The HER2-RADiCAL study (Response ADaptive CAre pLan) – Tailoring treatment for HER2 positive early breast cancer

PROTOCOL

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Chief Investigator:	Dr Iain Macpherson
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ICR The Institute of Cancer Research

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ADMINISTRATION

Clinical/Scientific Coordination

Chief Investigator:
Dr Iain Macpherson
The University of Glasgow and Beatson West of Scotland Cancer Centre
Tel: 0141 301 7128
iain.macpherson@glasgow.ac.uk

Surgical Lead:
Mr Stuart McIntosh
The Queen's University of Belfast
Tel: 02890972986
s.mcintosh@qub.ac.uk

TMG Co-Chair:
Professor David Cameron
The University of Edinburgh
Tel: 0131 651 8620
d.cameron@ed.ac.uk

Methodology Lead and TMG Co-Chair:
Professor Judith Bliss
The Institute of Cancer Research
Tel: 020 8722 4297/4013
judith.bliss@icr.ac.uk

Health Economics Lead:
Dr Peter Hall
The University of Edinburgh
Tel: 0131 6518510
p.s.hall@ed.ac.uk

Pathology Lead:
Dr Abeer Shaaban
University Hospitals Birmingham NHS Foundation Trust
Tel: 0121 3713356
abeer.shaaban@uhb.nhs.uk

Study Coordination

ICR-CTSU (a CRUK-funded, UKCRC Registered Clinical Trials Unit (CTU) and member of the NCRI Cancer CTU Group) is responsible for the central coordination of the study on behalf of the ICR, the Sponsor.

ICR Clinical Trials & Statistics Unit (ICR-CTSU)
Division of Clinical Studies
The Institute of Cancer Research
Sir Richard Doll Building, Cotswold Road
Sutton, Surrey SM2 5NG

ICR-CTSU Methodology Lead
Professor Judith Bliss
(see above)

ICR-CTSU Principal Statistician:
Lucy Kilburn
Tel: 020 8722 4080
lucy.kilburn@icr.ac.uk

ICR-CTSU Senior Statistician:
Holly Tovey
Tel: 020 8722 4466
holly.tovey@icr.ac.uk

ICR-CTSU Clinical Trials Programme Manager:
Sarah Kernaghan
Tel: 020 8722 4152
sarah.kernaghan@icr.ac.uk

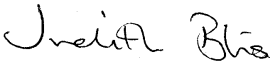
HER2-RADiCAL Clinical Trial Manager:
Katie Goddard
Tel: 020 8722 4185
her2radical-icrctsu@icr.ac.uk

Any questions relating to this protocol should be addressed in the first instance to the HER2-RADiCAL Clinical Trial Manager within ICR-CTSU:
Email: her2radical-icrctsu@icr.ac.uk
General enquiries: 020 8722 4185

PROTOCOL DEVELOPMENT GROUP

Dr Iain Macpherson	Chief Investigator	The University of Glasgow
Prof Judith Bliss	ICR-CTSU Methodology Lead, TMG Co-Chair	The Institute of Cancer Research, London
Prof David Cameron	TMG Co-Chair	The University of Edinburgh
Dr Peter Hall	Health Economics Lead	The University of Edinburgh
Dr Abeer Shaaban	Pathology Lead	University Hospitals Birmingham NHS Foundation Trust
Prof Andrew Wardley	Chief Investigator (previous)	
Mr Stuart McIntosh	Surgical Lead	The Queen's University of Belfast
Mairead Mackenzie	Patient Representative	Independent Cancer Patients' Voice
Hilary Stobart	Patient Representative	Independent Cancer Patients' Voice
Dr Indrani Bhattacharya	Collaborator	Cambridge University Hospitals NHS Foundation Trust
Dr Clinton Boyd	Collaborator	Belfast Health and Social Care Trust
Prof Charlotte Coles	Collaborator	Cambridge University Hospitals NHS Foundation Trust
Dr Ciara O'Brien	Collaborator	The Christie NHS Foundation Trust
Prof Cliona Kirwan	Collaborator	The Christie NHS Foundation Trust
Dr Alistair Ring	Collaborator	The Royal Marsden NHS Foundation Trust
Dr Duncan Wheatley	Collaborator	Royal Cornwall Hospitals NHS Trust
Claire Snowdon	Deputy Director, Director of Operations	ICR-CTSU, The Institute of Cancer Research, London
Lucy Kilburn	Principal Statistician	ICR-CTSU, The Institute of Cancer Research, London
Holly Tovey	Senior Statistician	ICR-CTSU, The Institute of Cancer Research, London
Sarah Kernaghan	Clinical Trials Programme Manager	ICR-CTSU, The Institute of Cancer Research, London
Katie Goddard	Clinical Trial Manager	ICR-CTSU, The Institute of Cancer Research, London

Protocol Authorised by:

Name & Role	Signature	Date
Dr Iain Macpherson Chief Investigator		05 August 2021
Prof Judith Bliss ICR-CTSU Methodology Lead		05 August 2021

This protocol describes the HER2-RADiCAL study and provides information about procedures for entering participants into this study. The protocol should not be used as a guide for the treatment of patients outside of this study.

Every care was taken in the preparation of this protocol, but corrections or amendments may be necessary. Protocol amendments will be circulated to participating sites as they occur, but sites entering patients for the first time are advised to contact ICR-CTSU to confirm they have the most recent version.

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This study has been reviewed by the NIHR HTA Programme, the Sponsor's Committee for Clinical Research and the NCRI Radiotherapy Trials Quality Assurance (RTTQA) Group.

HISTORY OF PROTOCOL AMENDENTS

PROTOCOL VERSION AND DATE	SUMMARY OF CHANGES

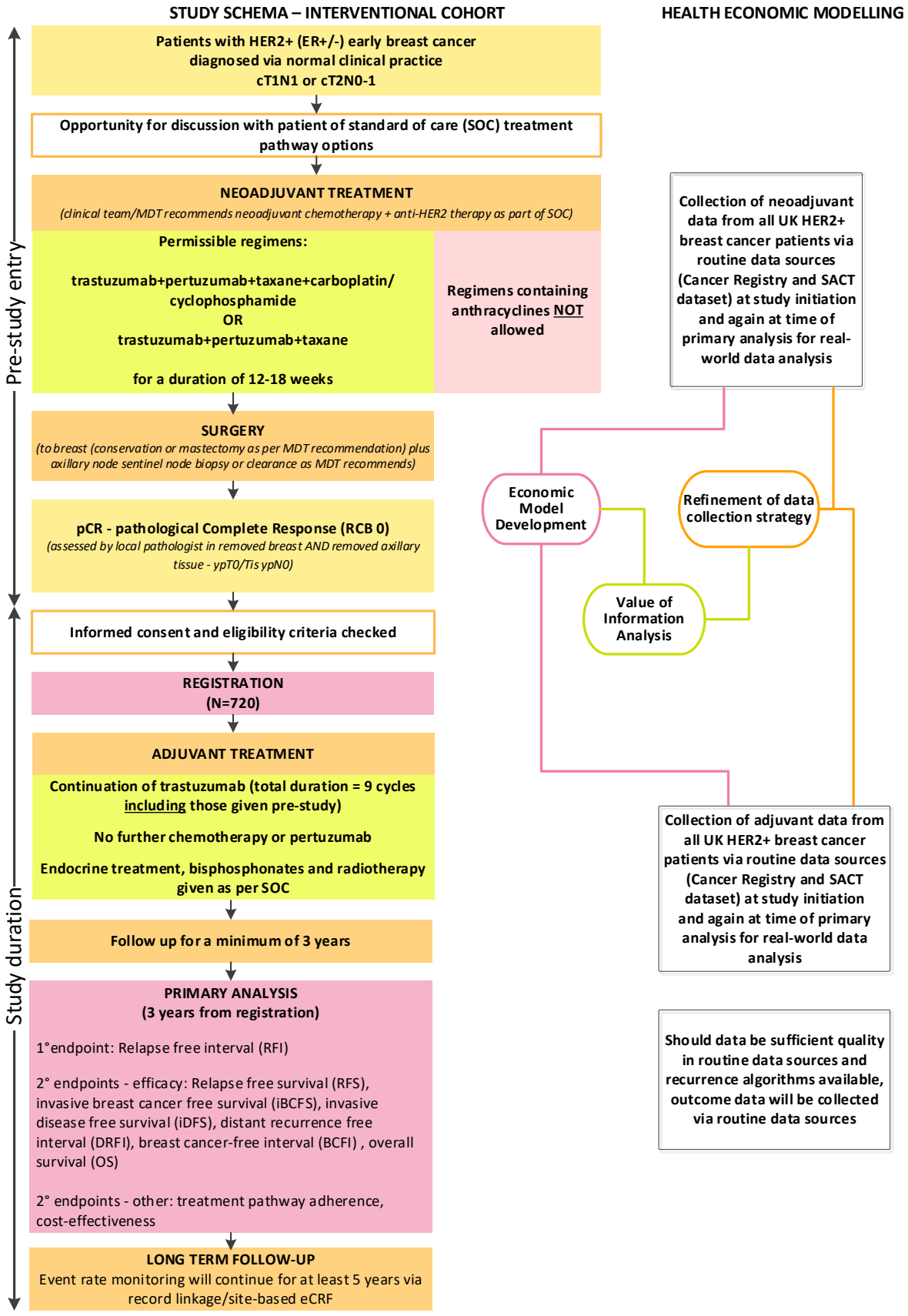
CONTENTS

HER2-RADiCAL STUDY SUMMARY

PROTOCOL TITLE	The HER2-RADiCAL study (Response ADaptive CAre pLan) – Tailoring treatment for HER2 positive early breast cancer
TARGET DISEASE	HER2 positive (HER2+) early breast cancer
STUDY OBJECTIVES	Primary Objective • To determine the efficacy of response-adapted (reduced) therapy in patients who at presentation have HER2+ early breast cancer with *intermediate risk of recurrence*, and by virtue of achieving pathological complete response (pCR) following neo-adjuvant, non-anthracycline containing, systemic therapy are reclassified as being at *low risk of recurrence*. Secondary Objectives • To determine adherence to/acceptability of the response-adapted treatment pathway. • To describe the observed current standard-of-care treatment pathway using UK population level routine NHS data. • To estimate the cost-effectiveness of response adapted therapy in comparison to both hypothetical maximal therapy and to observed standard therapy within the UK NHS. Exploratory Objective • To explore potential biomarkers associated with recurrence.
STUDY DESIGN	HER2-RADiCAL is a response-directed interventional cohort (single group) study embedded within a real-world data-driven clinical pathway model. The relevant response is pCR following neoadjuvant systemic therapy (neoSACT) which is used as a marker for identifying patients in whom subsequent selective therapy reduction is proposed.
STUDY POPULATION	Patients with HER2+ early breast cancer who have recently completed non-anthracycline-containing chemotherapy with concomitant trastuzumab and pertuzumab (neoSACT) and where no evidence of residual invasive cancer has been found at surgery either in the breast or in regional nodes (pCR; ypT0/Tis ypN0 M0).
RECRUITMENT TARGET	720 patients
TREATMENT REGIMEN	Patients will continue trastuzumab (initiated in the neoadjuvant setting) to complete 9 cycles (~6 months). Patients will receive no further chemotherapy or pertuzumab in the adjuvant setting.
PRIMARY ENDPOINT	Relapse free interval (RFI)
SECONDARY ENDPOINTS	• Relapse-free survival (RFS) • Invasive breast cancer free survival (iBCFS) • Invasive disease-free survival (iDFS) • Distant recurrence free interval (DRFI) • Breast cancer-free interval (BCFI) • Treatment pathway adherence • Cost-effectiveness
EXPLORATORY ENDPOINTS	Biomarkers including, but not limited to, tumour infiltrating immune cell populations.
STUDY WITHIN A TRIAL (SWAT)	A SWAT focussing on optimal provision of patient information in the context of systemic treatment response adaptation will be conducted.
FOLLOW UP	Primary analysis is planned after 3 years follow-up. Event rate monitoring will continue until at least 5 years via linkage to routinely collected data and/or site based eCRF with choice of follow up model dependent on viability of provision of real-time quality data to determine recurrence outcomes from routine sources.

STUDY SCHEMA

Figure 1. HER2-RADiCAL study schema



1. INTRODUCTION

The stepwise addition of new anti-cancer drugs to adjuvant treatment protocols has dramatically reduced the risk of recurrence after surgery for patients with early breast cancer. This is most notable in the population with HER2-positive (HER2+) breast cancer where many decades of clinical research have transformed the natural history of the disease (1). The regulatory model has led to continuous addition of treatments, with limited ability to individualise treatment according to therapeutic ratio. This has led to improvement in survival across the patient population at the cost of increasing acute and late treatment-related toxicity, including cardiac toxicity (2, 3), for individual patients, and increasingly complex and prolonged treatment schedules with ever-increasing demands on overstretched healthcare resources. For certain groups of patients, the risk of recurrence is now sufficiently low that the research focus has shifted to how best to refine current therapeutic pathways, to reduce toxicity and treatment burden, without sacrificing the efficacy gains of previous research. The corollary being that further treatment intensification is focused on those whose disease outcomes suggest that they still have the potential to benefit from better treatment.

Each year in the UK around 4000 patients are diagnosed with HER2+ early breast cancer (EBC) and receive chemotherapy and anti-HER2 therapy, either before or after surgery, with a total of one year of anti-HER2 therapy. For patients who receive pre-operative treatment, pathological complete response (pCR) to this initial therapy may act as a biomarker to identify patients who could safely receive less systemic therapy post-operatively. This would reduce toxicity and treatment burden for those patients as well providing substantial cost-savings to the NHS, permitting greater attention to be paid to those who require complex treatments. The potential utility for the dynamic biomarker, histopathological complete response ("pCR") is highlighted by the recognition of the absence of baseline features which can reliably segregate patient's recurrence risk. Using an efficient single-arm interventional cohort design, HER2-RADiCAL seeks to address this by testing the hypothesis that pCR to pre-operative chemotherapy and anti-HER2 drug therapy can be used as a functional response biomarker to select patients who can safely receive less intensive personalised therapy, with minimal or no loss of efficacy in the population.

1.1. Background

1.1.1. Current systemic therapy of HER2+ early breast cancer

Patients diagnosed with HER2+ EBC are treated with curative intent with systemic drug therapy, intended to eliminate any occult microscopic disease that has spread to distant organs, in conjunction with surgical removal of the primary tumour. This approach is underpinned by a large body of level 1 evidence accrued over several decades. Standard chemotherapy regimens reduce breast cancer mortality by approximately one third with an effect that is largely independent of timing relative to surgery (4). Subsequent pivotal RCTs, conducted in an era of breast cancer subtyping, demonstrated that disease-free survival (DFS) and overall survival (OS) of patients with HER2+ EBC could be further improved by the addition of a 1-year course of trastuzumab to existing chemotherapy regimens. The longest follow-up for the use of adjuvant anti-HER2 therapy comes from the HERA trial where, with a median follow-up of 11 years, a significant OS benefit was seen (Hazard Ratio (HR) 0.74, 95% Confidence Interval (CI): 0.64–0.86) with the addition of trastuzumab to adjuvant chemotherapy versus chemotherapy alone (5). No additional benefit was accrued with a longer 2-year course of trastuzumab. Combined analysis of the NSABP B-31 and NCCTG N9831 studies, with median follow-up of 8.4 years, also confirmed a maintained OS benefit (HR 0.63, 95% CI 0.54−0.73; p<0.001). The substantial improvement in patient outcomes achieved by the addition of trastuzumab to chemotherapy is largely driven by a reduction in early events, particularly during the first 3 years (5). More recently, the phase 3 APHINITY trial demonstrated further improvement in invasive DFS (iDFS) with the addition of 1 year of pertuzumab to chemotherapy and trastuzumab, though the clinically relevant effect was primarily evident in the node-positive population (HR 0.77; 95% CI, 0.62-0.96;

p=0.02) (6). Based on these data, chemotherapy plus trastuzumab and pertuzumab for one year are recommended by NICE and SMC for patients with node-positive breast cancer (7, 8). In patients without involved nodes the pertuzumab component is restricted to the shorter neoadjuvant phase (9, 10).

1.1.2. neoSACT as the optimum approach in HER2+ EBC

NeoSACT offers two important advantages over the alternative pathway of surgery followed by adjuvant SACT. First, neoSACT can facilitate less extensive surgery whether by permitting breast conserving surgery in women who, at presentation, would have required mastectomy, by minimising the volume of tissue resected to improve aesthetic outcomes from breast conservation, and potentially avoiding axillary dissection in node-positive patients with a negative post-neoSACT SLNB. Second, and perhaps more importantly, neoSACT provides an individualised assessment of the cancer's sensitivity to the SACT administered before surgery – measuring its response to treatment thereby giving arguably the most powerful prognostic information for the individual patient (4, 11). In contrast, SACT given in the adjuvant setting provides no measure of treatment effectiveness at the time of administration. pCR, defined as complete clearance of invasive cancer from the primary tumour and regional lymph nodes after neoSACT, is strongly prognostic in patients with HER2+ early breast cancer with a HR of 0.31 (95% CI: 0.21-0.50) for event-free survival (EFS) in a recent meta-analysis (12). Furthermore, absolute event rates have been observed to be low in patients identified as having a pCR. For example, the neoadjuvant KRISTINE trial recently reported a 3-year iDFS rate of 97.2% (95% CI: 94.7–100) in patients with pCR compared with only 87.4% (95% CI: 81.6–93.3) in patients with residual disease (13). Similarly, a multi-centre pooled analysis of over 1400 patients with HER2+ breast cancer reported a 5-year EFS rate of 94% (95% CI: 91-97) in those patients with pCR (14). What is more, the proportion of patients achieving pCR with chemotherapy and dual anti-HER2 antibody therapy can be high. In the NEOSPHERE study, neoadjuvant docetaxel plus pertuzumab and trastuzumab achieved a pCR in approximately 45% of patients compared with 29% of patients who received docetaxel and trastuzumab alone (15, 16) whilst the TRYPHAENA study reported pCR in 62% of patients treated with pertuzumab, trastuzumab and chemotherapy (17). These trials were conducted in an era where neoSACT was mainly used in higher stage patients for surgical reasons. Evolution of treatment to use neoSACT in patients fit for systemic anti-cancer therapy with any cT≥2 and/or cN1 (a population with similar baseline stage to that eligible for HER2-RADiCAL) may result in higher pCR rates, such as 91% with weekly paclitaxel, trastuzumab and pertuzumab in the ER-HER2+ subtype (18).

1.1.3. Use of neoSACT treatment response as an actionable biomarker

It has been recognised for some time that the presence or absence of pCR discriminates patients with HER2+ EBC into widely differing prognostic groups (19). However, it is only recently that the ability to act on this information to improve cancer outcome has been demonstrated. Specifically, for those patients who *do not* achieve a pCR, the KATHERINE trial showed that substituting adjuvant anti-HER2 antibody therapy with the antibody-drug conjugate, trastuzumab-emtansine (T-DM1) significantly improved outcomes leading to NICE and SMC approval in 2020 (20-22). In contrast there is no agreed response-adapted treatment plan for those patients who *do* achieve pCR and this is the question addressed by HER2-RADICAL.

Most patients treated with neoSACT in the studies that confirmed the good prognosis for patients with a pCR, still received (before and/or after surgery) full standard therapy with anthracyclines, taxanes and a year of anti-HER2 therapy. The potential contribution of adjuvant SACT administered after pCR has been partly addressed by a recent individual patient level meta-analysis of 27,895 patients (including over 7000 HER2+ patients) treated with neoSACT in either randomised trials or prospective or retrospective cohort studies with or without further adjuvant systemic therapy (12).

The association of pCR with improved EFS was observed to a similar extent in patients who received no subsequent adjuvant chemotherapy (HR 0.36, 95% CI: 0.27-0.54) and those who did receive adjuvant chemotherapy (HR 0.36, 95% CI: 0.19-0.67), with no significant difference between the groups (p=0.60). This suggests that once pCR has been achieved, survival benefit is maintained whether or not further adjuvant chemotherapy is given, although these data should be considered as hypothesis-generating.

Although additional treatment may not influence prognosis once pCR has been achieved, it is not entirely the case that "all pCRs are equal". Within the pCR group prognosis can be further stratified according to baseline stage with increasing tumour size and/or degree of nodal involvement consistently associated with higher risk of recurrence (23-27). For example, in the EORTC 10994/BIG 1-00 neoadjuvant chemotherapy study with almost 2000 patients (including 360 cases known to be HER2+), the only factor predicting for increased risk of distant recurrence after pCR was tumour size at baseline, with a HR for distant recurrence of 3.50 (95% CI: 1.64-7.48) in patients where the tumour size at baseline was larger than 5cm, compared with tumours that were 2cm or smaller (27). The relationship of other baseline pathological features such as tumour infiltrating lymphocytes is less well-established (28-30). With this in mind HER2-RADiCAL focusses the development of a response-adapted strategy away from those patients with higher baseline stage in whom pCR alone may not be sufficient to predict very high rates of relapse-free survival.

1.2. Rationale for de-escalation of anthracyclines in HER2+ EBC

Sequential chemotherapy including both a taxane and an anthracycline component (given in either sequence) has generally been considered the standard chemotherapy backbone for HER2+ early breast cancer. However, anthracyclines are associated with clinically significant late toxicities including cardiotoxicity and haematological secondary malignancy that may be under-reported in clinical trials (31) as they rarely have the 10+year follow-up needed to capture these late side-effects. The cardiotoxicity of anthracyclines is related to the cumulative dose administered and reflects cardiomyocyte injury and death that can lead to both early and late development of left ventricular dysfunction and clinical heart failure. A meta-analysis of 18 studies including 49,017 patients with various types of cancer (23,764 with breast cancer), with 22,815 treated with anthracyclines, reported clinically overt cardiotoxicity in 6% (95% CI: 3%-9%) and subclinical cardiotoxicity in 18% (95% CI 12%-24%) after a median follow-up of 9 years (32). Epirubicin is the most widely prescribed anthracycline in the UK. With 16.9 years median follow-up, the Danish DBCG 89D adjuvant breast cancer study reported a three-fold increased risk of late-onset clinical heart failure relative to non-anthracycline chemotherapy (HR 3.00, 95% CI 1.39-6.49, p<0.01). Absolute rates were low at 3.7% (95% CI 2.5-5.6) in the epirubicin group vs. 1.4% (95% CI 0.7-2.7) in the non-epirubicin group (33). Anthracycline-containing regimens are also associated with a small excess in cases of myelodysplasia and acute myeloid leukaemia (34). The absolute rate is low with an incidence of 0.34% (95% CI: 0.11-0.57) in over 2600 patients treated with adjuvant epirubicin for breast cancer and with median follow-up of 104 months (35). Whilst the risk/benefit ratio for anthracyclines remains favourable for most patients requiring adjuvant chemotherapy (36), this does not necessarily hold in those patients with an excellent breast cancer-specific prognosis (as indicated by pCR) where the need to avoid serious late toxicity is of particular importance.

Anthracycline-free chemotherapy regimens have emerged as an alternative to anthracyclines in HER2+ early breast cancer. Similar gains in DFS and OS were observed in the BCIRG006 study when trastuzumab was added to non-anthracycline chemotherapy and there were significantly fewer cases of heart failure and left ventricular function decline compared to the anthracycline group (37). Trastuzumab and pertuzumab have also been added to this and similar non-anthracycline regimens with high pCR rates observed. Another regimen now widely adopted in lower risk patients is single

agent taxane (paclitaxel) with trastuzumab. Based on data from the APT single group cohort study this regimen is associated with significantly less toxicity than combination chemotherapy regimens and excellent outcomes as discussed in detail below (38). Use of this regimen has been limited to patients with relatively low risk cancers reflecting the APT trial population. However, single agent taxane with trastuzumab and pertuzumab has been shown to result in very high pCR rates leading to the concept of this regimen as a "minimal standard therapy" with additional standard therapy (including anthracycline if appropriate) administered post-operatively in the event of non-pCR (39). The hypothesis that pCR, once achieved, is equally predictive of good long-term outcome in HER2+ EBC, regardless of chemotherapy backbone intensity, is supported by results of the KRISTINE neoadjuvant trial where pCR was associated with a reduced risk of an iDFS event (HR 0.24, 95% CI: 0.09-0.60) regardless of randomisation to treatments of quite different intensity (13).

1.3. Rationale for de-escalation of HER2-directed therapies in HER2+ EBC

The major safety issue identified during the development of trastuzumab was increased cardiac dysfunction, particularly when trastuzumab was given in combination with anthracyclines (40). In contrast to anthracycline-related cardiac dysfunction, which is dose-dependent and irreversible, trastuzumab-induced cardiotoxicity has been considered to be mostly reversible following treatment discontinuation (41). However, recent reports suggest that long-term cardiac damage may be underestimated and cardiac dysfunction may not fully normalise following trastuzumab withdrawal (42, 43). Long-term cardiac safety data from the pivotal adjuvant studies of trastuzumab in HER2+ early breast cancer, suggest that the incidence of cardiac adverse events is maintained at a relatively low level with continued follow-up (44). The addition of pertuzumab to adjuvant trastuzumab in APHINITY was associated with a small numerical increase in cardiac events although absolute rates remained low in both study groups at the relatively short median follow-up of 74 months.

The 1-year duration of trastuzumab or trastuzumab and pertuzumab used in the pivotal trials was chosen somewhat arbitrarily with only one of these trials, HERA, addressing the question of duration with inclusion of 1-year and 2-year trastuzumab treatment schedules. No evidence was observed for superiority of the longer duration (HR 0.99, 95% CI: 0.85−1.14; p > 0.051) (45). Recently, 5 randomised trials investigating the non-inferiority of trastuzumab durations of less than one year have reported mixed results in terms of their statistical significance but remarkably similar results in terms of the estimates of effect (i.e. HR and CI). The largest of these trials was the NIHR HTA-funded PERSEPHONE study (which randomised over 4000 UK patients to receive 12 months or 6 months trastuzumab). Four-year DFS was 89.8% for those allocated 12 months versus 89.4% in the 6-month group. The HR was 1.07 (90% CI 0.93–1.24) demonstrating non-inferiority against their predefined threshold with a significant p value of 0.011. Severe toxicity on at least one occasion (CTCAE grade ≥3, or 2 for palpitations) was reported in 24% of patients in the 12-month group compared with 19% of patients receiving 6 months treatment (p=0.0002) and there was a within trial estimated cost-saving of £9,793 per patient (46-48).

The PHARE study, which randomised 3384 French patients to 12 versus 6 months of trastuzumab, reported an adjusted HR for DFS in the 12-month group versus the 6-month group of 1.08 (95% CI 0.93–1.25; p=0.39) which crossed their non-inferiority margin of 1.15 thus they could not conclude non-inferiority of the 6-month duration in spite of the estimate of effect being very similar to PERSEPHONE. As in PERSEPHONE, cardiac events occurred in significantly more patients in the 12-month group (5.7% vs. 1.9%; p<0.0001) (49, 50). The smaller HORG study also failed to demonstrate non-inferiority for 6 months trastuzumab (HR 1.57; 95% CI: 0.86–2.10; p=0.137) whilst both SOLD (HR 1.39; 2-sided 90% CI: 1.12-1.72) and SHORTHER (HR 1.13; 90% CI: 0.89-1.42) were unable to conclude non-inferiority for a 9-week duration versus standard 12 months.

The discordant conclusions drawn by PHARE and PERSEPHONE despite near identical HRs have been debated extensively and reflect different statistical approaches to setting the pre-defined margin of non-inferiority. PERSEPHONE pre-specified an absolute difference of 3% in 4-year DFS, based on extensive consultation with clinicians and breast cancer patients/advocates. Based on an expected DFS rate in the control group of 80% an absolute 3% decrease in DFS represents a HR of 1.17. However, the actual event rate was lower than expected with a 4-year DFS rate of 89.8% in the 12-month group thus the 95% CI for the 3% non-inferiority margin extended to a HR of 1.31. In contrast PHARE pre-specified that the upper limit of the 95% CI for the HR should be less than 1.15 which, based on an estimated 2-year DFS of 85%, equated to a 2% absolute margin. The 2-year DFS was better than expected at 93.8% in the control arm, giving a corresponding non-inferiority absolute margin of 0.9%. Thus the difference in the rate of events *in absolute terms* was low in both studies with PERSEPHONE reporting a 4-year DFS rate of 89.4% (95% CI 87.9–90.7) in the 6-month group versus 89.8% (88.3–91.1) in the 12 month group and the final analysis of PHARE reporting 5 year DFS estimates of 86.2% (84.4–87.8) in the 12-month group versus 84.2% (82.4–85.9) in the 6-month group.

A recent trial level meta-analysis reported HRs for DFS and OS of 1.10 (95% CI, 0.99-1.23) and 1.14 (95% CI, 0.99-1.32) respectively for 6 versus 12-months trastuzumab. Moreover, the proportion of patients developing symptomatic heart failure was lower among those receiving shorter duration of trastuzumab compared with those receiving 1 year (3.9% vs 6.9%; RR 0.53; 95% CI, 0.38-0.74; p <0.001) (51). The implication of this is that, accepting a true hazard ratio of approximately 1.10, in a population selected to have a very low absolute risk of recurrence (for example, as defined by baseline stage and achieving pCR after neoSACT) then clinically meaningful loss of efficacy is unlikely if 6 months' trastuzumab is administered rather than the current standard of 12 months. On the other hand, the risk of cardiac toxicity, which is distributed across the population independent of prognosis, may be substantially reduced. The hazard ratios for DFS and OS were less favourable for trials of 9-12 weeks trastuzumab versus one year at 1.27 (95% CI, 1.07-1.51) and 1.25 (95% CI, 0.96-1.63) respectively, further supporting the choice of a PERSEPHONE-style 6-month duration in HER2-RADiCAL. Crucially, however, none of the trastuzumab duration trials have been able to describe the relative efficacy of 6 versus 12 months trastuzumab in patients who had received neoSACT with a pCR where the risk/benefit ratio may be markedly different.

1.4. Single group cohort studies and de-escalation of cancer therapy

Non-inferiority RCTs typically require large sample sizes to achieve sufficiently narrow confidence intervals. This may necessitate a lengthy recruitment period and with this comes the risk that the results are no longer relevant or are difficult to interpret in the face of evolutions in the treatment pathway that have occurred in the extended period from study conception to reporting of results. Single group cohort studies offer an appropriate alternative provided robust historical control data from patients treated with current standard of care are available and provided the absolute rates of disease related events amenable to changes in treatment are very low, so any deviation from that good prognosis paradigm can be classed as an unsatisfactory outcome for the study (52). Both of these criteria are met for HER2-RADiCAL.

There are a number of precedents that highlight the ability of single group cohort de-escalation studies to drive changes in cancer care within the UK and globally. Most relevant to HER2-RADiCAL is the APT study that enrolled 410 patients with stage 1 HER2+ cancers to receive a less intensive anthracycline-free adjuvant regimen consisting of weekly paclitaxel plus trastuzumab (38). Based on historical outcome data and given the known risks of treatment, an iDFS of 95% at 3 years was considered acceptable. In the event, at a median follow-up of 4 years, the 3 year iDFS rate was 98.7% (95% CI 97.6-99.8) and these data were rapidly accepted as practice-changing by the oncology community. With longer follow-up, 7-year iDFS of 93.3% (95% CI 90-96) was reported (53), with a third of the

observed events being non-cancer related deaths, observed as the trial population ages. In fact, of the 23 reported iDFS events only five were loco-regional recurrences (1.2%), four were distant recurrences (1%) with six contralateral breast cancers (1.5%) and eight intercurrent deaths (2.0%) observed. Thus only a minority of the iDFS events could have been influenced by treatment and the 7 year relapse-free-interval (RFI), the outcome that focusses on the events amenable to influence by the treatment, was 97.5% (95% CI 95.9-99.1).

The ongoing non-randomised CRUK-funded PRIMETIME study (CRUK C17918/A20015; ISRCTN41579286) tests de-escalation of adjuvant breast radiotherapy in a biomarker-defined cohort in whom the expected rate of local recurrence is so low that the potential absolute gain from radiotherapy does not outweigh the established associated risks. The study is powered to exclude an ipsilateral breast recurrence rate of 5% at 5 years. A similar non-randomised design has been adopted for the Canadian LUMINA study (NCT01791829). Both studies are designed to be practice-changing.

1.5. Use of pCR to adapt treatment in HER2+ EBC is a high priority internationally

Two other studies with a design similar to HER2-RADiCAL are being initiated outside the UK. In the US, the EA1181 (CompassHER2-pCR; primary endpoint=RFS H_0=92% H_1≥95% p=0.025(one-sided)) study (NCT04266249) extends to a higher risk patient population with the inclusion of patients with N2 disease and mandates 12 weeks' neoadjuvant taxane and trastuzumab plus pertuzumab. Participants with pCR are required to complete a full year of trastuzumab and pertuzumab following surgery. The Breast International Group (BIG) DECRESCENDO study (NCT04675827) also prescribes 12 weeks' neoadjuvant taxane/trastuzumab/pertuzumab, but only includes patients with HER2+, oestrogen receptor-negative and node-negative cancers, and like EA1181 mandates a full year of trastuzumab and pertuzumab. Thus, all three studies (EA1181 (CompassHER2-pCR), DECRESCENDO and HER2-RADiCAL have essentially equivalent neoadjuvant therapy but HER2-RADiCAL is the only one to reduce the post-surgery anti-HER2 therapy to monotherapy with trastuzumab and only for 6 months, based in large part on the results from PERSEPHONE. Initial discussions took place in Summer 2020 with the intention to plan for a prospective meta-analysis of these 3 trials.

2. STUDY OBJECTIVES

2.1. Primary Objective

- To determine the efficacy of response-adapted (reduced) therapy in patients who at presentation have HER2+ early breast cancer with *intermediate risk of recurrence*, and by virtue of achieving pCR (ypT0/is ypN0) following neo-adjuvant, non-anthracycline containing, systemic chemotherapy and dual antibody therapy (trastuzumab and pertuzumab) are reclassified as being at *low risk of recurrence*.

2.2. Secondary Objectives

- To determine adherence/acceptability to/of the response-adapted treatment pathway.
- To describe the observed current standard of care treatment pathway using UK population level routine NHS data.
- To estimate the cost-effectiveness of response adapted therapy in comparison to both hypothetical maximal therapy and to observed standard therapy within the UK NHS.

2.3. Exploratory Objectives

- To explore potential tumour biomarkers associated with recurrence.

3. STUDY DESIGN

3.1. Design

HER2-RADiCAL is a response-directed interventional cohort (single group) study. It uses treatment response (pCR) following neoSACT as a marker for selective therapy reduction.

Patients with HER2+ early breast cancer who have recently completed neoSACT with non-anthracycline-containing chemotherapy plus trastuzumab and pertuzumab and where no evidence of residual invasive cancer has been found at surgery either in the breast or sampled regional nodes (pCR; ypT0/Tis ypN0 M0) will be invited to participate.

All patients registered into the study will continue trastuzumab to complete a total of 9 cycles (approximately 6 months treatment) inclusive of those cycles administered in the (neo-) adjuvant setting prior to study entry. No further pertuzumab will be administered and no adjuvant chemotherapy is permitted. All patients will receive adjuvant radiotherapy, bisphosphonates and endocrine therapy as per local practice.

There exist various standard-of-care systemic therapy pathways for the HER2-RADiCAL eligible population and so the actual extent of reduction in comparison to each participants' planned standard of care pathway may vary. For example, based on current standards of care the trastuzumab duration of 9 cycles will represent a reduction in all patients whereas avoiding adjuvant pertuzumab represents a reduction primarily in node-positive patients who would ordinarily complete 12 months. Anthracycline-sparing chemotherapy represents a reduction for those patients who would, in a non-response adapted pathway, receive sequential taxane-anthracycline chemotherapy as used in the pivotal NEOSPHERE study.

Cost effectiveness of the response-adapted pathway will be investigated via a health economic model incorporating real-world 4-nation NHS data collected at the beginning and end of the study period.
Patients will attend follow-up visits as per local practice and patient updates will be provided on an annual basis for a minimum of five years. Longer term follow-up is planned via linkage to routine data.

Primary analysis is planned after 3 years follow-up. Event rate monitoring will continue until at least 5 years via linkage to routinely collected data and/or site based eCRF with choice of follow up model dependent on viability of provision of real-time quality data to determine recurrence outcomes from routine sources.

3.1.1. HER2-RADiCAL Locoregional management

Surgery

Eligible patients for HER2-RADiCAL will be those with a pCR following neoSACT, and patients must thus have had adequate surgery prior to study entry to allow histopathological confirmation of pCR.

It is recommended that at baseline, all clinically/radiologically suspicious areas should have been appropriately assessed to determine the extent of disease, and the tumour site(s) marked with marker clip(s).

Following completion of neoSACT, the breast should have been re-assessed clinically and radiologically to allow accurate surgical planning. Patients treated with breast conserving surgery should have undergone excision of all marked tumour areas, and this should have been confirmed both radiologically intra-operatively, and histopathologically post-operatively. After breast-conserving surgery margins must be clear of any residual ductal carcinoma in situ (residual classical lobular carcinoma in situ at margins is permitted).

Pre- or post-NeoSACT sentinel lymph node biopsy (SLNB) is acceptable for patients who were clinically node negative at diagnosis (cN0). However, where a patient has had a pre-neoSACT SLNB which was positive then it is not possible to confirm pCR, and such a patient would not be eligible.

Where pre-operative nodal involvement is confirmed (cN1), post-neoSACT lymphatic mapping should have been carried out in accordance with the UK Guidelines for Axillary Surgery Following Neoadjuvant Chemotherapy (54). Dual agent (radiocolloid/blue dye) lymphatic mapping should be carried out with three or more nodes retrieved at surgery, and evidence of tumour response should be identified in at least one axillary node at histopathological assessment. Retrieval of an involved lymph node marked at diagnosis (whether by tattooing or insertion of a marker clip according to local practice) is encouraged as this has been demonstrated to further reduce false negative rates (55). Alternatively, confirmation of complete response by post-neoSACT axillary clearance is also acceptable.

Radiotherapy
For patients undergoing breast conserving surgery, whole breast irradiation must be administered. Boost is at the discretion of the treating doctor but is generally recommended for patients 50 years or younger.

For post-mastectomy patients, radiotherapy is at the discretion of the investigator based on institutional standards but is recommended in patients who were node-positive at diagnosis. The use of bolus is as per institutional guidelines.

Regional node irradiation should be discussed with patients but is recommended in patients who were node-positive at diagnosis unless an axillary clearance has been performed or there is co-enrolment to a permitted study. The level of nodal radiotherapy is again as per institutional policy, or as per study protocol if the patient is co-enrolled in a permitted study. Patients who had no evidence of nodal involvement pre or post chemotherapy should not be generally recommended further nodal treatment other than the guided sentinel node sampling.

Radiotherapy planning and delivery should be carried out in accordance with the best current routine practice.

3.1.2. HER2-RADiCAL Pathology Requirements
pCR, determined by the local pathologist prior to study entry, is defined as the absence of residual invasive carcinoma in the breast and sampled axillary nodes (ypT0/Tis ypN0). Residual *in situ* carcinoma in the breast only (ypTis ypN0) is regarded as pCR as per the AJCC/TNM staging system (8th edition) and RCPath guidelines (56). Central pathology review of pCR status will be performed in a subset of patients as described in section 18.1.

3.1.3. HER2-RADiCAL Systemic Therapy Requirements
Participants must have received neo-adjuvant taxane-based non-anthracycline-containing chemotherapy with concomitant trastuzumab and pertuzumab administered according to local/national guidelines and standard practice at the site.

Acceptable non-anthracycline chemotherapy regimens include:
- Carboplatin with docetaxel or paclitaxel
- Cyclophosphamide with docetaxel or paclitaxel
- Docetaxel
- Paclitaxel

It is acceptable for paclitaxel/docetaxel to have been substituted with nab-paclitaxel. The expected duration of neo-SACT is 12-18 weeks. Earlier discontinuation (e.g. due to toxicity) is acceptable provided all other inclusion criteria are met. However, a minimum of three cycles trastuzumab and pertuzumab with chemotherapy must have been administered.

4. STUDY ENDPOINTS

4.1. Primary Endpoint

- Relapse-free interval (RFI)

4.2. Secondary Endpoints

- Relapse-free survival (RFS)
- Invasive breast cancer free survival (iBCFS)
- Invasive disease-free survival (iDFS)
- Distant recurrence free interval (DRFI)
- Breast cancer-free interval (BCFI)
- Overall survival (OS)
- Treatment pathway adherence
- Cost-effectiveness

4.3. Exploratory Endpoints

- Biomarkers including, but not limited to, tumour infiltrating immune cell populations

5. PATIENT SELECTION & ELIGIBILITY

5.1. Number of Participants

The aim is to recruit 720 participants.

5.2. Source of Participants

Participants will be recruited from sites in the UK. Potential participants will be identified in oncology clinics and discussed at multi-disciplinary team (MDT) meetings. Participants will be approached as early as possible in their treatment pathway.

5.3. Inclusion Criteria

1. Female or male, age ≥ 16
2. Histologically confirmed invasive breast cancer that is HER2-positive (IHC3+, and/or ISH positive/amplified) as determined by the local laboratory in accordance with national guidelines
3. Has received neoSACT with a non-anthracycline chemotherapy regimen with at least 3 cycles of concomitant trastuzumab and pertuzumab
4. pCR (ypT0/is ypN0) in breast and sampled regional lymph nodes as per local pathology reporting
5. Imaging of breast and axilla **prior** to initiation of neoSACT and either:
   a) Breast primary radiological measurement ≤ 20mm prior to neoSACT **and** limited nodal involvement (cN1) confirmed by axillary core biopsy or FNA (cT1N1)
      OR
   b) Breast primary radiological measurement >20mm but ≤ 50mm **and** node-negative (cT2N0) **or** limited nodal involvement (cT2N1)
6. Multiple ipsilateral cancers are permitted provided at least one meets the tumour size and axillary node inclusion criteria and none meet any of the exclusion criteria
7. Bilateral cancers are permitted provided at least one meets the tumour size and axillary node inclusion criteria and none meet any of the exclusion criteria
8. Pre-treatment diagnostic breast tumour biopsy sample available

9. Study consent ≤6 weeks after completing breast cancer surgery
10. Patient must be fit to continue treatment with trastuzumab and have no concomitant medical, psychiatric or social problems that might interfere with informed consent, adherence to the reduced treatment pathway or follow up
11. Provision of written informed consent to participate in HER2-RADiCAL

5.4. Exclusion Criteria

1. Evidence of metastatic disease at any time since diagnosis
2. Any residual invasive disease following neoSACT. This includes isolated tumour cells in axillary nodes or tissue or evidence of lymphovascular invasion in the breast. Persistent ductal or lobular non-invasive disease (DCIS or LCIS) is permitted. Resection margins must be deemed clear of any residual DCIS according to local MDT protocol.
3. Any planned further **resectional** surgery for breast cancer (including re-excision, mastectomy, or axillary surgery)
4. HER2-negative invasive breast carcinoma
5. Breast cancer with clinical stage of T≥3 at diagnosis
6. Evidence of scarring (or other pathological features consistent with previous malignant involvement) in ≥4 axillary nodes or clinical nodal stage N≥2 at any time
7. Positive SLNB pre-neoadjuvant systemic therapy as this precludes determination of pCR
8. Pregnant and/or lactating women
9. Female patient of child-bearing potential, unwilling to use an effective form of contraception during trastuzumab treatment and for 7 months after their last dose of trastuzumab (NB. See section 5.5 for further guidance)
10. Previous diagnosis of invasive breast carcinoma
11. Previous diagnosis of any other (non-breast) malignancy unless disease-free for at least 5 years and considered to be at low risk of recurrence or treated basal cell or localised squamous cell carcinoma of the skin or cervical intraepithelial neoplasia
12. Chemotherapy administered following surgery (NB. Pertuzumab and/or trastuzumab may have been continued after surgery as per local practice prior to trial entry)
13. Has received >9 cycles trastuzumab
14. Clinically significant cardiac disease within 12 months of starting trastuzumab, including unstable angina, acute myocardial infarction, New York Heart Association Class III or IV congestive heart failure, cerebral vascular accident, or cardiac arrhythmia associated with haemodynamic instability
15. Left ventricular ejection fraction (LVEF) less than 50% on most recent cardiac imaging
16. History of interstitial lung disease
17. Any medical or other contra-indication to continuing trastuzumab

5.5. Pregnancy testing and contraception

Females of child bearing potential (defined as premenopausal and not surgically sterilized or less than 1 year after the onset of menopause) will have a serum or urine pregnancy test within 10 days of study registration. A positive test at screening will result in exclusion. Subsequent pregnancy testing will be performed as per local standard practice during and after study treatment.

Female participants must be surgically sterile (i.e. have undergone a hysterectomy, bilateral salpingectomy or bilateral oophorectomy, bilateral tubal ligation) or have a sterilised sole partner, or be post-menopausal (defined as no menses for 12 months without an alternative medical cause), or must agree to use a highly effective non-hormonal contraceptive measure (as listed below) during the

period of study treatment and for 7 months after the last dose of study treatment. Highly effective methods of contraception include:

- Non-hormonal intrauterine device (intrauterine hormone-releasing system is acceptable if already in situ and patient has decided against removal following discussion with their doctor)
- Bilateral tubal occlusion
- Vasectomised partner
- Sexual abstinence defined as refraining from heterosexual intercourse if consistent with the preferred and usual lifestyle of the patient

6. SCREENING

6.1. Screening Log

All participating sites will be requested to keep a log of all patients with HER2+ EBC who are potentially eligible for this study. The information collected on the log will include:

- Date (month and year) patient started neoSACT
- Screening outcome (patient approached/accepted participation/declined participation)
- Reasons for not approaching/declining participation (if available)
- Study ID (if applicable)

This information will be used by the Trial Management Group (TMG) to monitor recruitment activity. No patient identifiable data will be sent to ICR-CTSU at this stage.

6.2. Procedure for Obtaining Informed Consent

The Principal Investigator (or designated individual) must ensure that each potential study patient is fully informed about the nature and objectives of the study and possible risks associated with participation. Ethics-approved HER2-RADiCAL pre-surgery patient information may be used to aid introduction of the study at an early stage. After surgery and confirmation of a pCR, potential participants should be given the current ethics approved HER2-RADiCAL post-surgery patient information sheet (PIS) and informed consent form (ICF) for their consideration. Patients should only be asked to consent to the study after they have had sufficient time to consider the study, and the opportunity to ask any further questions.

Remote consent is permitted providing the following steps are taken:

- A member of the research team should contact the patient to introduce the study and to organise a telephone appointment with an Investigator in order for the Investigator to discuss the study with the patient in detail.
- A copy of the ethics approved PIS and ICF should be sent to the patient by email or post ahead of the scheduled appointment so that the patient has sufficient time to review the study information. (If sending by post, two copies should be sent – one for the patient to retain and one to return to the site).
- During the telephone appointment the Investigator should complete the informed consent process remotely, discussing the study and ensuring that the patient is fully informed.
- If the patient agrees to consent the Investigator should ask the patient to initial the sections of the ICF and sign and date two copies. They should ask the patient to email/post one copy back to the site as soon as possible.
- The Investigator should record the date of verbal consent in the patient's clinical notes and on the remote consent file note provided, and then confirm to the patient that this consent has been noted.
- The ICF should be received from the patient within a week of consent. Sites should follow up with patients on any consent forms not received until they have been received, signed and filed.

- On receipt of the signed copy of the ICF from the patient, the consenting Investigator should add their signature and date of signing and attach it to the remote consent file note in the patient file.
- A completed copy should be emailed/posted to the patient for their records.

No protocol required assessments should be conducted until the HER2-RADiCAL consent form has been signed and dated by both the patient and the Investigator (or designated individual), unless they are performed routinely as part of standard patient care.

By consenting to HER2-RADiCAL patients will be required to consent to having archival tumour tissue collected for translational studies.

Confirmation of the patient's consent and the informed consent process must be documented in the patient's medical notes. A copy of the signed consent form should be provided to the patient and the original retained in the investigator site file, which must be available for verification by ICR-CTSU study staff or for regulatory inspection at any time.

6.3. Participation in Other Clinical Trials

Patients who fulfil the eligibility criteria will be given the opportunity to participate in HER2-RADiCAL if they have participated in other clinical trials prior to recruitment providing this with the agreement of the TMG of the relevant trial.

Participation in other interventional clinical trials after recruitment to HER2-RADiCAL will be permissible once the Trial Management Group has confirmed that the intervention in the second trial does not jeopardise the ability of HER2-RADiCAL to meet its objectives, nor be considered a safety issue for the patients.

7. REGISTRATION

Participants must be registered centrally with the ICR Clinical Trials & Statistics Unit (ICR-CTSU) once protocol required screening assessments have been completed.

Patients are registered by emailing the ICR-CTSU randomisation service:
randomisation-icrctsu@icr.ac.uk

A registration form must be completed prior to registration. The following information will be required at registration:

- Name of hospital, consultant and person registering patient
- Confirmation that patient has given written informed consent for study participation and for any sub-studies
- Confirmation that patient is eligible for the study
- Patient's full name, hospital number, date of birth, postcode and NHS/CHI number (or equivalent for international participants)

The caller will be given the patient's unique registration number (Study ID).

ICR-CTSU will send confirmation to the trial contact and pharmacist at the recruiting site to confirm a patient's entry into the study.

8. STUDY ASSESSMENTS

8.1. Screening Assessments

The following assessments should be conducted within 28 days prior to registration. Only those procedures required as part of standard patient care should be conducted prior to obtaining written informed consent from the patient for registration:

- Informed consent
- Baseline characteristics and relevant medical history (cardiovascular, previous malignancy)
- ECOG performance status
- Height and weight
- Pregnancy test within 10 days prior to registration
- Confirmation of eligibility
- Registration form submitted to ICR-CTSU

Cardiac monitoring including physical examination, electrocardiogram (ECG) and LVEF measurement should be conducted as per standard practice at the site; this may be every 3 months during treatment as per the trastuzumab SmPC and NICE guideline NG101 (57), or every 4 months as per the UK NCRI Recommendations consensus statement (58). It is therefore expected that cardiac monitoring will have been initiated as per local standard practice prior to study entry.

The pathology report confirming pCR (with patient identifiers redacted) will be requested by ICR-CTSU for all participants at registration.

An archival tissue sample (post-neoSACT surgical excision specimen) will be requested from sites by ICR-CTSU at registration for approximately 100 participants. (NB. Archival formalin fixed paraffin embedded (FFPE) blocks of primary tumour and nodal samples will be requested by ICR-CTSU at a later date. Further information on tissue sample collection is provided in section 18.3.)

After registration the patient should be asked to complete the EQ-5D and socioeconomic questionnaires.*

**The questionnaires that will be used to collect patient reported outcomes will be included via substantial amendment after the main study applications have been approved.*

8.2. On-treatment Assessments

- Trastuzumab should be given every 3 weeks (+/- 3 days) as per its label and/or standard practice at the site to complete a total duration of 9 cycles since the start of neoadjuvant trastuzumab treatment.
- Cardiac monitoring including physical examination, electrocardiogram (ECG) and LVEF measurement should be conducted as per standard practice at the site; this may be every 3 months during treatment as per the trastuzumab SmPC and NICE guideline NG101 (57), or every 4 months as per the UK NCRI Recommendations consensus statement (58).
- Adverse event reporting (limited to serious adverse reactions as described in section 10).
- Pregnancy tests should be conducted as per local standard practice during study treatment.

NB. Additional ad hoc visits may take place as necessary if clinically indicated or at the request of the patient if concerns are raised.

8.3. Post-treatment Follow-up Assessments

The following assessments should be conducted 30 days (+ up to 7 days) after last dose of trastuzumab. This visit may be conducted remotely (e.g. by telephone or video consultation):

- Adverse event reporting (limited to serious adverse reactions as described in section 10).
- EQ-5D and socioeconomic questionnaires*
- Pregnancy tests should be conducted as per local standard practice following study treatment.

**The questionnaires that will be used to collect patient reported outcomes will be included via substantial amendment after the main study applications have been approved.*

8.4. Annual Follow-up Assessments

- Patients will be followed up annually for 5 years
- It is recommended that the annual follow up is scheduled for the anniversary of study entry (+/- 2 months) where possible. However, follow up undertaken outside this expected timeframe will not be considered as protocol non-compliance.
- Telephone/video (e.g., Attend Anywhere) follow up is permitted.
- Patients should have annual mammograms for 5 years. Thereafter further imaging should be as per standard of care at the site.
- Patients will be required to complete EQ-5D and socioeconomic questionnaires annually for up to 5 years.

**The questionnaires that will be used to collect patient reported outcomes will be included via substantial amendment after the main study applications have been approved.*

NB. Additional ad hoc visits may take place as necessary if clinically indicated or at the request of the patient if concerns are raised.

Over the course of the study, the study team aim to transfer the provision of long term follow-up data (including data to determine recurrence outcomes) from research sites to routine data sources providing the patient has given consent to do so and the required information can be accessed from routine sources. This is intended to relieve the burden of long term follow-up on research sites, and as a move towards this, data collection in the eCRF for patients where no disease event has occurred is minimal.

8.5. Procedure at Disease Recurrence

Disease recurrence should be reported to ICR-CTSU on the appropriate eCRF. Patients should be treated as per local guidelines for metastatic disease/recurrence. There is no restriction on receiving investigational medicinal products for the treatment of metastatic disease.

In the case of relapse consent should be requested (not mandatory) to obtain a tissue sample of recurrent disease for patients who have a routine biopsy or surgical procedure conducted as part of their standard care and where excess tissue is available.

8.6. Discontinuation from Treatment

Participants may discontinue trastuzumab treatment at any time at their own request, or they may be discontinued at the discretion of the Principal Investigator. Reasons for discontinuation will include:

- Disease recurrence
- Unacceptable toxicity
- Pregnancy

Participants who discontinue treatment should continue to be followed-up and will still be included in the intention-to-treat analyses of the study.

8.7. Discontinuation from Follow up Visits

If a patient withdraws from further follow-up the patient withdrawal eCRF should be completed stating whether the patient i) no longer wishes to attend study follow-up visits but is happy for data to be extracted from medical records (more usual occurrence) or whether ii) the patient has withdrawn consent for any further information to be sent to the ICR-CTSU (rare occurrence).

8.8. Schedule of Assessments

Visit/Assessment	**Screening and registration (Day -28 to Day -1)**	**Day 1 of each cycle (+/- 3 days)**	**Post-treatment follow up (30 days post-treatment + up to 7 days)**	**Follow up (annually for up to 5 years post study entry)**
Informed consent (a)	x			
Baseline characteristics and medical history	x			
ECOG performance status, height and weight	x			
Eligibility checklist completed	x			
Cardiac monitoring	x (b)			
Pregnancy test	x (c)	x (c)	x (c)	
Registration form submitted to ICR-CTSU	x			
Retrieval of archival tissue sample (d)	x			x
Administration of trastuzumab (e)		x		
Serious adverse reactions (SARs) (f)	Continuous up to 30 days post-treatment			
EQ-5D QoL questionnaire (g)	x		x	x

Socioeconomic questionnaire (g)	x		x	x
Access to information from routine follow up				x
Annual mammogram				x
Disease status (survival and relapse)				x

(a) Written informed consent for registration should be obtained from the patient prior to conducting any protocol required assessments and procedures (unless required as part of standard patient care).
(b) Cardiac monitoring including physical examination, electrocardiogram (ECG) and LVEF measurement should be conducted as per standard practice at the site; this may be every 3 months during treatment as per the trastuzumab SmPC and NICE guideline NG101 (57), or every 4 months as per the UK NCRI Recommendations consensus statement (58). It is therefore expected that cardiac monitoring will have been initiated as per local standard practice prior to study entry.
(c) Pregnancy tests must be conducted within 10 days prior to registration. Pregnancy tests should be conducted as per local standard practice during and after study treatment.
(d) Archival tissue samples from the excision specimen (slides or digital images of slides of the tumour bed and lymph nodes) will be requested from sites by ICR-CTSU at study entry for approximately 100 participants. Archival tissue samples (FFPE blocks of primary tumour and nodal samples) will be requested for all patients by ICR-CTSU at a later date. A recurrence tumour tissue sample should be provided at relapse for patients who have a routine biopsy or surgical procedure conducted as part of their standard care and where excess tissue is available. Further information on tissue sample collection is provided in section 18.3.
(e) Trastuzumab should be given every 3 weeks for a total of 9 cycles including those cycles administered prior to study entry. The number of adjuvant cycles given within the HER2-RADiCAL study is reduced according to the number of cycles received prior to study entry.
(f) SARs occurring after registration and within 30 days of the last administration of trastuzumab must be reported (see section 10).
(g) The questionnaires that will be used to collect patient reported outcomes will be included via substantial amendment after the main study applications have been approved.
NB. Additional ad hoc visits may take place as necessary if clinically indicated or at the request of the patient if concerns are raised.

9. STUDY TREATMENT

Trastuzumab is an investigational medicinal product within HER2-RADiCAL (solely due to it being given for a shorter duration than the licence).

9.1. Dose, Schedule and Duration of Treatment

Trastuzumab (original or biosimilar) should be given every 3 weeks to complete a total of 9 cycles including those cycles administered prior to study entry; the number of cycles given within the HER2-RADiCAL study is reduced according to the number of cycles received prior to study entry.

Trastuzumab may be administered via IV or subcutaneous routes in accordance with the standard practice at the site and will be administered as per the SmPC and local guidelines. Subcutaneous trastuzumab is administered at a dose of 600mg every 3 weeks. Intravenous trastuzumab is administered at a dose of 6mg/kg body weight every 3 weeks (with loading dose of 8mg/kg if required). No dose reductions are permitted.

9.2. Prescription and Dispensing

Trastuzumab should be prescribed by the Investigator and dispensed from hospital pharmacy stock for the duration of the study.

9.3. Concomitant Therapy

Patients should receive radiotherapy, endocrine therapy and bisphosphonates as appropriate as per local/national guidelines.

All medication considered necessary for the participants' welfare and which is not expected to interfere with the evaluation of the study drugs may be given at the discretion of the investigator.

Currently available COVID-19 vaccines (Pfizer/BioNTech, Oxford University/AstraZeneca and Moderna) are allowed. Should any further COVID-19 vaccines become available, advice from the Chief Investigator will be issued as to whether these vaccines are permitted while patients are receiving trastuzumab treatment within the study.

9.4. Non-permissible Medications/Therapies

Non-permissible concurrent medications/therapies include:

- Other adjuvant systemic anti-cancer therapies (with the exception of adjuvant bisphosphonates, adjuvant endocrine therapy). In particular **no adjuvant chemotherapy** and **no adjuvant pertuzumab** or other HER2-targeting agent, with the exception of trastuzumab**,** is permitted after study registration.
- Investigational agents of any type for, or likely to be effective in, the adjuvant treatment of invasive breast cancer.
- Live vaccines are contraindicated during treatment with trastuzumab. NB. Currently available COVID-19 vaccines (Pfizer/BioNTech, Oxford University/AstraZeneca and Moderna) should not be considered live vaccines and are allowed. Should any further COVID-19 vaccines become available, advice from the Chief Investigator will be issued as to whether these vaccines are permitted while patients are receiving trastuzumab treatment within the study.

9.5. Dose Modifications, Interruptions and Delays

Trastuzumab toxicity will be managed as per the SmPC and local practice. No dose reductions are permitted for IV or subcutaneous trastuzumab.

Where trastuzumab dosing has been delayed the timing of restarting trastuzumab will be at the discretion of the treating clinician and as per the SmPC and patients should still receive a total of 9 cycles of treatment.

9.6. Overdoses

There is no experience with trastuzumab overdose in human clinical trials. Any overdose should be reported immediately to ICR-CTSU.

9.7. Discontinuation and Subsequent Therapy

Treatment should continue for the duration described in Section 9.1 or until unacceptable toxicity, pregnancy, or withdrawal of patient consent.

9.8. Drug Supplies, Labelling and Pharmacy Responsibilities

Trastuzumab is an investigational medicinal product within HER2-RADiCAL and should be prescribed by the Investigator and dispensed from hospital pharmacy stock for the duration of the study. The dispensed drug should be labelled with a local pharmacy dispensing label as per local policy; there will be no study-specific labelling.

Drug formulation, storage and destruction should be in accordance with local policy. Accountability records must be kept of all dispensing (including the dose prescribed, manufacturer, administration (IV/SC), batch number and expiry date) in accordance with the HER2-RADiCAL Pharmacy Guidance Notes. ICR-CTSU should be provided with confirmation of the local pharmacy's clinical trial drug handling and destruction procedures.

10. PHARMACOVIGILANCE

The safety profile of adjuvant trastuzumab in HER2+ EBC is very well established with common toxicities consistently identified across multiple studies and with over 15 years' real-world experience. The reduction in toxicity with 6 versus 12 months trastuzumab in this patient population has also been well-defined in several thousand patients enrolled in the PERSEPHONE, PHARE and other studies. The collection of extensive safety data in HER2-RADiCAL is therefore very unlikely to add important new information to the known safety profile of trastuzumab and so represents an inefficient use of clinical research resources. To address this HER2-RADiCAL will adopt selective safety data collection with collection of serious adverse reactions (SARs) only.

10.1. Definitions

Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence in a patient or clinical trial subject administered an investigational medicinal product that:

- results in death
- is life-threatening
- requires hospitalisation or prolongation of existing inpatients´ hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect

Important adverse events that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, may also be considered serious.

Pregnancy whilst participating in a trial is not considered an SAE but should be followed up for congenital anomalies or birth defects (see section 10.7).

Serious Adverse Reaction (SAR)

A SAR is an SAE that is suspected as having a causal relationship to the investigational medicinal product, as assessed by the investigator responsible for the care of the patient. A suspected causal relationship is defined as possibly, probably or definitely related (see definitions of causality table).

Definitions of causality

Relationship	Description
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the study medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments)
Probable	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out

Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse reaction, the nature or severity of which is not consistent with the information set out in the Reference Safety Information (RSI).

Reference Safety Information (RSI)

A list of medical events that defines which reactions are expected for the IMP within a given study and thus determining which (SARs) require expedited reporting. The RSI for the HER2-RADiCAL study is contained in Section 4.8 of the Summary of Product Characteristics (SmPC) for trastuzumab.

10.2. Reporting of Serious Adverse Reactions to ICR-CTSU

Any SAR that occurs after registration and within 30 days of the last administration of trastuzumab must be reported. All SARs should be reported to ICR-CTSU within 24 hours of the Principal Investigator (or designated representative) becoming aware of the event, by completing the HER2-RADiCAL SAR form and emailing to:

sae-icr@icr.ac.uk

For the attention of the HER2-RADiCAL study team

As much information as possible, including the Principal Investigator's assessment of causality, must be reported to ICR-CTSU in the first instance. Additional follow up information should be reported as soon as it is available. All SAR forms must be completed, signed and dated by the Principal Investigator or designated representative. The severity of SARs should be graded according to the NCIC-CTCAE criteria version 5.0. Whenever one or more toxicity/sign/symptom corresponds to a disease or a well-defined syndrome only the main disease/syndrome should be reported.

Data on adverse events that do not meet the above definition of a SAR will not be collected.

10.3. Review of Serious Adverse Reactions

The Chief Investigator (or nominated representative) will assess all reported SARs for causality and expectedness (NB. The Chief Investigator (or nominated representative) will not be asked to assess SARs reported for patients at their own site, an alternative reviewer will be sought.) The Chief Investigator cannot down-grade the Principal Investigator's assessment of causality. SARs assessed as being unexpected (SUSARs) will undergo expedited reporting to the relevant authorities and all other interested parties by ICR-CTSU (see 11.5). Sites should respond as soon as possible to requests from the Chief Investigator or nominated representative (via ICR-CTSU) for further information that may be required for final assessment of an SAE.

10.4. Expedited Reporting of SUSARs

If a SAR is identified as being a SUSAR by the Chief Investigator or nominated representative, and is fatal or life threatening, it will be reported by ICR-CTSU to the MHRA, the REC and the Sponsor, and all other interested parties within 7 days of being notified of the event. If an SAE is identified as a SUSAR by the Chief Investigator or nominated representative, and is not fatal or life threatening, it will be reported by ICR-CTSU to the MHRA, the REC and the Sponsor within 15 days of ICR-CTSU being notified of the event. ICR-CTSU will report any additional relevant information to the MHRA, REC and the Sponsor and as soon as possible, or within 8 days of the initial report of a fatal/life threatening SUSAR. The Principal Investigators at all actively recruiting sites will be informed of any SUSARs occurring within the study at appropriate intervals.

10.5. Follow up of Serious Adverse Reactions

SARs should be followed up until clinical recovery is complete or until disease has stabilised. SAR outcomes should be reported to ICR-CTSU using the relevant section of the SAR form as soon as the Principal Investigator or designee becomes aware of the outcome.

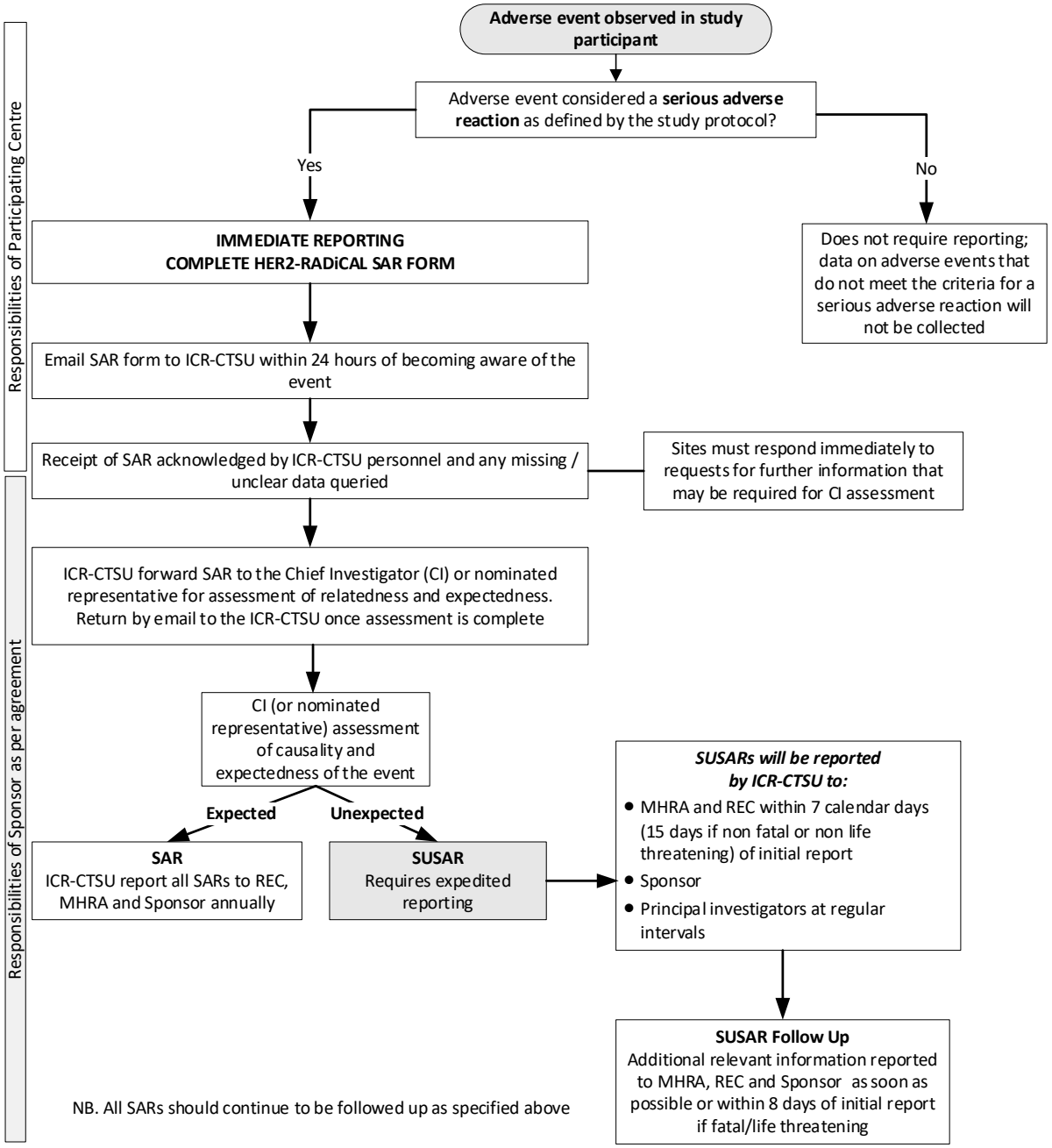
10.6. Annual Reporting of Serious Adverse Reactions

An annual report will be provided to the MHRA and the REC by ICR-CTSU and copied to the Sponsor at the end of the reporting year.

10.7. Reporting Pregnancies

If any study patient becomes pregnant while receiving study drug or up to 7 months after receiving study drug, this should be reported to ICR-CTSU using the pregnancy reporting form. Pregnancies should be followed up until conclusion and all follow-up information should be reported to ICR-CTSU. If the outcome of the pregnancy meets the definition of serious (i.e. congenital abnormality) this should be reported to ICR-CTSU following the SAR reporting procedures described above.

Figure 2. Flow diagram for SAR reporting, and action following report



11. STATISTICAL CONSIDERATIONS

11.1. Statistical Design and Sample Size Justification

11.1.1. Statistical Design

HER2-RADiCAL is a response-directed interventional cohort (single group) study embedded within a real-world data-driven clinical pathway model. It uses treatment response following neoSACT as a marker for selective therapy reduction for patients thus identified as having low risk HER2+ early breast cancer.

An interventional cohort design has been chosen to be more agile in response to the rapidly changing clinical landscape. By virtue of its smaller sample size it will provide results to inform clinical practice in a relevant clinical timeframe and much earlier than the traditional non-inferiority RCT without loss of precision of the estimate of effect. Such considerations are especially relevant in the case of treatment de-escalation in a patient population where the disease-related event-rate is rare due to the excellent prognosis. Supplementing the study with economic modelling of real-world data ensures maximal applicability and generalisability of the study's results.

Such a design avoids many of the challenges faced by randomised non-inferiority trials in the context of treatment de-escalation and rare disease outcome events. With the traditional design the sample size required to exclude a small but real potential absolute loss of efficacy when the event rates are so low is very large and thus corresponds to a very large number needed to treat/harm. Additionally, patient and clinician preferences tend to lead to recruitment of a highly selected randomised patient group which may limit the external generalisability of the study findings. The shorter time-frame required to complete the trial, due to smaller sample size and faster patient recruitment, is thus less susceptible to external changes in clinical practice and more likely to report findings in a time-period to influence practice both in the UK and internationally. Precedents have been set which record high patient advocate support and strong recruitment when such designs are used for example with the successful PRIMETIME avoidance of radiotherapy study and this support and preference have been reiterated in the context of HER2-RADiCAL.

The protocol-driven study cohort is one of three comparator pathways (pathway B) in the economic model; the other two comparators are (A) a non-response-adapted pathway/maximum therapy pathway (the standard clinical pathway prior to the study) and (C) a real-world representative pathway taken from 4-nation NHS data at the beginning and end of the study period, which are expected to involve national variation in response-adaptation and risk stratification driving the use of chemotherapy, trastuzumab, pertuzumab and T-DM1 in different ways.

11.1.2. Sample Size

In the eligible cohort of HER2+ patients with smaller tumours and limited nodal involvement who have a pCR following neoSACT, the incidence of relapse is expected to be ≤4% by 3 years. Should the incidence of relapse be >6.5% by 3 years the de-escalation treatment strategy would not be considered clinically acceptable (13, 59). Using Sample Size Tables for Clinical Studies software (60) a sample size of 691 has been calculated based on exact binomial probabilities (61) with alpha of 0.05 and power of 90% to exclude a 3-year recurrence rate of 6.5% (A'hern's single stage design). A total of 720 patients will be recruited to allow for a 4% drop-out rate. The IDMC will monitor drop-out and intercurrent death rate in order to advise any increase in sample size if either of these is higher than anticipated.

11.2. Treatment Allocation

There is no randomised treatment allocation. Eligible patients with HER2+ EBC with locally-determined pCR after taxane-based (non-anthracycline) neoadjuvant chemotherapy plus trastuzumab and pertuzumab will receive, after registering to the study, response adapted therapy comprising

i) completion of trastuzumab up to a total of 9 cycles (~6 months), and
ii) no further pertuzumab or adjuvant chemotherapy.

11.3. Endpoint Definitions

Efficacy endpoint definitions are consistent with the STEEP Guidelines (updated 2021, yet to be published, reference to be added once available).

11.3.1. Primary Endpoint

Relapse-free-interval (RFI) defined as time from registration to invasive local or distant relapse or death from breast cancer in the absence of a previously identified relapse (intercurrent deaths and second primary cancers censored). The primary time-point of interest will be 3 years.

11.3.2. Secondary Endpoints - Efficacy

Relapse-free-survival (RFS) defined as time from registration to invasive local or distant relapse or death from any cause (second primary cancers censored).

Invasive breast cancer free survival (iBCFS) defined as time from registration to invasive local or distant relapse or ipsilateral or contralateral invasive second primary breast cancer (non-breast second primary cancers censored) or death from any cause.

Invasive disease free survival (iDFS) defined as time from registration to invasive local or distant recurrence, new invasive second cancer or death from any cause.

Distant recurrence free interval (DRFI) defined as time from registration to distant recurrence or death from any cause (second primary cancers and intercurrent deaths censored).

Breast cancer-free interval (BCFI) defined as time from registration to invasive local or distant relapse, or ipsilateral or contralateral invasive second primary breast cancer or DCIS or death from breast cancer in the absence of a previously identified relapse (intercurrent deaths and second primary cancers censored).

Overall survival defined as time from registration to death from any cause.

11.3.3. Secondary Endpoints - Other

Treatment pathway adherence: non-adherence is defined as the proportion of patients who receive >9 cycles of trastuzumab or who receive further adjuvant systemic anti-HER2 treatment (e.g. pertuzumab) or chemotherapy prior to recurrence or second primary.

Cost-effectiveness: see Appendix 1 for details.

11.3.4. Exploratory Endpoints

Biomarkers including, but not limited to, tumour infiltrating immune cell populations.

11.4. Statistical Analysis Plan

The primary objective of the study will be assessed via formal hypothesis testing relating to the primary endpoint. In addition, estimates and 95%CIs will be produced for each of the secondary efficacy endpoints for the purposes of completion and transparency. No hypothesis testing is envisaged in relation to these secondary endpoints.

RFI will be analysed using survival analyses methods (e.g. Kaplan Meier graphs), primarily in an evaluable population, defined as all registered patients who complete a total of 9 cycles of trastuzumab (minimum 8 cycles) and who do not receive further adjuvant systemic anti-HER2 treatment (e.g. pertuzumab) or chemotherapy prior to recurrence or second primary. Those patients subsequently found to have residual disease via central review or otherwise will be non-evaluable. RFI will also be analysed in an intention to treat population as it will be important to report estimates using all patients who entered the study. Three year incidence will be reported with exact 95% CIs as the principal time-point of interest. Additionally 5- year estimates will also be reported with exact 95% CIs. Although the primary endpoint is a composite endpoint including local and distant recurrences, number of the local and distant recurrence will be reported. In the unexpected scenario that the incidence of intercurrent events is higher than anticipated an analysis incorporating competing risks will be explored.

Secondary disease related endpoints will be analysed using methodology similar to that used for the primary endpoint. Estimates at 3 and 5 years will be reported with exact 95% CIs. Treatment pathway adherence will be descriptive in nature, reported as proportions with 95%CIs and graphically as appropriate.

Further details of analysis methods will be specified in a Statistical Analysis Plan in accordance with ICR-CTSU Standard Operating Procedures.

11.5. Internal Pilot

The TMG will meet at approximately 9 months after the start of recruitment to assess the internal pilot phase of the study. Criteria for consideration of continuation of recruitment for the internal pilot phase are determined based on recruitment rates independent of event incidence as follows (see below for interim analyses/stopping rules based on event rates):

The study may close to further recruitment if 9 months after the first site opens to recruitment, the total number of patients recruited is fewer than 20 or fewer than 12 centres are open to recruitment.

This is based on an anticipated initial recruitment rate of 0.4 patients per centre per month, increasing to 0.62 at 12 months and 0.85 at 24 months, enabling recruitment of the full 720 patients within 3 years. This allows for the potential effects of COVID in the rate of site set up as well as acknowledging that sites will increasingly select standard of care regimens that permit study entry once the study is open, justifying the increasing rate per site over time. This will be kept under review depending on sites' capacity as they open.

11.6. Interim Analyses and Stopping Rules

Monitoring of incidence of events: A sequential monitoring plan will be employed with analyses of RFI conducted when median follow-up reaches 12, 24 and 36 months and final analysis when 36 month follow-up data is complete. At each interim analysis the incidence of relapse will be estimated with exact confidence intervals. In calculating the incidence of relapse, total follow-up for each individual will be taken into account and weighted according to incidence of relapse over time as observed from previous studies, i.e. accounting for the proportion of events expected to be observed within given time periods following surgery. A beta spending function will be used to ensure the power for the overall trial is not below 90%. The appropriate betas to use (which will determine the level of the confidence interval to calculate) at each analysis will be determined upfront following simulations with different estimates of design parameters and following discussion with the IDMC prior to any event data being reviewed. Details of the follow-up weighting and betas to be used will be detailed in the statistical analysis plan.

The Independent Data Monitoring Committee (IDMC) will review the estimated incidence of relapse and associated confidence interval at each interim analysis with consideration to stop if the lower limit of the CI around the estimated incidence of relapse is above 4%. For example if the first interim analysis was to use β=0.01, the 3 year event rate would be estimated with a 98% confidence interval. If the lower limit of the 98% confidence interval was >4% the IDMC could consider recommending early stopping due to futility.

A precedent for this approach to monitoring rare events in a single arm de-escalation trial has been set with the 111 trial (48, 61).

12. STUDY MANAGEMENT

12.1. Trial Management Group (TMG)

A Trial Management Group (TMG) will be set up and will include the Chief Investigator, ICR-CTSU Trials Methodology Lead, Surgical Lead, Co-investigators, consumer representatives and identified collaborators, the Trial Statistician and Clinical Trial Managers. Principal Investigators and key study personnel will be invited to join the TMG as appropriate to ensure representation from a range of sites and professional groups. The TMG will meet at regular intervals, and at least annually. Notwithstanding the legal obligations of the Sponsor, and Chief Investigator, the TMG have operational responsibility for the conduct of the study. The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSU.

12.2. Trial Steering Committee (TSC)

The study will fall under the remit of the ICR-CTSU Breast Systemic Trials Steering Committee whose independent membership comprises a Chairman (clinical), statistician, additional clinical members and a consumer representative. The TSC will meet at regular intervals, and at least annually. The TSC will provide expert independent oversight of the study on behalf of Sponsor, and funder. The Committee's terms of reference, roles and responsibilities are defined in a charter issued by ICR-CTSU.

12.3. Independent Data Monitoring Committee (IDMC)

An Independent Data Monitoring Committee (IDMC) will be set up to monitor the progress of the study and will comprise a Chairman and at least two further members with clinical, pathology or statistical expertise (at least one member must be a statistician and one must be a pathologist). Membership of the IDMC will be proposed by the TMG and approved by the TSC. The IDMC will meet in confidence at regular intervals, and at least annually. A statement of non-objection to continuation and/or summary findings and recommendations will be produced following each meeting. This will be submitted to the TMG and TSC, and in exceptional circumstances if required, the main REC and the MHRA. The IDMC will reserve the right to release any data on outcomes or SARs through the TSC to the TMG (and if appropriate to participants) if it determines at any stage that the combined evidence from this and other studies justifies it. The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSU.

13. RESEARCH GOVERNANCE

13.1. Sponsor Responsibilities

The sponsor, as defined by The Medicines for Human Use (Clinical Trials) Regulations 2004 as amended, of HER2-RADiCAL is The Institute of Cancer Research (ICR).

13.2. Participating Site Responsibilities

Responsibilities delegated to participating sites are defined in an agreement between the Sponsor and the individual site. The local Principal Investigator is responsible for the study team and study conduct at the participating site.

14. STUDY ADMINISTRATION & LOGISTICS

14.1. Site Activation

Before recruitment can commence at a site, the site agreement must have been signed by all required signatories, the required study documentation (as specified by ICR-CTSU) must be in place and a site initiation must have taken place. Site initiation may be by teleconference/webinar or by on site visit if deemed appropriate by ICR-CTSU. ICR-CTSU will provide the final confirmation that recruitment can commence at a site.

14.2. Data Acquisition

Electronic case report forms (eCRFs) will be used for the collection of study data. ICR-CTSU will provide guidance to sites to aid the completion of the eCRFs. The Trial Management Group reserves the right to amend or add to the eCRF template as appropriate. Such changes do not constitute a protocol amendment, and revised or additional forms should be used by sites in accordance with the guidelines provided by ICR-CTSU. Study data will be held on secure servers hosted by ICR.

Anonymised routine NHS records will be requested from national registries for all patients in the UK treated for HER2 positive early breast cancer. Pseudoanonymised routine NHS records will requested for the subset of patients participating in HER2-RADiCAL to enable linkage with study data and the collection of follow up data, including data to determine recurrence outcomes if available.

With patient consent, identifiable data (including initials, full name, date of birth, post code, hospital number and NHS or Community Health Index (CHI) number) will be transferred from ICR-CTSU to the national registries in 256 AES encrypted files via a Secure File Transfer Service in accordance with UK General Data Protection Regulation and the Data Protection Act 2018. The anonymised datasets, and matched pseudoanonymised datasets, will be sent to the ICR-CTSU from the national registries in 256 AES encrypted files via a Secure File Transfer Service. Data will be supplied in comma separated variable format, passwords for decryption will be transferred by telephone on receipt of the data from the Secure File Transfer Service. Passwords set by ICR-CTSU will be in accordance with ICR password policy.

Data will be transferred in accordance with UK General Data Protection Regulation and the Data Protection Act 2018 and the combined UK dataset will be analysed within secure servers hosted by the ICR. The ICR has completed the Data Security and Protection (DSP) Toolkit - organisation code 8J303.

14.3. Central Data Monitoring

Once data has been entered on the eCRF by the site personnel, ICR-CTSU will review it for compliance with the protocol, and for inconsistent or missing data in accordance with the study data management plan. Should any missing data or data anomalies be found, queries will be raised for resolution by the site. Any systematic inconsistencies identified through central data monitoring may trigger an on-site monitoring visit.

14.4. On-Site and Remote Monitoring

On-site monitoring visits or remote monitoring sessions may be conducted by ICR-CTSU in order to review essential documentation and carry out source data verification to confirm compliance with the

protocol, in accordance with the study monitoring plan. If an on-site monitoring visit/remote monitoring session is required, ICR-CTSU will contact the site to make the necessary arrangements. Once a date has been confirmed, the site should ensure that full patient notes of participants, including electronic notes, selected for source data verification are available for monitoring. If any problems are detected during the course of the monitoring activities, ICR-CTSU will work with the Principal Investigator or delegated individual to resolve issues and determine appropriate action.

14.5. Completion of the Study and Definition of Study End Date

The study end-date is deemed to be the date of last data capture.

14.6. Archiving

Essential study documents should be retained according to local policy and for a sufficient period for possible inspection by the regulatory authorities (at least 5 years after the date of last data capture). Documents should be securely stored and access restricted to authorised personnel.

15. PATIENT PROTECTION AND ETHICAL CONSIDERATIONS

15.1. Risk Assessment and Approval

This study has been formally assessed for risk and approved by the Sponsor's Committee for Clinical Research.

15.2. Public and Patient Involvement (PPI)

The UK breast cancer research community is recognised internationally for having been at the forefront of PPI involvement in trials with its close working partnership with patient advocacy groups, in particular Independent Cancer Patients Voice, NCRI PPI Group and NCRI Breast CSG PPI membership. Patient advocates have thus been involved in development of the study concept and design from the outset, through: i) membership of the NCRI Early Disease Subgroup of the Breast CSG; ii) evolution of the concept at the UK Breast Intergroup meeting; and iii) UK representation at a Breast International Group led focus group to ascertain cross-national views on reduced treatment burden, including in the light of pCR. Two patient advocate members of the Independent Cancer Patients' Voice group, who are named collaborators and members of the Protocol Development Group, have shaped the research by confirming that the main outcomes being evaluated are important to patients and the interventional cohort design is preferable to a RCT, which would take longer to get answers and need many more patients to be included. The patient advocates have been involved in protocol design, including methodology, sample collection and patient follow-up. Input from patient advocates has shaped the patient information materials and consent forms, which builds specifically on the materials developed for the CRUK PRIMETIME avoidance of radiotherapy study and the SWAT based Information Giving Study (62, 63). The patient advocates are key members of the study team and will be members of the Trial Management Group, with a role in overseeing the day-to-day management and the progress of the study, and will also have an important role in communicating the study results to patients and the public. In addition, in terms of study oversight, patient advocate representation is included as part of ICR-CTSU's Breast Systemic Therapy Trials TSC.

15.3. Ethics and Regulatory Approvals

The study will not commence at any participating site until the required approvals are in place. ICR-CTSU, on behalf of the Sponsor, will ensure that the study has received ethics approval from a research ethics committee (REC) for multi-centre trials, regulatory approval from the MHRA, HRA approval and relevant NHS Permissions. Before recruiting patients, the Principal Investigator at each site is responsible for obtaining local approvals.

15.4. Study Conduct

This study will be conducted according to the approved protocol and its amendments, supplementary guidance and manuals supplied by ICR-CTSU and in accordance with The Medicines for Human Use (Clinical Trials) Regulations 2004 as amended, the UK Policy Governance Framework for Health and Social Care and the principles of GCP.

15.5. Informed Consent

The Principal Investigator retains overall responsibility for the conduct of research at their site; this includes obtaining informed consent from participants. The PI must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to do so in accordance with the ethically approved protocol, principles of Good Clinical Practice and Declaration of Helsinki.

Patients should be asked to sign the current ethics approved HER2-RADiCAL consent form at study entry after receiving both verbal and written information about the study, having been given sufficient time to consider this information. All consent forms must be countersigned by the Principal Investigator or a designated individual. A signature log of delegated responsibilities, listing the designated individuals and the circumstances under which they may countersign consent forms, must be maintained at the participating site. This log, together with original copies of all signed patient consent forms, should be retained in the Site Investigator File and must be available for inspection. The current ethics approved HER2-RADiCAL patient information sheets should be provided in addition to any standard patient information sheets that are provided by the site and used in routine practice.

15.6. Patient Confidentiality

Patients will be asked to consent to their full name being collected at study entry in addition to their date of birth, hospital number, postcode and NHS number or equivalent to allow linkage with routinely collected NHS data and ensure accuracy in handling biological samples. All information about patients will be coded with the patient' Study ID and will be stored securely. It will be treated as strictly confidential and nothing that might identify any patient will be revealed to any third party.

Each investigator should keep a separate log of all participants' Study IDs, names, addresses and hospital numbers. The investigator must retain study documents (e.g. participants' written consent forms) in strict confidence. The investigator must ensure the participants' confidentiality is maintained at all times.

Representatives of ICR-CTSU and the regulatory authorities will require access to participants' hospital notes for quality assurance purposes. ICR-CTSU will maintain the confidentiality of participants at all times and will not reproduce or disclose any information by which participants could be identified.

15.7. Data Protection

All investigators and study staff must comply with applicable data protection laws at all times.

15.8. Insurance and Liability

Indemnity to meet the potential legal liability of investigators participating in this study is provided by the usual NHS indemnity arrangements.

16. FINANCIAL MATTERS

This study is investigator designed and led. The ICR has received funding from the National Institute for Health Research (NIHR) for the central coordination of the study. The study meets the criteria for R&D support as outlined in the Statement of Partnership on Non-Commercial R&D in the NHS in

England. The study is part of the NIHR Clinical Research Network (CRN) portfolio by virtue of its funding by the NIHR, and for similar networks in the three devolved UK nations. NIHR CRN (and their equivalents in the devolved UK nations) resources should therefore be made available for the study to cover UK specific research costs.

17. PUBLICATION POLICY

The main study results will be published in a peer-reviewed journal, on behalf of all collaborators. The manuscript will be prepared by a writing group, consisting of members of the TMG. Participating clinicians may be selected to join the writing group on the basis of intellectual and time input. All participating clinicians will be acknowledged in the publication.

Any presentations and publications relating to the study must be authorised by the TMG. Authorship of any secondary publications e.g. those relating to sub-studies, will reflect intellectual and time input into these studies. Authorship of all publication will usually be in accordance with ICMJE guidance.

No investigator may present or attempt to publish data relating to the HER2-RADiCAL study without prior permission from the TMG.

18. ASSOCIATED STUDIES

18.1. Patient Reported Outcomes

Patient reported outcomes (PRO) collection will be incorporated into the study via substantial amendment once the precise design of the PRO substudy has been defined. EQ-5D and socioeconomic data will be collected however the questionnaires that will be used to collect this data will be included via substantial amendment after the main study applications have been approved. Patient reported outcomes will initially be collected using paper questionnaires, an electronic patient reported outcomes (ePRO) system will be set up after the main study is open to recruitment and patients will switch to electronic reporting. Further details are provided in Appendix 1.

18.2. Studies Within a Trial (SWAT): Information Giving Study

A SWAT focussing on optimal provision of patient information in the context of systemic treatment de-escalation building on similar work on radiotherapy in PRIMETIME (62, 63) will be developed in parallel with study initiation and subsequently incorporated via substantial amendment (Appendix 2).

18.3. Tissue Sample Collection and Central Pathology Review

Tissue samples must be collected in accordance with the HER2-RADiCAL Pathology and Tissue Sample Collection Guidelines. Principal Investigators are asked to nominate a Lead Pathologist/Biomedical Scientist (BMS) who will be responsible for overseeing the labelling and shipment of samples.

For the translational substudies (details of which are provided in Appendix 3), archival FFPE blocks of primary tumour and nodal samples (including pre-neoSACT diagnostic biopsies and post-neoSACT surgical excision specimens), if applicable, will be requested by ICR-CTSU at a later date. Instructions for the shipment of samples will be provided in the HER2-RADiCAL Pathology and Tissue Sample Collection Guidelines.

A tissue sample of recurrent disease should be provided at relapse for patients who have a routine biopsy or surgical procedure conducted as part of their standard care and where excess tissue is available and the patient has provided consent.

Samples will be stored at the Human Biomaterials Resource Centre (HBRC) in Birmingham and at The Institute of Cancer Research.

If diagnostic material is urgently needed by the local site team, please contact the HER2-RADiCAL Trial Manager (her2radical-icrctsu@icr.ac.uk) who will arrange for immediate retrieval of the material and return to the Pathology Department from which it was requested. In cases where material is sparse the Pathology Lead will ensure that sufficient material remains for diagnostic purposes.

Please be aware that it will be the responsibility of the local research team to obtain their patient's pathology material if the material is stored at a separate site to the registering hospital.

Archival tissue from the post-neoSACT surgical excisions of 100 patients will be reviewed centrally by the Central Histopathology Review Pathologists to confirm pCR. It is anticipated that this will comprise 2-5 patients from each participating diagnostic Pathology Laboratory. The HER2-RADiCAL study team will identify those patients selected for central pathology review and request their corresponding scanned images/slides for scanning. The slides of tumour bed and lymph nodes (as minimum) will be scanned either locally (if the facility of scanning is available) or sent to the Human Biomaterials Resource Centre (HBRC), University of Birmingham, at the address below for central scanning:

Human Biomaterials Resource Centre (HBRC)
University of Birmingham
Hospital Drive
Birmingham, B15 2TT

Local pathologists should ensure that accurate documentation of block taking is included in the histology reports from the surgically excised lesions (as per UK guidelines) and where possible to use the Residual Cancer Burden (RCB) calculator (http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=jsconvert3) in order to allow the central review to re-assess and, for example, to determine tumour size in at least two dimensions if a residual has been identified. If a residual invasive carcinoma is identified, the patient will be considered non-evaluable and central pathology review results feedback to the originating team. Further management of the patient will then be at the discretion of the originating team.

19. REFERENCES

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A1. HEALTH ECONOMICS

A1.1 Rationale for the health economic approach

The UK process for HTA developed by NICE, including the Cancer Drugs Fund, provides a defence against the rapidly increasing costs of cancer drugs, but despite this treating HER2+ early breast cancer is now one of the most expensive cancer pathways. This is due to several factors: (i) rapid implementation of several blockbuster pharmaceuticals, (ii) pharma-driven patient eligibility definitions, (iii) non-evidence based treatment durations, (iv) additive rather than replacement new therapies, (v) "evergreening" strategies such as on-patent subcutaneous alternatives to IV trastuzumab. This is also despite the PERSEPHONE RCT providing evidence for the de-escalation of 12 months trastuzumab to 6 months, with significant cost savings, perhaps in part because it took over 10 years to complete, during which time the introduction of newer drugs into the clinical pathway means that it now lacks generalisation to the whole HER2+early breast cancer pathway. Other attempts to curtail rapidly escalating pharmaceutical costs for cancer such as 'Value Based Pricing' and various proposed risk sharing schemes have also failed to check costs without losing clinical efficacy. New approaches are therefore needed to deal with the challenges of a rapidly developing treatment pathway with additional new therapies: what is needed are new biomarker options (such as pCR) to better individualise treatment options.

A1.2 Model concept

A NICE-standard health economic decision model will be specified at the outset of the study, building on our previous UK modelling and will use mathematical simulation to represent the UK clinical pathway for early breast cancer. Simulated patients transition between health states including, 'disease free', 'local recurrence', 'new primary cancer', 'distant recurrence', 'cardiac toxicity' and 'cause-specific death'.

The primary output from the health-economic model is cost-effectiveness defined as lifetime cost per QALY. The comparators in the economic model are:

Pathway A MAXIMUM THERAPY HYPOTHETICAL COMPARATOR: (e.g. 1 year trastuzumab +/- pertuzumab and anthracycline chemotherapy)

Pathway B INTERVENTION GROUP: pCR-directed de-escalation (6 months/9 cycles trastuzumab and omission of anthracycline in patients achieving pCR)

Pathway C CURRENT OBSERVED STANDARD CARE: as estimated from whole-population UK routine linked data, comprising a mixture of anti-HER2 therapy and chemotherapy options, specified at the beginning and again at the end of the study. Pathway B is embedded within Pathway C.

A1.3 Model data acquisition

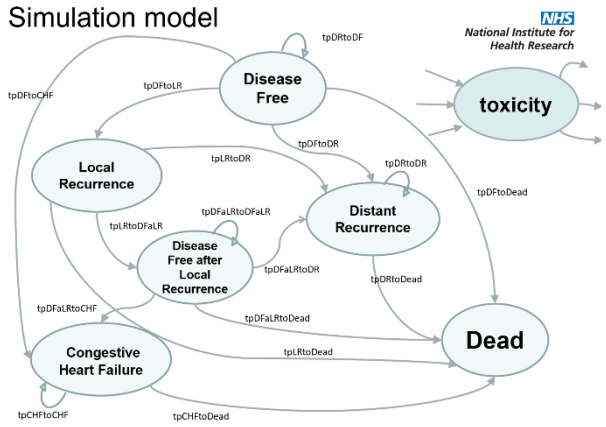
Data informing the economic model will be derived from multiple sources. The underpinning clinical pathways and case-mix description will be taken from data extracts from the cancer registries and SACT datasets in the four UK nations. This will include all HER2+ early breast cancer patients in the UK including those in the HER2-RADiCAL study and those treated in routine care out-with the study. The study team has a track record of accessing and analysing these datasets. Baseline descriptors will include cancer staging variables, co-morbidities (Charlson score derived from inpatient coding), ethnicity, sex, rurality and socioeconomic status. Secondary care healthcare costs and major toxicities during the treatment period and initial follow-up period will be additionally derived from in-patient and out-patient data (HES and SMR) using ICD-10 codes, OPCS codes and standardised HRG-based unit cost assignment. Linkage will be by NHS/CHI number. However, since these datasets do not routinely collect all relapse events, recurrences will only be measurable in the study population using electronic remote data capture, and recurrence rates in the general population will need to be inferred from published literature and prior economic models in this area.

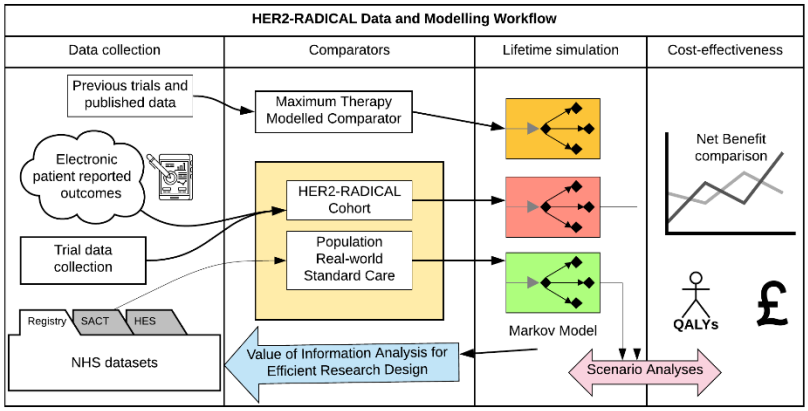
Anonymised routine NHS records will be requested for all patients in the UK treated for HER2 positive early breast cancer. Terms of access to unconsented data (patients who have not consented within HER2-RADICAL) will be in compliance with the General Data Protection Regulation and the Data Protection Act 2018. The combined UK dataset will be analysed within secure servers hosted by The Institute of Cancer Research (ICR). The ICR has completed the Data Security and Protection (DSP) Toolkit - organisation code 8J303.

Quality of life (QoL) data informing the economic model will largely be derived from prior studies that have measured QoL in representative health states that will comprise the model structure. Additional EQ-5D QoL measurement will be obtained in the study population during the study follow-up period using online electronic capture to provide a more granular profile of QoL on- and off- study treatments utilising systems under development as part of ICR-CTSU's CRUK funded CTU Core Programme.

A1.4 Model development, parameterisation and evidence synthesis

The model will be informed by interrogation of real-world data from the Cancer Registries and SACT databases in England, Scotland, Wales and Northern Ireland. Data extracts will start from 2017, allowing the description of a timeline of clinical pathway evolution. This will provide information on patient case-mix with respect to cancer stage, co-morbidity and socioeconomic status. It will also provide data on intended and delivered chemotherapy regimens and anti-HER2 therapy durations and how these change over time with respect to neoadjuvant or adjuvant timing and treatment duration. HER2-RADiCAL registered patients will be a nested cohort within the whole-UK real-world cohort. Treatment effect sizes and health state utilities will be obtained by systematic review and synthesis of the published literature and our previous trials in this area, following best practice methods for evidence synthesis (64). We will also explore any observed opportunities for treatment effect inference that may exist through natural experimentation based on our previous work (65, 66). Costs will be assigned to units of resource consumption using standard NHS reference sources, enhanced by our previous prospective data collection and micro-costing on this topic (67-69). Micro-costing of the pathological response assessment process will be undertaken through consultation or observation of our pathology team.





A1.5 Within-trial measurement of costs and outcomes

Secondary care resource use and medications will be captured using the study case report forms in a manner suitable for the assignment of unit costs. This will be light-touch, relying predominantly on

routine NHS records. In the absence of a randomised comparison, observed QoL/utility outcomes and wider societal costs will be of limited use in directly informing the economic evaluation, however, in addition to obtaining utility parameters from the published literature and previous studies, a QoL/utility profile will be obtained through electronic EQ-5D to aid in the understanding of the impact of toxicity on QoL. Basic baseline and follow-up information will be collected to enable an assessment of the generalisability and transferability of the results including socioeconomic factors, employment/return to work and fulfilment of carer responsibilities.

A1.6 Analysis of uncertainty

The base case model will be evaluated using probabilistic sensitivity analysis with uncertainty in the Incremental Net Benefit (INB) presented using the cost-effectiveness acceptability frontier. We have, however, seen this approach has limited impact on policy in the context of previous oncology de-escalation studies. For this reason, we will undertake best-worst case scenario analysis to estimate the 'maximum acceptable loss' in efficacy that results in a negative INB for a range of willingness-to-pay thresholds. The probabilistic measure 'conditional expected INB' will be used in one-way sensitivity analysis (70). This will permit a more complete understanding, accessible to policy makers, of the potential effect of de-escalation on cost-effectiveness with respect to the competing risks of breast cancer recurrence, new primary cancers and deaths due to cancer, treatment toxicity and other causes.

A1.7 Research value

In the first year of the grant the prototype economic model will be developed and populated by an initial NHS data extract. This will be used to conduct a Value of information Analysis which will allow the ongoing research design and data capture strategy to be maximised in its ability to inform the economic model at the end of the study (71).

A2. STUDIES WITHIN A TRIAL (SWAT): INFORMATION GIVING STUDY

A SWAT focussing on optimal provision of patient information in the context of systemic treatment de-escalation building on similar recently reported work on radiotherapy in PRIMETIME (62, 63) will be set-up after the main study is open to recruitment. Further details of the SWAT will be added via substantial amendment.

A3. TRANSLATIONAL SUB-STUDIES

A3.1 Participation in translational sub-studies

Patient consent to donate archival FFPE blocks and slides of primary tumour and nodal samples (including pre-neoSACT diagnostic biopsies and post-neoSACT surgical excision specimens) for research is mandatory for study entry. Optional consent will also be sought to analyse tissue from any relapsed or metastatic tumour samples that may be collected as standard of care for use in future translational research studies. If relevant to the planned translational work, anonymised copies of routine imaging scans may also be collected. Optional consent will be sought for this.

If provision of FFPE blocks is not possible, 10-20 slides of freshly prepared unstained 4-5 micron sections from the archival tumour block may be provided. Slides/blocks of the consented patients will be retrospectively collected, anonymised and stored at the Human Biomaterials Resource Centre (HBRC) in Birmingham and the Biobank facility at Institute for Cancer Research (ICR). Separate funding will be sought for tissue collection, storage and translational research work.

A3.2 Outline of the translational work

Further funding will be sought for translational studies as the study progresses.

Ki67

A decrease in the proliferation index as determined by KI67 immunohistochemistry has been shown to be predictive of neoadjuvant response and prognostic for better patient survival in different breast tumour subtypes (72). The Ki67 proliferation will be analysed by immunohistochemistry in primary diagnostic core biopsy of all samples and expression correlated with patient disease free and overall survival. Assessment will be done following the guidelines of the International Ki67 in Breast Cancer Working Group (73-75).

Profiling of the tumour microenvironment

Tumour infiltrating lymphocytes (TILs) have been shown to play an important role in determining the response to neoadjuvant chemotherapy in HER2 positive breast cancer (76). Differential expression and co-localisation of immune cells within the epithelial stromal interphase may be related to response and patient survival (29).

The expression and distribution of TILs will be scores on H&E sections by the trial pathologists as per the International Immunooncology Biomarkers Working Group (77). In addition, detailed profiling of the tumour microenvironment by Immunohistochemical/immunofluorescence staining for CD3, CD20, CD8, FOXP3, CD68 will be performed. Other markers of interest that have been shown to be related to the tumour immune response include the tetraspanin family (e.g., CD151 and tetraspanin 6) may also be analysed in tissue sections and correlated with patient survival (78). Techniques for the analysis of the tumour immune microenvironment may develop as the study progresses and other tumour/stromal markers that may become of interest during the course of the study will be considered.

HER2 copy number and ratio

We will explore the hypothesis that the HER2 copy number and HER2/CEP17 ratio as measured by Fluorescence Insitu Hybridisation (FISH) correlate with neoadjuvant chemotherapy response and tumour behaviour in HER2 positive breast cancer (79, 80). We will analyse the HER2 status including HER2 gene copy number and HER2/CEP17 ratio in primary and metastatic tumour tissues and correlate with patient outcome. In addition, the immunohistochemical expression of HER2 will be assessed in the same samples, correlated with HER2 expression and patient outcome.

Genomic characterisation of primary carcinoma

Comparison of the genomic profile between tumours that relapsed/metastasised and those that did not will be done by DNA/RNA extraction and whole genome sequencing (WGS). The ACOSOG Z1041 (Alliance) trial analysis showed a genomic profile for HER2 positive tumours likely to achieve pCR (81). This can be further verified in the current trial with assessment of the relationship of the molecular signature to patient outcome. Other techniques that may be used include RNA extraction, RNA sequencing, exome sequencing and other related techniques. Similar techniques may be applied to tissue obtained from recurrent/metastatic disease.

A4. WHO PERFORMANCE STATUS

Grade	*Performance Status*
0	*Able to carry out all normal activity without restriction.*
1	*Restricted in physically strenuous activity but ambulatory and able to carry out light work.*
2	*Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours.*
3	*Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.*
4	*Completely disabled; cannot carry on any self-care; totally confined to bed or chair.*

A5. GLOSSARY

CI	Confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
DFS	Disease-free survival
EBC	Early breast cancer
eCRFs	Electronic case report forms
EFS	Event-free survival
ePRO	Electronic patient reported outcomes
HER2+	HER2 positive
HR	Hazard ratio
ICF	Informed consent form
iDFS	Invasive disease free survival
IDMC	Independent Data Monitoring Committee
MFS	Distant metastasis free survival
neoSACT	Neoadjuvant systemic therapy
NICE	The National Institute for Health and Care Excellence
OS	Overall survival
pCR	Pathological complete response
PIS	Patient information sheet
PPI	Public and patient involvement
RCB	Residual Cancer Burden
REC	Research ethics committee
RFI	Relapse free interval
RFS	Relapse free survival
RSI	Reference safety information
SAE	Serious adverse event
SAR	Serious adverse reaction
SLNB	Sentinel lymph node biopsy
SMC	Scottish Medicines Consortium
SUSAR	Suspected unexpected serious adverse reaction
SWAT	Study within a trial
TIL	Tumour infiltrating lymphocyte
TMG	Trial Management Group
TSC	Trial Steering Committee
WGS	Whole genome sequencing