophosphamide Docetaxel
ECG	Electrocardiogram
ECHO	Echocardiography
ECMF	Epirubicin Cyclophosphomide Methotrexate 5-Fluorouracil
ECOG	Eastern Co-operative Oncology Group
ECP	Epirubicin Cyclophosphamide Paclitaxel
EF	Ejection Fraction
ER	Oestrogen receptor
EudraCT	European Clinical Trials Database
FBC	Full Blood Count
FEC	5-Fluorouracil Epirubicin Cyclophosphamide
FISH	Fluorescent In Situ Hybridisation
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
Hb	Hemoglobin
HER2	Human Epidermal growth factor Receptor 2
HR	Hazard Ratio
HTA	Heath Technology Assessment Programme
IHC	Immuno-Histo-Chemistry
IMP	Investigational Medicinal Product
INCa	Institut National du Cancer
ISRCTN	International Standard Randomised Controlled Trial Number
IV	Intravenous
LVEF	Left Ventricular Ejection Fraction
MHRA	Medicines and Healthcare products Regulatory Agency
MUGA	MUltiple Gated Acquisition scan
NCCHTA	National Co-ordinating Centre for the Heath Technology Assessments
NCI	National Cancer Institute (USA)
NCRI	National Cancer Research Institute.
NEJM	New England Journal of Medicine
NIHR	National Institute for Health Research
NETSCC	NIHR Evaluation, Trials and Studies Coordinating Centre
NSABP	National Surgical Adjuvant Breast and Bowel Project
NYHA	New-York Heart Association
OS	Overall Survival
P	probability
PI	Principal Investigator
PO	by mouth
PSSRU	Personal Social Services Research Unit (PSSRU)
q	every
QALYs	Quality adjusted life years
QoL	Quality of Life
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Caracteristics
SNP	Single Nucleotide Polymorphism
Subcut	Sub-cutaneous
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAC	Docetaxel Doxorubicin Cyclophosphamide
TBA	To Be Appointed
TMG	Trial Management Group
ULN	Upper Limit of Normal
WBC	White blood cell count
WHO	World Health Organisation

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1. Trial Summary

***PERSEPHONE* - Primary objective:** A phase III, randomised trial comparing 6 months (9 cycles) trastuzumab treatment with 12 months (18 cycles), in patients with HER2 positive early breast cancer, in terms of efficacy (disease-free and overall survival), cost-effectiveness (Health Resource Use and Quality of Life) and safety (cardiac and other toxicity).

***PERSEPHONE* - Secondary objectives - Sub-studies:**

1. ***Trans - PERSEPHONE:*** Tumour blocks (paraffin-embedded) will be collected prospectively from patients in the study, for molecular and candidate gene analysis as prognostic and predictive markers (separate protocol).
2. ***Trans - PERSEPHONE - SNPs:*** Blood samples will be collected prospectively from patients in the study, for Single Nucleotide Polymorphism analysis to research genetic / pharmaco-genetic determinants of prognosis and treatment response (separate protocol).

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Phase III co-ordinating centre:	Warwick Clinical Trials Unit
Translational co-ordinating centre:	Experimental Cancer Medicine Centre (NCRI and CRUK) and NIHR Cambridge Biomedical Research Centre University of Cambridge and Cambridge University Hospitals NHS Foundation Trust
Translational Sub-committee:	Carlos Caldas (Chairman), Elena Provenzano, Helena Earl, Anne-Laure Vallier, Linda Jones and Jean Abraham.
Number of patients to be enrolled:	4,000
Indication:	Early breast cancer patients, HER2 positive, eligible for adjuvant or neo-adjuvant chemotherapy.
Trial Sponsors:	Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge
PHARE Group France:	Xavier Pivot (CI), Iris Pauporte (Management and Regulatory Affairs).

Rationale

The incidence of breast cancer continues to rise in Western Europe and the US with breast cancer remaining a major health problem despite considerable improvements in treatment of the disease both in the adjuvant and in the metastatic setting. Trastuzumab (Herceptin®) treatment in patients with early stage HER2 positive breast cancer, has proved a major advance and has demonstrated the enormous value of HER2-targeted therapy in the adjuvant setting for HER2 positive breast cancer in particular. However, the use of 12 months trastuzumab in the majority of studies is not based on evidence. It is reasonable to consider that since the beneficial effect of adjuvant trastuzumab is detected early in follow-up (median 1 year), that the majority of the adjuvant benefit results from the first 6 months of therapy. This hypothesis is supported by evidence from the FinHer study which, with only 9 weeks trastuzumab demonstrates a similar-sized benefit to 12 months treatment, when given concurrently with chemotherapy. The recent publication of the HERA results after 8 years follow-up, demonstrates that 24 months trastuzumab is not superior to 12 months. This result was predicted by our group in the development of the PERSEPHONE trial. PERSEPHONE will compare 6 months (9 cycles) treatment with 12 months (18 cycles), in terms of safety and efficacy.

Primary endpoint

Disease-free survival non-inferiority (equivalence) of 6 months (9 cycles) trastuzumab compared with 12 months (18 cycles) in patients with early breast cancer.

Secondary endpoints

- Overall survival non-inferiority (equivalence) of 6 months trastuzumab to 12 months in patients with early breast cancer.
- Expected incremental cost effectiveness (Cost per Quality Adjusted Life Year Gained) for 6 months trastuzumab versus 12 months trastuzumab.
- Cardiac function as assessed by left ventricular ejection fraction (LVEF) during trastuzumab therapy, and analysis of predictive factors for development of cardiac damage.

Study design

- A phase III, prospective, randomised trial of trastuzumab duration (6 months versus 12 months) in the adjuvant and neo-adjuvant setting for patients with early stage HER2 positive breast cancer.
- Detailed data on resource use and quality of life will be collected in an early cohort of PERSEPHONE patients (300-500 patients) for Health Economic Analysis. Quality of life data will be collected on all patients (EuroQoL).
- Assessment of cardiac function will be made with reference to methods used for assessment and age and other co-morbidities as risk factors. Cardiac function will be routinely assessed by LVEF measurements for all trial patients beginning with the one taken prior to the first trastuzumab dose and then throughout trastuzumab treatment done according to standard practice (minimum of 4 monthly).

Sample size determination

The power calculations assume that the disease-free survival (DFS) of the standard treatment of 12 months trastuzumab will be 80% at 4 years. On this basis, with 5% 1-sided significance and 85% power, a trial randomising 4000 patients in total (2000 in each arm) will have the ability to prove non-inferiority of the experimental arm, defining non-inferiority as ‘no worse than 3%’ below the control arm 4 year DFS.

Analysis

- Primary endpoint of disease-free survival will be assessed using Kaplan-Meier survival curves and treatment tested using Cox Proportional Hazards analysis, with and without adjustment for the stratification and baseline prognostic factors, on an intention-to-treat basis.
- Secondary outcomes of overall survival will be assessed using Kaplan-Meier survival curves and treatment tested using Cox Proportional Hazards analysis, with and without adjustment for the stratification and baseline prognostic factors, on an intention-to-treat basis.
- The analyses of all other secondary endpoints will be undertaken using the appropriate statistical analysis tools.

Duration of treatment

The trial employs either 6 (9 cycles) or 12 months (18 cycles) trastuzumab in patients with early stage breast cancer. All patients will receive chemotherapy either in the adjuvant or neo-adjuvant setting. Trastuzumab will be given either concurrently or sequentially with respect to chemotherapy, and so the total duration of treatment (chemotherapy and trastuzumab) will vary depending on the precise combination employed.

Key inclusion criteria

- Patients with histologically confirmed invasive breast cancer.
- HER2 positive breast cancer (3+, or 2+ and ISH amplified).
- Patient of sufficient risk to require chemotherapy (anthracycline-based [no taxane], or taxane-based [with anthracyclines], or taxane-based [no anthracyclines] combinations).
- Adjuvant or neo-adjuvant chemotherapy.

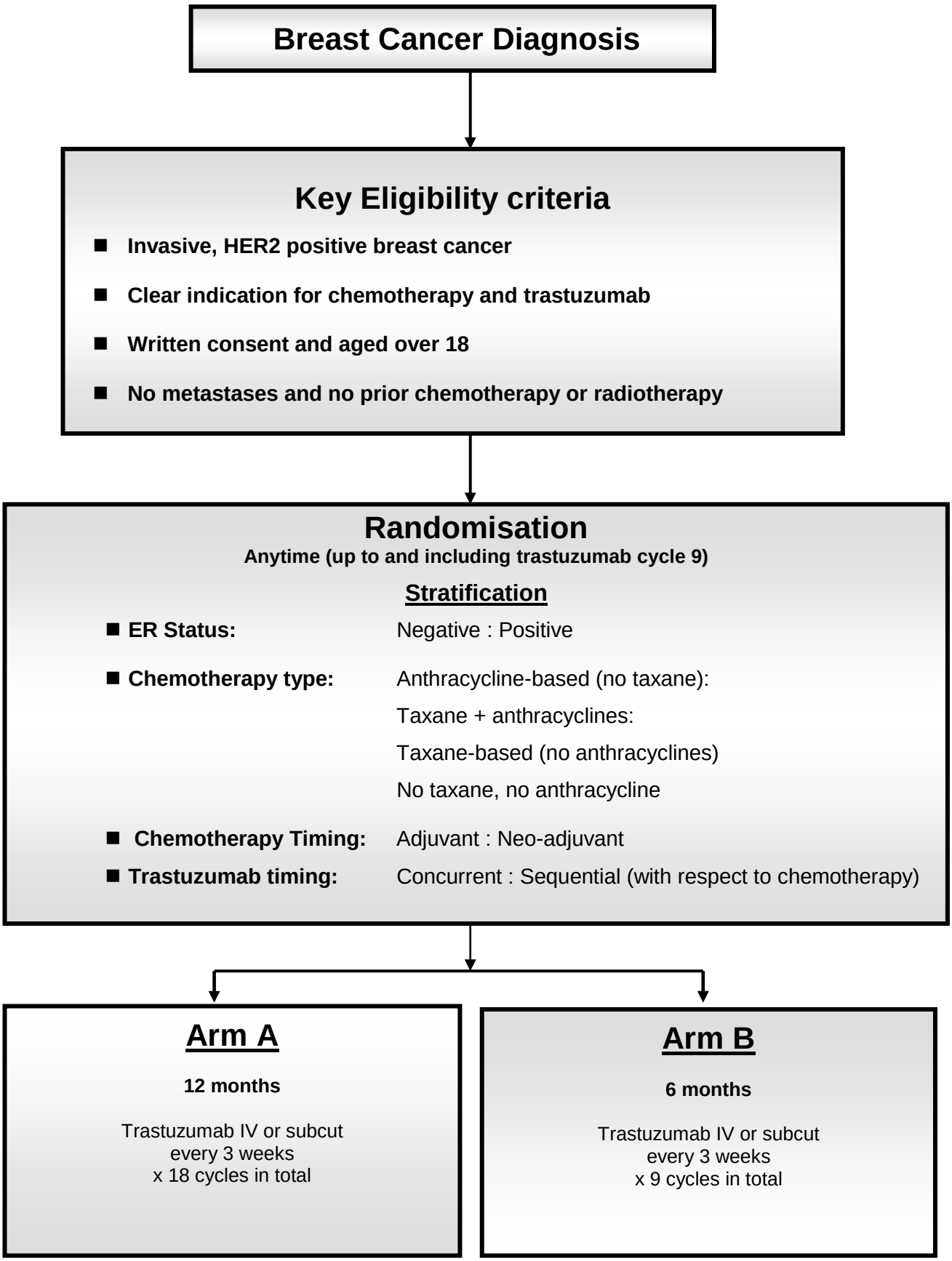
Key exclusion criteria

- Not suitable for chemotherapy in the opinion of the responsible clinician.
- Evidence of metastatic disease.
- Previous malignancy unless treated by surgery alone and disease-free for 10 years.

PERSEPHONE – Sub-studies:

- ***Trans - PERSEPHONE:*** Tissue blocks (paraffin-embedded) will be collected to discover molecular predictors of survival with respect to duration of trastuzumab treatment. Analysis of tissue will involve (i) tissue microarrays for immunohistochemistry (IHC) of protein gene products and in situ hybridisation analysis, and (ii) whole-genome profiling using expression and DNA microarrays.
- ***Trans - PERSEPHONE – SNPs:*** Blood samples will be used to discover single nucleotide polymorphisms (SNPs) as genetic / pharmacogenetic determinants of prognosis, toxicity and treatment outcome.

2. Trial Schema



3. Introduction

Trastuzumab (Herceptin®) has been tested extensively in the adjuvant setting in women with HER2 positive early breast cancer, and shown to provide significant benefits in terms of disease-free and overall survival compared to adjuvant chemotherapy alone. The results of three large randomised trials were presented in a special session at the American Society of Clinical Oncology 2005 (ASCO), and detailed interim analyses of the trials were published in the New England Journal of Medicine (NEJM) in October 2005 (1,2). The clinical improvement for trastuzumab is the largest benefit ever seen in breast cancer trials, and is remarkable both for its magnitude, and also the demonstration of benefit so early in follow-up.

The HERceptin Adjuvant (HERA) trial was an international, multi-centre, randomised trial, which compared one or two years trastuzumab given every 3 weeks, with observation in patients with HER2-positive and either node-negative or node-positive breast cancer, who had completed loco-regional therapy and at least 4 cycles of neoadjuvant or adjuvant chemotherapy. 1694 patients were assigned 2 years trastuzumab, 1694 one year, and 1693 were in the observation arm with chemotherapy alone. Results were reported in the NEJM paper for the one year trastuzumab compared with chemotherapy alone (1). At the first planned interim analysis (median follow-up 1 year), 347 events (recurrence of breast cancer, contra-lateral breast cancer, second non-breast malignant disease, or death) were observed: 127 events in the trastuzumab group and 220 in the observation group. The unadjusted hazard ratio (HR) for an event in the trastuzumab group compared with the observation group was 0.54 (95% Confidence Interval, 0.43-0.67; P<0.0001 by the log rank test crossing the interim analysis boundary), representing an absolute benefit in terms of disease-free survival (DFS) at 2 years of 8.4 percentage points. Severe cardiac toxicity developed in 0.5 percent of the women treated with trastuzumab. The 2-year follow-up analysis of the HERA trial has now been published in the Lancet and demonstrates a benefit for overall survival (OS) as well as DFS (HR for OS = 0.66 [95% CI 0.47-0.91]; p=0.0115: updated HR for DFS = 0.64 [95% CI 0.54-0.76]; p<0.0001) (3). These results show that trastuzumab after adjuvant chemotherapy has a significant benefit after a median follow-up of 2 years. The emergence of this benefit after only 2 years reinforces the importance of trastuzumab in the treatment of patients with HER2-positive early breast cancer.

The second paper published in the NEJM (2) included the combined results of two US trials, which compared adjuvant chemotherapy with or without concurrent trastuzumab in women with surgically removed HER2-positive breast cancer. The National Surgical Adjuvant Breast and Bowel Project trial NSABP-B-31 compared doxorubicin and cyclophosphamide followed by paclitaxel every 3 weeks (group 1) with the same regimen plus 12 months of trastuzumab beginning with the first dose of paclitaxel (group 2). The North Central Cancer Treatment Group trial N9831 compared three regimens: doxorubicin and cyclophosphamide followed by weekly paclitaxel (group A), the same regimen followed by 52 weeks of trastuzumab after paclitaxel (group B), and the same regimen plus 52 weeks of trastuzumab initiated concomitantly with paclitaxel (group C). The studies were amended to include a joint analysis comparing groups 1 and A (the control group) with groups 2 and C (the trastuzumab group). Group B was excluded because trastuzumab was not given concurrently with paclitaxel. By March 15, 2005, 394 events (recurrence, second primary cancer, or death before recurrence) had been reported, triggering the first scheduled interim analysis. Of these, 133 were in the trastuzumab group and 261 in the control group (hazard ratio, 0.48; P<0.0001). This result crossed the early stopping boundary. The absolute difference in disease-free survival between the trastuzumab group and the control group was 12 percent at three years. Trastuzumab therapy was associated with a 33 percent reduction in the risk of death (P=0.015). The three-year cumulative incidence of class III or IV congestive heart failure or death from cardiac causes in the trastuzumab group was 4.1 percent in trial B-31 and 2.9 percent in trial N9831. Trastuzumab combined with paclitaxel after doxorubicin and cyclophosphamide improves outcomes among women with surgically removed HER2-positive breast cancer.

The BCIRG study of trastuzumab in women with early breast cancer (BCIRG 006) examined concurrent treatment of trastuzumab with a non-anthracycline-containing chemotherapy regimen (docetaxel and either carboplatin or cisplatin). Interim results were reported by Slamon at the 2005/06 San Antonio Breast Cancer Conferences (4,5). BCIRG 006 was a large, randomized phase III trial of adjuvant doxorubicin, cyclophosphamide followed by docetaxel with or without trastuzumab versus trastuzumab, docetaxel and either carboplatin or cisplatin (TC[H]) in women with HER2-expressing node positive or high risk node-negative operable breast cancer. This study showed significant improvement in DFS for the use of Herceptin®. At San Antonio 2005 a subgroup analysis demonstrated an interesting interaction between HER2 over-expression and co-expression of topoisomerase II alpha, and the benefit of anthracycline treatment (6,7). Patients with combined over-expression were disadvantaged on the TCH arm, presumed due to the lack of an anthracycline, despite the addition of trastuzumab. However, the updated results presented at San Antonio in 2006 did not confirm topoisomerase II alpha overexpression as a predictive marker for anthracycline benefit. This study now simply confirms the effect of the

addition of trastuzumab to chemotherapy in women with early HER2 positive breast cancer. The putative effect of co-overexpression of topo-II alpha requires further investigation with regard to interaction with anthracyclines.

Beneficial results for trastuzumab given for just 9 weeks, concurrently with docetaxel or vinorelbine were reported from the FinHer study at the San Antonio Breast Cancer Conference 2005, and in the NEJM in February 2006 (8). This study compared docetaxel with vinorelbine for the adjuvant treatment of patients with early breast cancer. Women with tumors that over-expressed HER2 were also assigned to receive chemotherapy with or without concomitant trastuzumab. A total of 1010 women were recruited with axillary-node-positive or high-risk node-negative cancer to receive three cycles of docetaxel or vinorelbine, followed by (in both groups) three cycles of fluorouracil, epirubicin, and cyclophosphamide. The 232 women whose tumors had an amplified HER2 gene were further assigned to receive or not to receive nine weekly trastuzumab infusions, concurrently with the docetaxel or vinorelbine. The primary end point was recurrence-free survival. Recurrence-free survival at three years was better with docetaxel than with vinorelbine [91 percent vs. 86 percent; hazard ratio for recurrence or death, 0.58; 95 percent confidence interval, 0.40 to 0.85; P=0.005), but overall survival did not differ between the groups (P=0.15)]. Within the subgroup of patients who had HER2-positive cancer, those who received trastuzumab had better three-year recurrence-free survival than those who did not receive the antibody (89 percent vs. 78 percent; hazard ratio for recurrence or death, 0.42; 95 percent confidence interval, 0.21 to 0.83; P=0.01). Docetaxel was associated with more adverse effects than was vinorelbine. Importantly despite trastuzumab being given immediately before anthracyclines, this arm was not associated with decreased left ventricular ejection fraction or cardiac failure. Adjuvant treatment with docetaxel, as compared with vinorelbine, improves recurrence-free survival in women with early breast cancer. A short course of trastuzumab administered concomitantly with docetaxel or vinorelbine is effective in women with breast cancer who have an amplified HER2 gene.

The above studies clearly demonstrate the effectiveness of adjuvant trastuzumab in patients with HER2 positive breast cancer, however important questions about adjuvant trastuzumab in women with early breast cancer still remain, in particular the duration of therapy question (9). All studies reported have used 12 months trastuzumab apart from the FinHer study, which used just 9 weeks of therapy, immediately post-operatively with either docetaxel or vinorelbine. The choice of 12 months trastuzumab in the large studies is not evidence-based, and it would be reasonable to hypothesise that since the effect of adjuvant trastuzumab is detected so early in follow-up (median follow-up 1 year), that the majority of the adjuvant effect is being seen in the first 6 months of therapy. Based on these Finnish results, the French Group (Institut National du Cancer [INCa]) has developed the PHARE clinical trial to compare 6 versus 12 months trastuzumab. In an International Collaboration with the PHARE group, ***PERSEPHONE*** will carry out a pre-planned joint analysis of results, which will allow an equivalence or non-inferiority comparison between 6 and 12 months duration of trastuzumab at the 2% level (absolute). The International Collaboration requires at least 7,000 patients to be entered, but the statisticians on the project are encouraging randomisation of as many patients as possible to improve the 'certainty' of the outcome of the trial. In a recent article in Cancer World (10) the French group detailed that to be significant an International collaboration requires recruitment of over 4000 patients in the UK.

PERSEPHONE will allow recruitment of HER2-positive patients who require chemotherapy. Patients can have either adjuvant or neo-adjuvant chemotherapy, anthracycline or taxane-based chemotherapy, and trastuzumab either concurrently or sequentially with chemotherapy. Patients will be randomized before the 10th cycle of trastuzumab treatment, and health resource use and quality of life data will be collected on all patients during trastuzumab therapy.

Trastuzumab is the first targeted biological therapy to have reported demonstrable benefit in the adjuvant setting in cancer, but there are many similar compounds in the pipelines of all global pharmaceutical companies. It is very important that an international collaboration tackles the question of duration of such therapy. The question of the potential equivalence of 6 months and 12 months therapy, whilst of enormous importance to the wider cancer community, would not be in the immediate interests of the commercial sector to answer. The success of this study will be dependent on non-commercial, academic, and national groups collaborating in an effort to maximize recruitment. The ***PERSEPHONE*** group is clear that it will also be important to answer the more generic question about newer targeted therapies:

'Is 6 months of targeted biological therapy for early cancer, sufficient?'

Additional Information for Amended Protocol Introduction September 2013

The development of trastuzumab in the early 2000's has provided a paradigm shift in adjuvant treatment of HER2 positive early breast cancer. The results of three adjuvant trials were reported in 2005 and are discussed above. Recently the long-term follow-up results of HERA have been presented and are now published, confirming significant benefit for 12 months trastuzumab compared with control at 8 years median follow-up (a). This is despite nearly 50% of patients in the control arm 'crossing over' to receive adjuvant trastuzumab after the results had been reported. There is no dispute about the significant benefit of adjuvant trastuzumab in HER2 positive breast cancer.

The HERA trial also tests 24 months versus 12 months trastuzumab. The report shows no additional benefit from 24 months, and therefore 12 months remains the standard of care in 2013 throughout the world (a). In the accompanying editorial 'Duration of adjuvant trastuzumab: shorter beats longer' (b), Heikki Joensuu states that 'the results of the HERA trial are in line with the biology and clinical behavior of HER2-positive breast cancer. These are frequently aggressive tumours that usually recur early. The HERA results lend support to the hypothesis that patients with HER2 amplification do not benefit from long treatment durations with HER2-targeted therapy, but "might be managed best with effective regimens of short duration.' The median follow-up in the HERA trial is now 8 years, but interestingly had the trial been analysed and reported after only 3 years, a benefit for 2 years trastuzumab would have been found. With more prolonged follow-up, both 1 and 2 year disease-free and overall survival curves are identical, and any earlier difference has disappeared.

The question which remains is – *'Are shorter than 12 month durations of adjuvant trastuzumab non-inferior*?' FinHer demonstrates significant benefit from just 9 weeks trastuzumab given upfront with concomitant taxane-based chemotherapy. The FinHer result led to PERSEPHONE and 3 other trials to address the question of non-inferiority of shorter durations of trastuzumab.

The International SOLD trial from Joensuu's group examines 9 weeks +/- 12 months adjuvant trastuzumab. The shorter duration trastuzumab is given in the same way as in the FinHer trial (concomitantly with taxane-based upfront adjuvant treatment). The second trial with the same design is SHORTHer, funded by the Italian government and led by Professor Conte. This trial had a target recruitment of over 2500 patients, but was stopped early with 1100 patients when funding was completed. The SOLD trial continues international recruitment at the present time and has recruited over 1300 of a proposed 2400 patients.

The PHARE trial funded by the Institute National du Cancer (INCa) in France has the same design as PERSEPHONE and completed recruitment in 2010. The PERSEPHONE TMG has worked closely with the PHARE group and there is a planned collaboration for a meta-analysis when PERSEPHONE has completed recruitment and follow-up phase and been reported. The preliminary results of PHARE have now been presented (ESMO 2012 and San Antonio Breast Cancer Symposium 2012) and published (c). These results are preliminary and inconclusive, the follow-up is relatively short (median 3.5 years) although the results do not prove ***non-inferiority.*** The caveat is that results have been presented after only 42 months median follow up. Examining the mature DFS and OS curves (median follow-up 8 years) from the HERA trial, there is a clear separation of the 24 month versus 12 month curves after 3 years, but this disappears with more prolonged follow-up. This time point is the same time point at which PHARE has been published. The PHARE results do show that in a prospectively stratified analysis of subgroups, it was only the ER-negative patients receiving sequential chemotherapy and trastuzumab, who appeared to be significantly disadvantaged by receiving the 6 month duration of trastuzumab.

After the presentation of the PHARE and HERA data in 2012, the PERSEPHONE Independent Data Monitoring and Safety Committee have confidentially examined the data within the trial. They have advised the PERSEPHONE Trial Management Group, and Trial Steering Group, that there are no adverse signals within this data, and they have advised that this important trial continues. On the strength of their advice, the NIHR HTA has agreed a funding grant extension to complete recruitment of 4,000 patients and to allow appropriate follow-up.

The new subcutaneous formulation of trastuzumab has been shown to be equivalent to intravenous trastuzumab (d) and will now be incorporated in this newly amended PERSEPHONE protocol.

4. Objectives and endpoints of the study

Primary objective

A phase III, randomised trial comparing 6 months (9 cycles) trastuzumab treatment with 12 months (18 cycles), in patients with HER2 positive early breast cancer, in terms of efficacy (disease-free and overall survival), cost-effectiveness (Health Resource Use and Quality of Life) and safety (cardiac and other toxicity).

Primary endpoint

- Disease-free survival non-inferiority (equivalence) of 6 months (9 cycles) compared with 12 months (18 cycles) trastuzumab in patients with early breast cancer.

Secondary endpoints (clinical)

- Overall survival non-inferiority (equivalence) of 6 months (9 cycles) compared with 12 months (18 cycles) trastuzumab in patients with early breast cancer.
- Expected incremental cost effectiveness (Cost per Quality Adjusted Life Year Gained) for 6 months (9 cycles) versus 12 months (18 cycles) trastuzumab.
- Cardiac function as assessed by left ventricular ejection fraction (LVEF) during trastuzumab therapy, and analysis of predictive factors for development of cardiac damage.

Secondary objectives - Sub-studies:

- Trans - PERSEPHONE: Tumour blocks (paraffin-embedded) will be collected prospectively from patients in the study, for molecular and candidate gene analysis as prognostic and predictive markers (separate protocol).
- Trans - PERSEPHONE - SNPs: Blood samples will be collected prospectively from patients in the study, for Single Nucleotide Polymorphism analysis to research genetic / pharmaco-genetic determinants of prognosis and treatment response (separate protocol).

5. *PERSEPHONE*: trial design

This is a phase III clinical trial randomising 4000 patients in total to receive either 6 months (9 cycles) of trastuzumab (experimental arm) or 12 months (18 cycles) of trastuzumab (standard arm).

5.1 First 100 concomitant chemotherapy and trastuzumab patients 'pilot' study

Since the second part of the various chemotherapy schedules (taxanes or CMF) can be given concomitantly with trastuzumab, the first 100 patients on ***PERSEPHONE*** receiving concomitant chemotherapy and trastuzumab will provide data 'in real time' on serious adverse effects and treatment delay, for this category of patient. These data will be collected and analysed by the ***PERSEPHONE*** trial office and discussed by the independent Data and Safety Monitoring Committee.

Update: a review of this data was conducted in December 2010 and no problems were observed at the time.

5.2 Eligibility criteria

Inclusion criteria

- Histological diagnosis of invasive breast cancer.
- No evidence of metastatic disease.
- Known hormone receptor status.
- Overexpression of HER2 receptor.

  Bilateral breast cancers are eligible provided that one of the tumours is overexpressing the HER2 receptor.
- Clear indication for neo-adjuvant or adjuvant chemotherapy based on clinical and histopathological features.
- Patient fit to receive neo-adjuvant or adjuvant chemotherapy and trastuzumab in the opinion of the responsible physician.
- No previous diagnosis of malignancy unless:
  - managed by surgical treatment only, and disease-free for 10 years.
  - previous basal cell carcinoma, cervical carcinoma *in situ* or ductal carcinoma *in situ* of the breast.
- Non-pregnant and non-lactating, with no intention of pregnancy during chemotherapy, and agrees to adopt adequate contraceptive measures if pre-menopausal and sexually active.
- No concomitant medical or psychiatric problems that might prevent completion of treatment or follow-up.
- Patients 18 years or older.
- Written informed consent for the study given at any time before the 10th cycle of trastuzumab.

Exclusion criteria

- No significant concomitant cardiac disease or significant concomitant co-morbidity in the opinion of the responsible physician adding to the risks associated with trastuzumab or cytotoxic chemotherapy.
- Inability to comply with protocol requirements.
- Patient having received more than 9 cycles of trastuzumab.
- Any other condition, which in the local investigator's opinion would make the patient unsuitable for participating in the trial.

5.3 Schedule of assessments and procedures (see Appendix 1)

Pre-randomisation screening investigations

Pathology investigations

ER status must be defined at randomisation.
Definitive HER2 status must be available at randomisation.

Definition of HER2 positive overexpression

Hospitals which are entering patients into the trial must ensure that laboratories are complying with the UK Guidelines for HER2 testing (11).

Cardiac investigations

Cardiac function should be assessed by physical examination and by echocardiography [ECHO] or multi-gated acquisition cardiac scanning [MUGA*], Any other assessment methods should be discussed with the PERSEPHONE trials office.
*An ARSAC certificate is not required if the MUGA are carried out according to standard practice at the centre.

LVEF assessments expected for trial patients

LVEF assessments are expected for all trial patients. This begins with the assessment undertaken prior to the first trastuzumab dose and then continues throughout trastuzumab treatment, to be done according to standard practice (minimum of 4 monthly).

When an LVEF percentage is not available, the cardiologist should state in the report if the LVEF is normal or abnormal. The cardiology report must be sent to the PERSEPHONE trial office.

LVEF results must be classed as 'normal' for trastuzumab treatment to continue as planned.

A decision to administer or 'hold' a dose of trastuzumab on account of a reduced LVEF must be made based on the recommendations made in the current SmPC (Summary of Product Characteristics).

In case of reduced LVEF, please refer to section "6.4 Management in response to cardiac toxicity".

Staging investigations

Required staging investigations will be minimal in keeping with standard UK practice in breast cancer management. All examinations will need to be completed in compliance with local Ionising Radiation Medical Exposure Regulations (IRMER) Employer's Procedures at each site. An ARSAC certificate is not required if the investigations (CXR, CT scan or isotope bone scan) are carried out according to standard practice at the centre.

All patients should have a full blood count (FBC), biochemical screen, to include liver and bone function tests.
In the case of abnormal full blood count or abnormal liver or bone biochemistry*, further staging investigations are advised, in accordance with standard practice at the centre.

***Recommendations** — *Hb $\leq$10 g/dL; WBC $\leq 3 \times 10^9$/L; platelets $\leq$150 x 10^9/L*
AST/ALT ≥ 2 x ULN, Alkaline phosphatase ≥ 2 ULN

6. PERSEPHONE treatment plan

6.1 Trial treatment

The trial treatment is trastuzumab and it is considered as an Investigational Medicinal Product.

Route

Trastuzumab can be given either intravenously or sub-cutaneously. Switch between the routes of treatment is at the discretion of the treating clinician.

Randomisation

Patients will be randomised to:

Research arm: Patients will receive 9 cycles of trastuzumab (6 months arm).

or

***Standard arm*:** Patients will receive 18 cycles of trastuzumab (12 month arm).

Dose is expected to be given every 3 weeks as per SmPC. Where standard practice differs, please contact the trial office for approval.

Dose

Intravenous route

The starting / loading dose of trastuzumab is 8mg/kg.

The maintenance dose (6mg/kg) is given 3 weeks after the starting / loading dose, and subsequent doses are given 3 weekly at 6mg/kg.

To be administered as per standard practice.

Where standard practice differs, please contact the trial office for approval.

Subcutaneous route

There is no loading dose for subcutaneous trastuzumab administration.

Subcutaneous trastuzumab is to be given at a fixed dose of 600 mg in a volume of 5ml as per SmPC**.**

Where standard practice differs, please contact the trial office for approval.

Trastuzumab delays

- Patients are not allowed to 'hold' treatment on account of **cardiac toxicity** on more than two occasions for more than a total of 3 months. This is because it is likely that minimum length of a 'hold' because of cardiac dysfunction will be 6 weeks and therefore a maximum of two "holds" will be allowed for cardiac toxicity.

- Sites using chemotherapy protocols with up-front taxanes and concomitant trastuzumab, will probably discontinue trastuzumab during subsequent anthracyclines. Timing of restarting trastuzumab in these circumstances will be at their discretion and may be more than 3 months.

- Sites can discontinue trastuzumab during the course of radiotherapy if it is local practice. Timing of restarting trastuzumab in these circumstances will be at the discretion of the treating clinician and may be more than 3 months.

- For patients who hold treatment for other reasons, the timing of restarting trastuzumab will be at the discretion of the treating clinician and may be more than 3 months.

- Patients who have a 'hold' of trastuzumab for whatever reason, should receive a total of either 9 or 18 cycles depending on their randomised treatment arm.

Trastuzumab ± chemotherapy in *PERSEPHONE* delivered outside of the Participating site

Trastuzumab can be administered to trial patients off-site if it is part of the standard practice at the site and once the trials office has given their Green light. Additional contracts need to be in place before this commences so please contact the trial office.

6.2 Timing of Chemotherapy

All chemotherapy regimens are acceptable on the *PERSEPHONE* trial.

Patients can receive trastuzumab sequential to or concurrent with adjuvant or neo-adjuvant chemotherapy.

Adjuvant chemotherapy

Sequential treatment

Trastuzumab can be administered sequentially following **all types of adjuvant breast cancer chemotherapy**.

Concurrent treatment

The decision to give trastuzumab concurrently with chemotherapy is made by the responsible treating clinician in accordance with local standard protocols. In cases where trastuzumab can be administered concurrently, the treatment can be started with any cycle of chemotherapy.

Neo-adjuvant chemotherapy

Sequential treatment

Trastuzumab can start before or after surgery. If starting just before surgery, trastuzumab treatment can continue every three weeks without interruption even during the peri-operative period.

Concurrent treatment

The decision to give trastuzumab concurrently with chemotherapy is made by the responsible treating clinician in accordance with local standard protocols. In cases where trastuzumab is to be administered concurrently, the treatment can be started with any cycle of chemotherapy. Trastuzumab treatment can also continue every three weeks without interruption during the peri-operative period, at the discretion of the local clinician.

6.3 Standard chemotherapy treatments

All patients randomised will be scheduled to receive standard chemotherapy regimens as per local institutional protocols. These protocols will depend on the prognosis of the patient and during the 'lifetime' of the trial, depending on licensing and NICE guidance.

Chemotherapy will be administered following the normal practice of the centre with respect to all concomitant medication and procedures for the safe administration of cytotoxic chemotherapy.

Reverse-sequence taxane-first chemotherapy

There is now some evidence that taxane-first sequencing may produce higher response rates in neo-adjuvant therapy (28). Reversed sequence treatment to allow immediate concomitant taxane and trastuzumab is permitted in the trial.

6.4 Management in response to cardiac toxicity

Delayed scheduled doses

Intravenous route

If the administration of trastuzumab is more than 28 days since the day of the previous dose, the treatment should be restarted with a loading dose of 8mg/kg followed by the usual maintenance dose of 6mg/kg every 3 weeks thereafter. Where standard practice differs, please contact the trial office for approval.

Subcutaneous route

There is no loading dose for subcutaneous trastuzumab. If the administration of trastuzumab is more than 28 days since the day of the previous dose, the treatment should be restarted with the usual dose of 600mg followed by another dose of 600 mg every 3 weeks thereafter.

Treatment cannot be held on account of cardiac toxicity for more than a total of 3 months. It is likely that minimum length of a 'hold' due to cardiac dysfunction will be 6 weeks and therefore a maximum of two "holds" will be allowed for cardiac toxicity during the course of the trial.

Trastuzumab related toxicity

Infusion-Associated Symptoms

Patients with pulmonary disease or pre-existing respiratory compromise may be at increased risk from serious infusion-associated symptoms and need to be monitored with extreme caution.

During the first infusion with trastuzumab, a symptom complex commonly consisting of chills and/or fever is observed in about 40% of patients. The symptoms are usually mild to moderate in severity. They rarely cause trastuzumab discontinuation. Other signs and/or symptoms may include nausea, vomiting, pain, rigors, haedache, dizziness, dyspnoea, hypotension, rash and asthenia. These symptoms occur infrequently with subsequent trastuzumab infusions. Very rarely patients experience a severe/life threatening-infusion-related event.

If infusion symptoms develop, stop the infusion until resolved. Supportive treatment: oxygen, beta agonists, antihistamines or corticosteroids for example can be administered. Restart the infusion at a slower rate when symptoms have resolved. If hypersensitivity occurs again, STOP INFUSION.

Patients who experience mild, moderate or severe infusion reactions on the first dose can be retreated with trastuzumab. Premedication with corticosteroids, antihistamines, and antipyretics before subsequent trastuzumab infusion are recommended.

There are no data regarding the most appropriate method of identification of patients who may be retreated with trastuzumab after experiencing a severe hypersensitivity reaction. Trastuzumab has been readministered to some patients who fully recovered from a previous severe reaction and prior to readministration of trastuzumab, the majority of these patients were prophylactically treated with pre-medications including antihistamines and corticosteroids. While some of these patients tolerated retreatment, others had severe reactions again despite the use of prophylatic pre-medication.

Cardiac symptoms

LVEF will be monitored prior to the first trastuzumab dose and then throughout trastuzumab treatment, done according to standard practice (minimum of 4 monthly). All patients must have a baseline LVEF assessment i.e. undertaken pre-trastuzumab treatment. If not available please contact the coordination team.

ECHO or MUGA are acceptable for the trial however, research teams must be aware that **MUGA use radiation** and it therefore constitutes a non-negligible risk for the patient. Whenever possible, ECHO should be performed.

LVEF reduction should be managed as per SmPC.

If the treatment is held due to a reduction of the LVEF, a new measurement should be planned after 6 weeks of a temporary halt. If according to the SmPC, the measurement is satisfactory then the treatment can resume. If the measurement is not satisfactory, the treatment remains suspended and a repeat LVEF assessment should be performed within approximately 6 weeks. **A maximum of 3 months hold is allowed for cardiac toxicity reasons**. If the delay is longer than 3 months for cardiac toxicity reasons then a Withdrawal form must be completed (refer to Section 6.6).

If an adverse event is related to cardiac dysfunction, an additional measurement should be performed.

If the LVEF reduction is symptomatic it must be reported as a SAE.

All LVEF assessments must be reported on the trial Case Report Forms.

In case of New York Heart Association class III/IV cardiac function (Appendix 4), trastuzumab has to be discontinued even after resolution of symptoms or normalisation of LVEF. However, patients will remain in the study and complete all assessments as planned.

Dyspnoea, oedema and reduced cardiac LVEF have been observed with trastuzumab. They are generally more common when trastuzumab is given concomitantly with the chemotherapy. Treatment commonly includes diuretics, cardiac glycosides, and/or angiotensin-converting enzyme inhibitors (ACE inhibitors).

Haematological

An increased incidence of anaemia, leukopenia and thrombocytopenia is observed in patients receiving trastuzumab and chemotherapy. Haematological toxicity is infrequent following the administration of single agent trastuzumab.

All toxicity will be managed at the discretion of the doctor as per standard practice.

6.5 Disease progression

If at any stage there is suspicion of disease progression or relapse, this should be confirmed radiologically. The PERSEPHONE trial office must then been notified of progression (during the treatment phase) on the *Withdrawal Form* or any relapse (recurrence post-treatment) on the *Relapse and Death Form*. In both cases, further treatment remains at the discretion of the treating clinician.

6.6 Patient withdrawal

Patients should discontinue trial medication in the following circumstances:

- The patient opts to withdraw from the trial or chooses not to comply with study procedures.
- The patient is inadvertently enrolled without meeting the eligibility criteria (except in extenuating circumstances in which case continuation must be agreed with the trial office).
- The patient has not recovered from toxicity to an extent that allows further trastuzumab treatment.
- The Investigator decides that the patient should be withdrawn from the trial due to toxicity.
- The patient becomes pregnant and decides to continue her pregnancy.
- Confirmed disease progression (according to WHO criteria).
- Relocation during treatment to a site not participating in the trial.

Withdrawal of patients for any reason should be communicated to the ***PERSEPHONE*** trial office as soon as possible. Reasons for withdrawal should be recorded on the *Withdrawal Form* and the *Treatment Summary Form*.

Follow-up data will be collected on all withdrawn patients (this also applies to patients who opt to withdraw consent for the trial unless they explicitly forbid further data to be collected).

6.7 Endocrine therapy

Concurrent hormone therapies are not recommended with chemotherapy, but can be used concurrently with trastuzumab. Hormonal treatment received by the patient must be recorded on the *Annual Follow-up Form*.

Following completion of chemotherapy and definitive surgery, systemic hormonal therapy is advised for women with ER-positive disease. All endocrine therapy is at the discretion of the responsible clinician in accordance with standard local therapy protocols; the following are guidelines only. For women who remain pre-menopausal after completion of chemotherapy, hormonal therapy options include ovarian suppression and tamoxifen. Entry into the Breast International Group (BIG) EORTC trial SOFT or TEXT should be considered. For postmenopausal women, tamoxifen or aromatase inhibitors can be used for a minimum of 5 years (or tamoxifen for 2-3 years switching to an aromatase inhibitor 2-3 years [19]).

6.8 Radiotherapy

Radiotherapy will be given after definitive surgery according to local protocols.

Radiotherapy can be given concomitantly with trastuzumab. If radiotherapy treatment is given this must be recorded on the *Radiotherapy Form*.

7. Tissue and blood collection

7.1 Tissue block collection (Trans - *PERSEPHONE*)

Trans - PERSEPHONE: Tissue blocks (paraffin-embedded) will be collected to discover molecular predictors of survival with respect to duration of trastuzumab treatment. Analysis of tumour and normal tissue will involve (i) tissue microarrays for immunohistochemistry (IHC) of protein gene products and in situ hybridisation analysis, and (ii) whole-genome profiling using expression and DNA microarrays.

Centres are strongly encouraged to provide tissue for the ***Trans - PERSEPHONE*** sub-study, after obtaining informed consent from patients (see *PERSEPHONE* patient information sheet and consent form). The collection will be done by contacting the pathologists directly.

1) Adjuvant setting

Following randomisation, pathologists will be asked to provide representative samples of tissue as follows:

- a representative paraffin-embedded block of the tumour
- a paraffin-embedded block containing normal tissue (same quadrant as the tumour).

2) Neo-adjuvant setting

Following surgery, pathologists will be asked to provide:

- a representative diagnostic tumour block (core biopsy)
- a representative paraffin-embedded block of the tumour (from operation post chemotherapy)
- a paraffin embedded block containing normal tissue (same quadrant as the tumour).

A small amount of representative tissue will be removed from the blocks and processed by the Cambridge Translational Cancer Research Laboratories. **Blocks will be then sent back to the pathology department**.

7.2 Blood collection for Pharmacogenetics / Genetics Study (Trans - *PERSEPHONE* - SNPs)

Patients consenting to take part in the **Trans - *PERSEPHONE* - SNPs** sub-study will be asked to give a blood sample (2x9 ml EDTA) on one occasion at any time before, during or after chemotherapy. If blood samples are taken during the chemotherapy phase, they should preferably be taken close to or on the day that patients are due to receive a cycle of chemotherapy, in order to provide adequate cell counts to give enough DNA to assay.

Samples will be used to assay for pharmacogenetics studies and prognostic and predictive candidate germline mutations.

8. Study organisation

8.1 Randomisation of patients

Randomisation can take place any time prior to the 10th cycle of trastuzumab treatment.

A sufficient amount of time needs to be taken into consideration to organise the pre-treatment assessments.

An eligibility form should be completed prior to randomisation. Details should then be phoned or faxed through to Warwick Clinical Trials Unit, **between 9 am and 5 pm, Monday to Friday**.

☎: 0247 6150 402 🖷: 0247 6151 586

The name of the investigator directly responsible for the patient's care will be requested at randomisation. Investigators must be pre-registered with the trials unit before they are permitted to enrol patients on the trial.

8.2 Data collection

Case report forms will be designed by Cambridge Clinical Trials Unit – Cancer Theme in collaboration with the Warwick Clinical Trials Unit and comprise the following:

Table 1: **Standard forms and summary of data collected**

Form	Brief summary of data recorded
1.Eligibility Form	Confirmation of full inclusion criteria and satisfactory staging investigations.
2.Randomisation Form	Details of stratification variables; optional consent issues; patient randomisation number and treatment allocated. Patient height and weight.
3.Diagnosis biopsy form for Neo-adjuvant patients	Diagnostic biopsy histology; details of planned surgery.
4.Surgery Form	Full details of tumour excision and histology.
5.Trastuzumab Treatment Form	Trastuzumab therapy and cardiology assessments details per 3 month period (+/- 4 cycles).
6.Treatment Summary Form	Date, dose and drugs given for each cycle of chemotherapy. Number of trastuzumab cycles received. Additional cardiology assessments.
8. Radiotherapy Form	If radiotherapy was given; area treated and number of doses.
9. Principal Investigator declaration Form	Confirmation that the data have been collected according regulation and protocol.
10. Annual Follow-Up Forms	Endocrine treatment details, late toxicities, relapse, date and cause of death if applicable.

Ad hoc forms

- Serious Adverse Event form (refer to section 9.2).
- Relapse/Death Report form (refer to section 10.2).
- Hospital Transfer form.

Data collection will be the responsibility of Warwick Clinical Trials Unit and Cambridge Clinical Trials Centre – Cancer Theme. Sample collection, anonymisation, and good laboratory practice will be the responsibility of Cambridge Clinical Trials Unit – Cancer Theme and Cambridge Translational Cancer Research Laboratories. All data will be handled and stored in accordance with the 2018 Data Protection Act which includes General Data Protection Regulations (GDPR).

Schedule of case report form and quality of life questionnaire

CRFs are required for all Persephone patients and cover 3 monthly periods of trastuzumab treatment. All details of trastuzumab treatment are required for all patients including doses received prior to randomisation. Please detail the doses but not the toxicities for patients who have received trastuzumab prior to be being randomised.

8.3 Data quality assurance & monitoring

Case report forms must be submitted to the ***PERSEPHONE*** office in a timely manner. On receipt, all forms will be checked for completeness and congruity. Forms containing empty data fields or data anomalies will be queried and returned to site for resolution.

8.4 Conduct of study

PERSEPHONE will be conducted in accordance with UK legislation and Good Clinical Practice (GCP) Guidelines. See section 17.

All participating clinical investigators will be required to sign an investigator agreement and supply the trial office with a current curriculum vitae.

All site personnel involved in the conduct of the trial will be asked to attend a start-up meeting which will cover trial rationale, protocol procedures, and collection and reporting of data. These meetings will be conducted by the ***PERSEPHONE*** trial office personnel either in person or by telephone if appropriate. Following this, all sites will be provided with an investigator site file containing instructional materials and documentation required for the conduct of the trial. The ***PERSEPHONE*** trial office will offer continued support for site staff via telephone, fax, email, and mail.

8.5 End of trial and archiving

End of the trial

The end of the intervention period of the trial will be 1 year after the last patient has been randomised into the trial (September 2016).

The non-interventional observation period of the trial will continue for at least 10 years following the administration of the last dose of the trastuzumab to the last patient or after the last biological material has been processed whichever comes later.

Archiving period

The archiving period will begin after the last date of data capture. All essential trial documents (including patient notes) must be retained for at least 5 years following the end of the trial. The trial Sponsor will notify the centres when documents may be destroyed.

8. 6 Trial Management Group

This group will be responsible for the day-to-day running of the study and will meet regularly. This consists of the Chief Investigator (Helena Earl) and other applicants on the HTA grant award (Janet Dunn) together with coordinators (Cambridge and Warwick), Louise Hiller (trial statistician, Warwick), data managers and data clerks (Cambridge and Warwick).

8. 7 Trial Steering Committee

All members are identified in the trial summary. The Trial Steering Committee will meet to formally discuss the conduct of the trial and to receive reports and agree all publications. The Chief Investigator will discuss all matters of importance with regard to the conduct and running of the study, as and when this may prove necessary.

8. 8 Independent Data and Safety Monitoring Committees (iDSMCs)

An independent Data and Safety Monitoring Committee has been established for this trial and their main objective is 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 or safety and efficacy.
Reports containing recruitment, protocol compliance, safety data and interim analyses of outcomes will be presented for review alongside results from other relevant trials. The iDSMC will advise on whether the trial should be stopped prematurely at any time for ethical or safety reasons, including unexpected frequency or severity of toxicity, early indication of inferior outcome in the experimental arm or publication of new data.

A member of the PERSEPHONE iDSMC serves on the PHARE iDSMC with the roles and responsibilities clearly defined for each committee.

8. 9 Monitoring by NIHR HTA

The NIHR Evaluation, Trials and Studies Coordinating Centre, Health Technology Assessments [NIHRHTA] (the funders of the *PERSEPHONE* Trial), will appoint an **Independent Trial Steering Committee**, which will consist of an independent chairman (oncologist), and 2 other independent members (breast surgeon and statistician). The trial conduct and progress will be monitored by the NIHRHTA and the Independent Trial Steering Committee, will receive 6 monthly reports on the trial, and following completion a full report in the form of a monograph for publication by the HTA. The NIHRHTA must be informed of any intended publications or presentations at national or international conference (oral or poster) 28 days or more before presentation or publication.

9. Safety reporting

The collection and reporting of data on Adverse Events and Serious Adverse Events will be in accordance with EU Directive 2001/20/EC and UK legislation. Pharmacovigilance will be managed by the Cambridge Clinical Trials Unit – Cancer Theme, which includes the assessment and reporting of all Serious Adverse Events (SAEs) in the trial, together with the assessment and reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs).

9.1 Adverse Events (AE)

An AE is defined as any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

The incidence and nature of AEs is an important endpoint for this study and all AEs should be documented on the Adverse Event/Toxicity forms completed for each cycle of trastuzumab within the trial. However, the following should NOT be reported as an AE:

- Chemotherapy related toxicity
- A pre-existing condition, unless the condition worsens or episodes increase in frequency during the reporting period and the investigator deems this related to use of the study drug
- Symptoms relating to disease progression or death unless the investigator deems them related to use of the study drug
- Symptoms related to treatment for disease progression

9.2 Serious Adverse Events (SAEs)

Definitions

A SAE is any untoward medical occurrence that at any dose results in:

- death
- initial or prolonged inpatient hospitalisation (excluding hospitalisation for study drug administration) *****
- a life-threatening experience (i.e. immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly or birth defect

and for the purpose of this trial:

- symptomatic LVEF reduction
- other medical event deemed important by the PI

***** Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure, for continued observation. Hospitalisation for a pre-existing condition, including elective procedures, which has not worsened, does not constitute a serious adverse event.

Reporting SAEs

Please complete and fax all SAEs Forms to the Cambridge Clinical Trials Unit on 🖷: +44 (0)122 3348 071

For SAE related queries please telephone either:

Cambridge Persephone Trial Office on ☎: + 44 (0)122 3348 086 OR

Warwick Persephone Trial Office on ☎: +44 (0)247 6150 492

Monday to Friday between 9am and 5pm

Documenting SAEs

The responsible clinician must determine the severity of an event (according to the NCI CTCAE version 3.0), and relatedness of the events to the study drugs. Seriousness, relatedness, and expectedness (using the trastuzumab SmPC as a reference) will also be independently assessed by the Chief Investigator (or Deputy). A Serious Adverse Event judged by the Investigator or Chief Investigator to have a reasonable causal relationship with the trial medication will be regarded as a Serious Adverse Reaction (SAR). If the event meets the definition of a Serious Adverse Reaction that is unexpected in nature it will be classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

Reporting period for SAEs

Details of all SAEs will be documented from the point of randomisation within the trial until 30 days post-treatment (i.e. 30 days from last administration of the study drug).

SAEs occurring after a patient's 30-day follow-up assessment should be reported only if the investigator believes that the study drug or a protocol procedure may have caused the event.

Follow-up of SAEs

In the case of a SAE, the subject must be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until disease has stabilised. Follow-up may continue after completion of protocol treatment if necessary. Follow-up information will be noted on the Serious Adverse Event Form by ticking the box marked 'follow-up' and sending to the ***PERSEPHONE*** Translational office as information becomes available. Extra annotated information and/or copies of test results should also be provided where available.

Reporting of SARs to regulatory authorities

The ***PERSEPHONE*** Office at the Cambridge Clinical Trials Unit – Cancer Theme will report all fatal or life threatening SUSARs to the Medicines and Healthcare products Regulatory Agency (MHRA), the Research Ethics Committee (REC) and the Sponsor within 7 days of receiving initial notification from the site. Any follow-up information will be provided within an additional 8 days. Non-fatal and non-life threatening SUSARs will be reported within 15 days. The Sponsor will also submit an annual Development Safety Update Report to the MHRA and the coordination team to the REC.

The Cambridge Clinical Trials Unit – Cancer Theme will forward details of SUSARs to all Investigators on a regular basis.

10. Patient follow-up

10.1 Follow-up schedule

Patients will be followed-up routinely every 3 months for the first year following the start of trastuzumab treatment, then 6-monthly for the subsequent year, and then yearly (for Quality of Life please see section 11). Follow-up data will be requested annually based on the anniversary of the trastuzumab treatment start date.

10.2 Relapse and death

Long-term follow-up will include dates and sites of first relapse (see Table 2), both local and systemic treatment at relapse, and date and cause of death. This is necessary for the trial's endpoints of disease-free and overall survival. As soon as definite confirmation has been obtained, a *Relapse and Death Form* should be completed and returned to the Warwick Clinical Trial unit. Patients who relapse should remain on follow-up.

Patients that have relapsed

Please complete *Trastuzumab Treatment Form* and *Treatment Summary Form* detailing only trial trastuzumab and not trastuzumab administered after the date of relapse.

***Table 2*: Definition of relapse and death**

Loco-regional	Ipsilateral breast/ chest wall, axillary and ipsilateral supraclavicular nodal relapse
Distant	Distant relapse (excluding ipsilateral supraclavicular nodes)
2nd primary	Including contralateral malignant breast disease
Death	Death from any cause

11. Quality of life study

Quality of life sub-study will be carried out using the EQ-5D. Quality of life data will be collected at different time points as follows (see Appendix 1):

Prior to the commencement of trastuzumab

- 3-monthly for a year following the start of trastuzumab (both arms of the trial) (3 monthly questionnaire)
- then every 6 months up to year 2 (6 monthly questionnaire).

The Table below takes into account that patients can be randomised at any time prior to receiving their 10th cycle of trastuzumab, not all questionnaires will be required for those patients randomised at later stages.

Randomisation point	**Baseline questionnaire**	**3 monthly questionnaire**				**6 monthly questionnaire**	
	0	3	6	9	12	18	24
Before trastuzumab starts	√	√	√	√	√	√	√
During first 1-3 months of trastuzumab starting	-	√	√	√	√	√	√
During first 4-6 months of trastuzumab starting	-	-	√	√	√	√	√

12. Health economics study

Economic evaluation of PERSEPHONE

The objective of the economic evaluation is to identify within the trial the long term incremental cost effectiveness ratio for trastuzumab compared to standard care of surgery/radiotherapy/chemotherapy in the treatment of patients with early breast cancer.

Within trial cost effectiveness analysis

Measurement of outcomes

The primary outcome measure of the trial is disease free survival. The trial economic evaluation will, for consistency, use the same primary outcome measure. However, as economic evaluations are designed to inform resource allocation decisions, evaluations will also be produced using overall survival and Quality adjusted life years (QALYs) outcome measures. These measures are more useful for comparing the value of trastuzumab with all uses of limited health care resources [20]. Data on disease free survival and overall survival will be collected as part of the Case Report Form (CRF).
The estimation of QALYs requires the production of utility weights for each health state observed in the trial population. We will use the EQ-5D (EuroQol) instrument for this purpose. [21,22]. The EQ-5D is a very simple instrument to complete and will therefore be collected at baseline and at 3 monthly intervals until the end of follow-up. This will limit the need to interpolate quality of life between observation points and the associated inaccuracy in the estimation of the Health related Qol differences between therapies [23].

Measurement of resource use

NHS resource use associated with each treatment modality will be collected through the CRF (investigations, drugs, referrals for other services).

Identifying unit costs: Unit costs for health service resources will be obtained from national sources such as the PSSRU, the BNF and NHS Reference cost database. Where national unit costs are not available the finance departments of trusts participating in the study will be asked to provide local cost data. The mean of these costs will be used as the unit cost estimate in the analysis.

Perspective for analysis

The primary cost effectiveness analyses will adopt the perspective of the NHS and social services. Secondary analyses will adopt a societal perspective taking account of productivity costs and out-of-pocket expenditures incurred by the patients. There is currently substantial uncertainty about the best method for estimating productivity costs. If this uncertainty has been resolved at the time of the analysis we will adopt the recommended method, if not we will undertake sensitivity analysis to demonstrate the impact of using friction cost based estimate rather than human capital based estimates of productivity costs.

Discounting

There remains some uncertainty regarding the correct approach to discounting costs and benefits. The analysis will follow the recommendations current at the time. Under current recommendations this would mean that costs and outcomes would be discounted at 3.5% per annum [24-26].

Analysis of uncertainty

The non-parametric bootstrap method will be used to produce a within-trial probabilistic sensitivity analysis of the incremental cost effectiveness ratio. In addition to presenting the expected incremental cost effectiveness ratio, we will present the scatterplot on the cost effectiveness plane, the 95% cost effectiveness ellipse and the cost effectiveness acceptability curve [20].

Sub-group analyses

Where analyses of the clinical outcome data suggest a substantial difference in absolute benefit from treatment in *a priori* identifiable groups, cost effectiveness analyses will be presented for these sub-groups. The definition of substantial will inevitably involve some subjective judgement which will be made in discussion with clinicians, not relying solely on evidence for statistical significance, but also taking account of *inter alia*, the biological plausibility of a differential absolute effect.

Modelling the long term cost effectiveness of trastuzumab

A long term cost effectiveness analysis is required to capture the full impact of any therapy where it is possible that there is a difference in mortality between the interventions.

The exact structure of the cost effectiveness model will be established in discussions with the clinicians on the study team and after analysis of the adverse event data observed in the trial. It is likely that the model will be a markov or semi-markov state model. As far as possible the transition rates for the model will be estimated from the clinical trial data. Model parameters for which data could not be collected within the trial; e.g. long term outcomes following cardiovascular adverse events, we will follow recommended best practice in identifying and synthesising the best available evidence in the literature [26,27].

The long term cost effectiveness modelling will adopt the strategies for addressing issues of perspective and discounting as the within trial analysis.

Details of trastuzumab treatment related toxicity will be collected with each cycle of treatment using the NCI CTCAE scoring system. Data will also be collected on hospital admissions, extra outpatient visits, use of anti-emetics, antibiotics, vascular treatment, and other supportive drugs to contribute to a health economics analysis of additional health costs related to the treatment and the study. All visits to the heath professional sector and the prescribed treatment will have to be collected.

Data will be collected as follows (Appendix 1):

- Prior to trastuzumab commencing
- 3-monthly for a year following the start of the trastuzumab (3 monthly questionnaire)
- then every 6 months up to year 2 (6 monthly questionnaire).

13. Concurrent studies

Any concurrent studies need to be approved as compatible by the Trial Management Group.

14. Statistical considerations

14.1 Sample size determination

The power calculations assume that the disease-free survival (DFS) of the standard treatment of 12 months trastuzumab will be 80% at 4 years. On this basis, with 5% 1-sided significance and 85% power, a trial randomising 4000 patients in total (2000 in each arm) will have the ability to prove non-inferiority of the experimental arm, defining non-inferiority as 'no worse than 3%' below the control arm 4 year DFS.

14.2 Analysis

Disease-free survival will be calculated from the date of diagnostic biopsy to the date of first relapse or death, if no date of relapse is recorded, or the censor date. The primary outcome of DFS will be carried out on all cause mortality and relapse, and assessed using Kaplan-Meier survival curves. Treatments, with and without adjustment for the stratification and baseline prognostic factors, will be compared using Cox Proportional Hazards analysis. These analyses will be carried out on an intention-to-treat basis. Safety and toxicity will be reported descriptively. Specialist health care economic modelling will be carried out by Professor Clare Hulme at the University of Leeds. Secondary endpoint of overall survival (OS) will be calculated from the date of diagnostic biopsy to the date of death, or to the censor date. Analyses of all other secondary endpoints will be undertaken using the appropriate statistical analysis tools.

Based on previous documentation of the frequency of the toxicities to be recorded in this trial, the 4000 patients recruited will adequately power the analysis of the secondary outcome of toxicity to detect any clinically relevant differences between treatments, if they exist. Additionally, despite previous studies showing trastuzumab to be well tolerated, we plan to monitor dose intensity in all patients. 4000 patients will be adequate to detect any differences between treatment arms in Dose Intensity.

14.3 PERSEPHONE independent Data and Safety Monitoring Committee (iDSMC)

All data analyses will be supplied to an iDSMC which will be asked to give advice on whether the accumulated data from this trial, together with the results from other relevant published trials, justifies the continuing recruitment of further patients. Reports containing recruitment, protocol compliance, safety data and interim analyses of outcomes will be presented for review alongside results from other relevant trials. The iDSMC will advise on whether the trial should be stopped prematurely at any time for ethical or safety reasons, including unexpected frequency or severity of toxicity, early indication of inferior outcome in the experimental arm or publication of new data.

This Committee will first meet following enrolment of 500 patients or 1 year from the first patient randomised. The projected iDSMC meeting schedule is listed in 14.4.

Following the publication of the PHARE trial data, the iDSMC reviewed unplanned interim analyses in October 2012 and June 2013.

Although the number of patients required was determined at the 5% level of significance (1-sided), in order to control the overall alpha level, the interim analysis of the primary outcome will be reported to the iDSMC using conservative tests with significance determined by a p-value of 0.01. The final analysis will be reported using the standard 5% level of significance (1-sided). Presentation of final results to iDSMC will include DFS, toxicity, dose-intensity and health care economics, as well as other sub-study outcomes.

14.4 Revised Milestones (November 2018 – protocol version 5.0)

PERSEPHONE randomised 4088 patients from 152 centres in the UK.

The trial was launched in September 2007 and completed recruitment on 31st July 2015. The following milestones are based on actual, revised and projected milestones.

October 2007:	First patient randomised.
October 2009:	350 patients recruited.
December 2010:	1000 patients recruited.
April 2012:	2000 patients recruited.
October 2012:	iDSMC First interim analysis at the request of the iDSMC following presentation of PHARE data.
December 2012:	iDSMC Data review.
June 2013:	iDSMC Interim analysis at the request of the iDSMC following presentation of PHARE data.
October 2013:	3000 patients recruited.
June 2014:	iDSMC Data review.
June 2015:	iDSMC Data review.
End of July 2015:	4088 patients recruited.
September 2016:	End of intervention phase of the trial.
December 2017:	Interim analysis of primary outcome data – event driven analysis after 500 disease free survival events.
October 2025:	End of non-intervention follow-up phase of trial.

15. Pharmacy issues

For the purpose of this trial, trastuzumab is an IMP.

Neither trastuzumab nor any other treatment is supplied for the purpose of the ***PERSEPHONE*** trial. Please use hospital stock as per standard policy.

Patients can be randomised at any time before the cycle 10th of trastuzumab. Therefore, it is very important for pharmacy department to identify trial patients at an early stage to ensure that from the date of randomisation, the patient receives trastuzumab and that all trial documentation is completed as necessary, including the trial specific Pharmacy forms.

Investigational product must be stored in a secure area under the appropriate physical conditions for the product.

Please refer to the SmPC or local procedures for detailed instructions related to:

- storage conditions
- injection preparation
- handling of injection reactions
- observations required during injection administration
- stability

All pharmacy aspects of the trial at participating sites are the responsibility of the Principal Investigator, who may delegate this responsibility to the local pharmacist, or other appropriately qualified personnel, who will be the Pharmacy Lead. The Pharmacy Lead will ensure that appropriate records are maintained. The site pharmacy must maintain accountability records for trastuzumab: including but not limited to: batch number, dispensing, storage conditions and destruction of part vials medication. Template accountability forms will be supplied, However, sites are permitted to use their own drug accountability records providing the same information is captured, as a minimum. Any dispensed unused IMPs, part-used vials should be disposed of immediately at site according to local procedures. For further details, refer to Pharmacy guidelines provided in the Pharmacy Site File.

Dose for intravenous route

Please refer to the Pharmacy guidelines.

Dose banding

Dose banding is acceptable and should be decided according to local policy.

Dose capping

Dose capping is acceptable and should be decided according to local policy.

Dose revision

It is recommended that weight is carefully considered prior to each cycle of trastuzumab. It is recommended that a change in the patient's body weight of 10% or more generates a revision of the dose.

16. Sponsorship and indemnity

Cambridge University Hospitals NHS Foundation Trust and University of Cambridge are joint Sponsors of PERSEPHONE.

Cambridge University Hospitals NHS Foundation Trust, as a member of the NHS Clinical Negligence Scheme for Trusts, will accept full financial liability for harm caused to participants in the clinical trial caused through the negligence of its employees and honorary contract holders. There are no specific arrangements for compensation should a participant be harmed through participation in the trial, but no-one has acted negligently.

The University of Cambridge will arrange insurance for negligent harm caused as a result of protocol design and for non-negligent harm arising through participation in the clinical trial.

17. Ethical and regulatory issues

17.1 Ethical considerations

The trial will be conducted in full conformance with the principles of the Declaration of Helsinki and in accordance with UK legislation. The trial will also adhere to the principles of Good Clinical Practice (GCP).

Copies of the World Medical Association Declaration of Helsinki and GCP Guidelines can be obtained from Warwick Clinical Trials Unit or from the World Medical Association (http://www.wma.net/e/ethicsunit/helsinki.htm) or European Agency for the Evaluation of Medicinal Products website: (http://www.emea.eu.int/pdfs/human/ich/013595en.pdf) respectively.

17.2 Informed consent

The Principal Investigator is responsible for ensuring that the patient understands the risks and benefits of participating in the trial using the approved patient information sheet and the consent forms, answering any questions the patient may have throughout the trial, and sharing any new information that may be relevant to the patient's willingness to continue his/her participation in the trial in a timely manner.

It is the responsibility of the Principal Investigator to obtain written informed consent from each patient prior to performance of any protocol procedures and prior to the administration of study drug in order to document that the patient is satisfied with her understanding of the risks and benefits of participating in the trial and wishes to participate.

Informed consent should be obtained by the Principal Investigator, or delegated to a consultant oncologist, co-investigator or an oncology registrar or other sufficiently trained individual at the discretion of the Principal Investigator and as detailed on the signature/ responsibilities/delegation log.

17.3 Patient confidentiality

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the 2018 Data Protection Act. Patients will be identified using only their unique trial number, initials and date of birth on case report forms (with the exception of eligibility and randomisation) and any correspondence between the ***PERSEPHONE*** trial office and the participating site will include initials and trial number. If required, hospital numbers may be given over the phone to those directly involved with the patient's trial participation.

The Principal Investigator must maintain trial documents (e.g. patients' written consent forms) in strict confidence. In case of exceptional circumstances and/or governmental queries, it will be necessary to have access to the complete trial records, provided that patient confidentiality is protected.

Warwick 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 of the patient's breast cancer.

18. Financial matters

PERSEPHONE is an investigator-designed and -led trial, which will be funded through project grants. The trial has been independently peer reviewed through the National Coordinating Centre for Health Technology Assessment (NIHRHTA) which funds the dedicated personnel. There are no funds available for Investigator payments or pharmacy fees in this trial.
Pathology departments will receive a per-patient payment for supplying the requested pathology material.
Research offices will receive a per-patient payment for supplying the requested blood sample.

19. Publication policy

The main trial results will be published in the name of the trial in a peer-reviewed journal, on behalf of all collaborators. The manuscript will be prepared by a writing group, appointed from amongst the collaborators. The Cambridge Clinical Trials Unit – Cancer Theme and Warwick Clinical Trials Unit and all participating centres and Investigators will be acknowledged in this publication. All presentations and publications relating to the trial must

be authorised by the Trial Management Group, and the NIHR HTA must be given 28 days notice of any presentations or publications arising from the trial, both during recruitment and after analysis.

The impact of various scenarios of results on investigators, and the potential change of practice, will be ascertained by a survey prior to wider release through an investigator results meeting.

The impact of accruing evidence from trastuzumab duration trials on investigators, and their resultant change(s) of practice, will be ascertained by surveys.

Each survey sent out will assume implicit consent from the Persephone Investigators on the return of the surveys. All new individual surveys will only be sent to Persephone Investigators and as such will have approval through the Persephone protocol.

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Appendix 1: Timetable of events and investigations for PERSEPHONE

Schedule of investigations during on-study phase

Event	**Prior to randomisation**	**Trastuzumab treatment visit** Every 3 months for a year after starting trastuzumab treatment ***Patients on the research arm MUST follow the same follow-up schedule as those on the standard arm***	**Follow-up visits** Every 6 months in year 2. Annually thereafter for 8 years.
Informed consent for trial	X		
ER status	X		
HER2 status	X		
Full blood count	X		
Biochemical screen	X		
Chest X-ray (or Chest CT if standard practice)	If suspicion of metastases		
Whole body scintigraphy and liver ultrasound or abdominal CT scan			
Medical history	X		
Physical examination, weight.	X[a]	X[a]	X[af]
LVEF assessment	Done as per standard practice	X[b]	
ECOG performance status	X	X	X
Quality of Life questionnaire	X[c]	X[d]	X[e]
Healthcare resource used assessment questionnaire	X[c]	X[d]	X[e]
Serious Adverse Events		X	
Survival / recurrence disease status		X	X

a Includes clinical follow-up, and questioning patients regarding symptoms of progression or recurrent breast cancer.
b To be carried out after 4 and 8 months of trastuzumab.
c Patient to complete the baseline questionnaire.
d Patient to complete the 3 monthly questionnaire.
e Patient to complete the 6 monthly questionnaire at 18 months and 24 months.
f Once a patient has been discharged from clinical review, physical examinations do not need to be performed for the purpose of the trial. Telephone follow-up is permitted for patients who have been discharged from clinical review. Follow-up by email is permitted subject to local information governance policies.

Appendix 2: TNM Staging System for Breast Cancer

The American Joint Committee on Cancer (AJCC) staging system.

Definitions of TNM

Primary Tumour (T)

- TX Primary tumour cannot be assessed
- T0 No evidence of primary tumour
- Tis Carcinoma *in situ*: intraductal carcinoma, lobular carcinoma *in situ*, or Paget's disease of the nipple with no tumour
- T1 Tumour ≤2 cm in greatest dimension
  - T1mic Micro-invasion ≤0.1cm in greatest dimension
  - T1a Tumour >0.1 but ≤0.5 cm or less in greatest dimension
  - T1b Tumour >0.5 cm but ≤1 cm in greatest dimension
  - T1c Tumour >1 cm but ≤2 cm in greatest dimension
- T2 Tumour >2 cm but ≤5 cm in greatest dimension
- T3 Tumour >5 cm in greatest dimension
- T4 Tumour of any size with direct extension to (a) chest wall or (b) skin, only as described below.
  - T4a Extension to chest wall, not including pectoralis muscle
  - T4b Edema (including peau d'orange) or ulceration of the skin of the breast or satellite skin nodules confined to the same breast
  - T4c Both (T4a and T4b)
  - T4d Inflammatory carcinoma

Note: Paget's disease associated with a tumor is classified according to the size of the tumour.

Regional Lymph Nodes (N)

- NX Regional lymph nodes cannot be assessed (for example, previously removed)
- N0 No regional lymph node metastasis
- N1 Metastasis to movable ipsilateral axillary lymph node(s)
- N2 Metastasis to ipsilateral axillary lymph node(s) fixed or matted, or in clinically apparent ipsilateral internal mammary nodes in the absence of clinically evident* axillary lymph node metastasis
  - N2a Metastasis in ipsilateral axillary lymph nodes fixed (or matted) to one another or to other structures
  - N2b Metastasis only in clinically apparent* ipsilateral internal mammary nodes *and* in the absence of clinically evident axillary lymph node metastasis
- N3 Metastasis to ipsilateral infraclavicular lymph node(s) with or without axillary lymph node involvement, or in clinically apparent* ipsilateral internal mammary lymph node(s) and in the presence of clinically evident axillary or internal mammary lymph node involvement; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
  - N3a Metastasis in ipsilateral infraclavicular lymph node(s)
  - N3b Metastasis in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
  - N3c Metastasis in ipsilateral supraclavicular lymph node(s)

*** Clinically apparent is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination or grossly visible pathologically.**

Distant Metastasis (M)

- MX Presence of distant metastasis cannot be assessed
- M0 No distant metastasis
- M1 Distant metastasis

Stage grouping

STAGE GROUPING	T	N	M
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T0	N1*	M0
	T1	N1**	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2*	M0
	T1	N2**	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

Appendix 3: ECOG performance status

Grade	Description
0	Normal activity: asymptomatic
1	Symptomatic: fully ambulatory
2	Symptomatic: in bed < 50% of time
3	Symptomatic: in bed > 50% of time - not bedridden
4	100% bedridden

Appendix 4: The Stages of Heart Failure – NYHA Classification:

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.