Public Health Scotland (PHS)

Scottish Clinical Trials Research Unit (SCTRU)

MRC SUPREMO TRIAL

(BIG 2-04)

(**S**elective **U**se of **P**ostoperative **R**adiotherapy Aft**E**r **M**astect**O**my)

ISRCTN61145589

Scottish Clinical Trials Research Unit Work Instructions

For Centres Participating in the MRC SUPREMO Trial

- *This document must be kept within the Site Investigator File*
- *Updates will be sent to centres accordingly*
- *Please keep a copy of all previous versions*

Final Version 6.0 Effective Date October 2020
All SUPREMO Sites

Document Control: SUPREMO Work Instructions for Centres Participating in the Supremo Trial

Document Control	
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Author(s)	Kathleen Riddle, Fidelis Muturi
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Document History			
Version	**Date**	**Comment**	**Author(s)**
V6.0	October 2020	Minor amendments: ISD and NSS changed to Public Health Scotland and SCTRU and SUPREMO email addresses changed	Fidelis Muturi
V5.0	January 2020	Minor Additions and Minor Amendments Relating to SAE faxing Removed Addition of Appendices 5 & 6 (SAE Forms separate attachments)	Kathleen Riddle & Fidelis Muturi
V4.0	October 2016	Minor amendments and addition of appendices	Niki Couper
V3.0	May 2013	Minor amendments and addition appendices	Eve Macdonald
V2.0	Dec 2015	Minor amendments and addition of the c sub-study instructions	Eve Macdonald
V1.0	May 2006		Nicole Sergenson

SECTION 1 - Patient Consent Procedures

Purpose

To ensure that:

- All patients approached receive optimal information regarding the trial and its sub-studies.
- Informed consent is gained from all patients in accordance with the principles of GCP.
- Informed consent is documented and dealt with appropriately.

Scope

Information and consent procedures within participating centres for all patients:

- Approached to participate in SUPREMO (main study and TRANS-SUPREMO).
- Offered entry into SUPREMO sub-studies (Quality of Life, Health Economics).
- (Cardiac sub-study suspended to recruitment in Dec 2010)

Procedure

Staff at centres participating in the sub-studies should offer all eligible patients the opportunity to take part.

Patients should have a verbal explanation of the trial and its sub-studies and be given a copy of the most recent version of the MREC approved patient information sheet (version 29) for the
-Main trial and TRANS-SUPREMO
-Quality of Life and Health Economics (if participating).

- The patient information sheets should be printed onto hospital headed notepaper.
- The patient information sheets should be accompanied by the standard information given to patients within each centre about radiotherapy.

Where possible, patients should be given at least 24 hours to review the patient information sheet. Consent forms should be printed on hospital headed paper.

All participating patients must sign the most recent versions of the SUPREMO consent forms for the main trial and for the sub-studies (version 29).
Boxes should be initialled (not ticked) to indicate that the patient is consenting to each section of the form.

Care should be taken to ensure that the patient initials all boxes for the parts of the TRANS-SUPREMO study that they have agreed to and provides a separate signature. Only patients who have agreed to take part in the Quality of Life and/or Health Economics sub-studies should sign the Quality of Life and Health Economics consent form. Separate signatures should be obtained for the Quality of Life and Health Economics sub-studies.

There should be 4 copies of the patient consent form. The original should be kept in a folder containing all signed patient consent forms for the centre, a copy should be sent to the trials office. One copy should be given to the patient and the other kept in patient's hospital notes.

The Principal Investigator may nominate responsible person(s) as representatives to sign patient consent forms on their behalf, if this complies with the local policy. These representatives should be stated on the delegation log (refer to appendix 1), which has been signed by the Principal Investigator. The original delegation log should be kept in the Investigator Site File containing all patient consent forms for the centre and a copy sent to the trials office. Any subsequent staff changes should be notified to the trials office on an updated copy of the delegation log which needs to be signed off by the PI.

The SUPREMO consent forms (main trial and sub-studies) should be signed and dated by the patient and clinician taking consent. The patient's SUPREMO trial number should be entered on the consent forms after the patient has been randomised.

The folder containing signed consent forms will be inspected at all monitoring/audit visits to verify that:

- There are signed consent forms for the main trial and sub-studies (as applicable) for all trial patients.
- The correct version of the consent form has been used.
- All forms are appropriately signed, dated and initialled by the patient and clinician
- There have been no trial procedures performed prior to consent being given.

SECTION 2 - Randomisation

Purpose

To explain how a patient should be randomised and the steps that should be taken pre-randomisation.

Scope

All patients consenting to the MRC SUPREMO main trial and associated sub-studies.

Procedure

- Randomisation should occur when radiotherapy is normally discussed.

- The randomisation checklist (page 8/10 of the main trial CRFs) should be completed prior to randomisation and the top copy must be returned to the Scottish Clinical Trials Research Unit, Edinburgh, within **2 weeks of randomisation**.

- Each centre will keep a register of all patients on the Screening Log provided in the Investigator Site File (electronic copies can also be sent upon request) Reasons for not entering patients in the trial will be recorded. The Scottish Clinical Trials Research Unit will request the Screening Summary Form to be returned quarterly to the Trials Office. After surgery, eligibility will be confirmed. Patients who are interested will be given the patient information sheets for the main trial and associated sub-studies and will have the opportunity to ask questions about the trial and have time to consider whether they wish to take part (at least 24 hours after receiving the PIS). Written informed consent for participation will be obtained.

- Consenting patients will be randomised by the Scottish Clinical Trials Research Unit in Edinburgh.

- For UK & Ireland centres - in order to randomise a patient please phone the Scottish Clinical Trials Research Unit on +44 (0) 131 275 7276 or +44 (0) 131 316 4278 (Monday - Thursday 9am-5pm, Friday 9am-4pm UK Time) and ensure you have a copy of the eligibility checklist with all information completed. When randomised, the trial ID and treatment allocation will be given over the phone and then fax confirmation will be sent to the Safe Haven Fax number at site. In the appropriate section at the bottom please sign and date and return to SCTRU fax number on +44 (0) 131 275 7512 to confirm receipt.

- For international centres - please fax a copy of the completed randomisation checklist (pages 8-10 of the main trial CRFs) and a copy of the patient's signed and dated consent form (see comments below for Australia) to the Scottish Clinical Trials Research Unit in the UK on 001 44 131 275 7512. The patient will then be randomised by SCTRU and a copy of the randomisation form with the study ID number and treatment arm will be sent to the Safe Haven Fax number and named recipient at site (due to time differences between the UK and international sites, the confirmation fax returned to the centre may not be faxed until the following day). In the appropriate section at the bottom, please sign and date and return to the SCTRU fax number on 001 44 131 275 7512.

- For sites in UK - please send a copy of the patient consent form(s) by recorded delivery mail to the Scottish Clinical Trials Research Unit (local policies permitting).

- For sites in Australia – please send a copy of the patient consent form(s) to TROG trial coordinator for review

- Once the patient has been formally entered into the trial by the return of the Randomisation form from SCTRU to the site, the GP letter should be sent directly from the centre to the patient's general practitioner.

SECTION 3 - Case Report Form (CRF) Completion and Query Handling

Purpose

- To ensure correct completion of SUPREMO trial CRFs at the required time points.
- To minimise data queries.

Scope

All SUPREMO trial CRFs;
- CRF Version 2, Protocol Version 29
- CRF Version 1, Protocol version 26 & 27
- Cardiac sub-study CRF Version 1
- Cardiac sub-study (Repeat Echocardiograms) CRF Version 1

Procedure

General Instructions

1. Responsibility for the completion of the CRF lies with the Principal Investigator (PI), however, responsibility may be delegated to other appropriately qualified and trained staff by completing the Delegation Log (refer to appendix 1). The Delegation Log should be completed and signed by the PI for each person to whom responsibilities have been delegated.

2. Responsibility for the completeness and accuracy of the CRF remains with the PI who should sign a CRF signature page for each patient, once the patient has completed the trial. This responsibility cannot be delegated.
3. If information has been provided in a verbal communication, it should be detailed in the patient's medical notes.
4. Information recorded on CRFs should be verifiable from the patient's medical notes (Dictated hospital notes alone should not be relied upon, where possible, clinic data, GP letters and summary information should be checked in addition to the dictated notes).
5. If data is not available at a particular visit and the patient will be seen again prior to the allocated time frame of a particular form, it is often helpful to place a reminder in the hospital notes asking for the information required.
6. CRF pages should be completed in a timely manner, signed and dated by the responsible person who completed the page.
7. Top copies of CRFs (with wet ink signatures) must be returned to the Contact at the Coordinating Centre. The bottom carbon copies should be retained in the SUPREMO CRF booklet at centre.

   Name: SUPREMO Trial Team

   Address: Scottish Clinical Trials Research Unit,

Public Health Scotland
Scottish Clinical Trials Research Unit
Area 143A
Gyle Square
1 South Gyle Crescent
Edinburgh, EH12 9EB

8. CRFs and Queries contain confidential patient information and should be forwarded to the coordinating centre in line with local policy on handling confidential patient information.
9. Centres should request further CRF's by emailing **phs.supremo@phs.scot**

General Completion Instructions

1. Data should be entered accurately and legibly with a black or blue ball point pen and using adequate pressure to ensure data is legible across all copies.
2. Errors should be corrected by scoring through with a single line (to avoid obscuring the original data) and a new entry made alongside. Correction fluid or correction tape should never be used. All corrections or additions should be initialled and dated by a responsible person as defined in the delegation log.
3. Header and Footer information should be completed on every page.
4. All boxes should be completed. If the question is not applicable then enter 'NA' in the answer box, if the information is not known then enter 'NK' and if a test or measurement was not done then enter 'ND'. Blank fields will usually result in a data query.
5. Dates should be written in the format dd/mm/yyyy, where day or month is not known enter 'NK'.
6. Where there is no data for a whole page, the headers and footers should be completed and the page scored through with reason (e.g. not required, not done) signed and dated.
7. Information should be recorded in the space provided, do not write additional information in the margin.
8. All patients randomised into the SUPREMO trial will be followed up on an intent to treat basis (unless patient requests to withdraw from the study).

Changes to CRF Pages

1. Where an update is required and the original CRF page has been returned to the coordinating centre, the copy of the CRF held at site should be amended, initialled and dated. A photocopy should be taken and marked "Treat as Original" and signed and dated. The photocopy with wet ink signature and date should be sent to the coordinating centre.

Case Report Form Completion – Main Trial

Patients consented and randomised to protocol version 26 and 27 should complete CRF version 1 for the full trial follow up. Patients consented and randomised to protocol version 29 should complete CRF version 2 for the full trial follow up. Data submitted on the incorrect version of the CRF will not be accepted and will be returned to site for re-completion.

Randomisation Checklist

This form should be completed prior to randomising the patient with exception of allocated treatment, trial number and date of randomisation fields which will be completed after.

- Please ensure patient meets all inclusion/exclusion criteria
- Indicate if the patient is participating in all parts of the TRANS-SUPREMO sub-study
- If patient is taking part in Quality of Life, ensure booklet is completed before the patient finds out their treatment allocation.
- If patient is taking part in the Health Economics sub-study, ensure the correct coloured booklet is given to the patient
- Ensure patient has signed consent forms for main trial and any sub-studies prior to randomisation.

After randomisation the following fields should be completed: Treatment arm, date randomised, trial ID and date that form is completed.

PI to sign and date page 9 once completed.

Initial Clinical Data Form

This form should be completed with the patient present. Please note the following points:

Surgery Details

- If mastectomy was the date of last definitive surgery enter this date in Q1 and score through Q2.
- If patient has a mastectomy, then further surgery e.g. an axillary node clearance then enter the date of last surgery in Q1 and mastectomy date in Q2.
- For DIEP reconstruction select ‘autologous tissue’.

Baseline Cardiac Risk Factors:

- Questions to be completed for all patients.
- Assess patient's physical activity status (referring to *Guidelines for Cardiac Risk Factors* at the start of main CRF Booklet) and tick one box only.

Blood for TRANS-SUPREMO

- If patient is not participating in TRANS-SUPREMO please tick N/A and leave date blank.
- If patient is participating in TRANS-SUPREMO study please tick box to confirm that blood sample has been taken. If blood sample is not taken on day of randomisation, please complete this question when the blood has been taken and return CRF page 12 at this time.
- If patient has consented to tissue collection only for TRANS-SUPREMO then No should be recorded with the comment "Tissue only."
- Please refer to the SUPREMO laboratory manual for guidelines on taking, storing and collection of all blood samples.

Page 1 of the Initial Clinical data form should be returned to Scottish Clinical Trials Research Unit **within 2 weeks** of randomisation.

Neoadjuvant Form

This form is required for all patients randomised to protocol V29. If patient does not receive neoadjuvant systemic therapy, tick No to question 1 and then sign and date form only.

This form should be completed based on assessments of the tumor prior to neoadjuvant systemic therapy.

Mastectomy Pathology Form

This form should be completed post-randomisation.

- Please ensure that Pathology Number recorded relates to the invasive primary tumour, not core biopsy.
- Maximum dimension of invasive component of tumour: Enter the maximum dimension of the invasive component of the tumour only. Do not enter the whole tumour size (invasive + DCIS). For multi focal tumours only the largest invasive tumour size should be entered on the CRF page (not the sum of all invasive dimensions).
- Tumour pathology: If tumour is mixed then record as Other and specify "Mixed" with details

- Do not record DCIS as this is not considered as invasive.
- If tumour is multifocal then record characteristics of largest individual foci.
- If following neoadjuvant therapy, there has been a complete pathological response, please record tumour size as 0mm and tumour type as 'Other' with applicable comment. 'Not specified/unknown' should be selected for Q7-11.
- Total number of nodes examined/ involved: can be from one or more surgical/axillary procedures.
- 'Possible' lymphatic/vascular invasion should be recorded as 'No' with applicable comment.
- Please return this form with anonymised copies of the Histopathology reports for **all** surgeries relating to the primary tumours to SCTRU office. If not all reports relating to primary tumours are provided this may result in a query as SCTRU requires all to confirm eligibility.

Completion of Chemotherapy Form

This form should be completed following completion of chemotherapy.

Please record all chemotherapy, both neoadjuvant and post-operative.

- Protocol v29 patients (CRF V2): Response is required to both Q1 and Q2. Do not leave either question blank. If responses to both questions 1 and 2 are No then proceed to sign and date the page at the bottom leaving the rest of the page blank.
- Protocol V27 patients (CRF V1): If patient did not receive chemotherapy complete header details, score through page with comment 'no chemotherapy' and sign and date form.
- Please indicate the total intended dose of anthracyline given over the whole course of treatment expressed in mg/m2. i.e. if intended dose is 90mg/m2 for 4 courses then 360mg/m2 should be entered. Actual dose should be calculated as above however for total dose anthracycline received
- Please record all taxanes.

Completion Of Radiotherapy Form

This page is required for all patients not only those receiving radiotherapy (header statement on CRF page is incorrect)

- Protocol v29 patients (CRF V2): For patients, who did not receive radiotherapy, tick No to question 1, then sign and date the form and send to SCTRU.
- Protocol V27 patients (CRF V1): If patient did not receive radiotherapy complete header details, score through radiotherapy treatment section with comment 'no radiotherapy'. Acute Radiation Morbidity section of the page must be completed for all patients.

- Question 4: Target absorbed dose should be provided in units Gy.
- Question 15: Please indicate only whether radiotherapy to chest wall as per treatment arm was completed as per local policy. This question does not relate to radiotherapy to medial SCF and/or IMC.

Acute Morbidity - Protocol V27 patients (CRF V1):

- Please tick one column only per organ tissue. (referring to *RTOG/EORTC **acute** morbidity scoring system* at beginning of main CRF Booklet).
- Must be completed for all patients regardless of whether or not they are randomised to radiotherapy.

Initial Follow Up Form

This form should be completed with the patient present and must be completed for all patients. Form should be completed once radiotherapy has been completed (if randomised to RT) or three months after post-operative chemotherapy or three months post-last definitive surgery (if not randomised to receive RT).

Hormone Treatment

- Please indicate all endocrine therapy drugs received and their start and stop dates (if appropriate).
- Please complete Date last known to be alive even if the same date as date of examination.

Acute Morbidity - Protocol V29 patients (CRF V2):

- Please tick one column only per organ tissue. (referring to *RTOG/EORTC **acute** morbidity scoring system* at beginning of main CRF Booklet).
- Must be completed for all patients regardless of whether or not they are randomised to radiotherapy.

12, 24, 36, 48, 60, 72, 84, 96, 108 and 120- Month Follow Up Form

These forms should be completed with the patient present and must be completed for all patients. Form should be completed annually from date of last definitive surgery.

All patients should remain on physical follow up for the full trial follow up (10 years); each patient consents to this at the start of the trial. Any centres that do cease physical follow up post 5 years should confirm their policy in advance and detail how they will conduct follow up for all patients.

- For any patients inadvertently discharged at 5 years' attempts should be made to recall these patients for physical follow up visits.

- If any patients decline physical follow up for specific reasoning (i.e. travelling long distances to site) then telephone based consultations should be scheduled at annual follow up time points so this valuable data can be retrieved. If the data is retrieved by telephone, please annotate on top of the CRF 'Telephone follow up only' and initial an date.
- Please record all start and stop dates for changes in endocrine therapy and Trastuzumab (Herceptin) or any other biological agents.
- If there have been no changes in treatment since previous follow-up, please indicate either No or N/A, please do not leave blank.
- See note on previous page relating to date last known to be alive/date of exam.
- Breast reconstruction, N/A should only be ticked if the patient has had previous reconstruction.

Late Morbidity

- Please tick one column only per organ tissue. (referring to *RTOG/EORTC **late** morbidity scoring system* at the beginning of main CRF Booklet). Please complete this section for all patients regardless whether they have had Radiotherapy or not.

Notification Of New Recurrence/ New Primary Form

To be completed following first locoregional / distant or contralateral recurrence and for all chest wall or locoregional recurrences/ new primaries even if not the first event.

If a previous recurrence has been reported (and a CRF page submitted to SCTRU) and patient has a second Recurrence/New Primary, then a new Recurrence/ New Primary CRF will need to be sent from the site to SCTRU, and not an updated copy of the original Recurrence/New Primary CRF.

Progression/Recurrence details (if applicable and not yet reported)

- If first locoregional recurrence please tick all sites that apply and enter date recurrence confirmed. Tick No if not applicable.
- If first contralateral recurrence please tick all sites that apply and enter date recurrence confirmed. Tick No if not applicable.
- For contralateral breast, indicate date confirmed and type (Invasive or DCIS only). If invasive plus DCIS please tick invasive only. Tick No if not applicable.
- For first distant metastases, indicate date confirmed and list first site(s) of metastases. Tick No if not applicable.
- Pathology number is required for any locoregional/ contralateral or distant recurrences. If no pathology number available, please write reason (i.e. identified on scan) to avoid query.
- For non-breast primary indicate date confirmed and list all sites of new primary. Tick No if not applicable.
- If treatment received for recurrence or new primary, please tick all that apply.

Blood for TRANS-SUPREMO

- If patient is participating in TRANS-SUPREMO study, please tick box to confirm that blood sample has been taken and enter date sample was taken. If sample not taken tick No and add an explanatory comment.
- Please refer to the SUPREMO lab manual for guidelines on taking, storing and collection of all blood samples.

PI to sign and date recurrence/new primary form once completed.

Notification of Death

To be completed on receiving notification of patient's death.

- Please specify main cause of death. If patient's cause of death is cardiac related, specify type of cardiac event. If patient's cause of death is metastatic disease related to primary breast cancer, then select Breast Cancer.
- If patient is found to have an unreported recurrence, then complete recurrence/new primary form.
- Check SAE guidelines to see if patient's death satisfies the criteria for an SAE.

PI to sign and date recurrence/new primary form once completed and complete Notification of Termination CRF.

Notification of Termination

To be completed if patient withdraws from the study due to patient withdrawing consent from the main trial and all sub-studies, if the patient dies, if they have completed all visits or for any other applicable withdrawal reason.

Protocol V27 patients (CRF V1): There is no protocol termination page within the CRF booklet therefore please photocopy protocol termination page within appendix 4 and use this to record any deviations in this set of patients. At study completion the PI should sign page and wet ink copy should be sent to SCTRU.

Protocol V29 patients (CRF V2): Please use protocol termination CRF page 33 at the back of the CRF booklet.

PI to sign and date form only when all information from relevant visits has been completed.

Notification of Protocol Deviation

Please record any protocol deviations for the patient as these occur. A copy of the CRF should be sent to SCTRU as any deviations are recorded so SCTRU have a record of all deviations asap.

Protocol V29 patients (CRF V2): Please use protocol deviation CRF page 34 at the back of the CRF booklet.

Protocol V26/27 patients (CRF V1): There is no protocol deviation page within the CRF booklet therefore please photocopy protocol deviation page within appendix 3 and use this to record any deviations in this set of patients. As above a copy of this should be completed and returned to SCTRU as any deviations are recorded.

- Record any deviations to the protocol on this page. **Start each deviation with the date the deviation occurred.**
- A deviation is defined as: Any departure from the approved protocol, trial documents or any other information relating to the conduct of the trial that does not result in harm to the trial participants and does not significantly affect the study outcomes.
- Examples of deviations may include, but are not limited to:
    - A protocol visit date deviation outside the study visit window;
    - Isolated incident of a missed or incomplete study procedure (e.g. lab test);
    - Isolated incident of a missed or incomplete study evaluation (e.g. exam).

- Any deviations that meet the criteria of a "protocol violation" should be reported to the trials unit immediately. A violation is defined as: Any departure from the approved protocol, trial documents or any other information relating to the conduct of the study which may affect the safety of trial participants or the study outcomes.
- Examples of violations may include, but are not limited to:
    - Failure to obtain informed consent (i.e. no documentary evidence);
    - Enrolment of participants that do not meet the inclusion/exclusion criteria;
    - Undertaking a trial procedure not approved by the main REC, Licensing Authority or local NHS R&D department (unless for immediate safety reasons);
    - Failure to report adverse events, serious adverse events or SUSARs in accordance with the legislation and sponsor and protocol requirements, such that trial participants, or the public, are put at significant risk;

PI to sign on completion of patient's participation in study (patient withdrawal or death). Responsibility for signing this page cannot be delegated to another member of the trial staff.

Case Report Form Completion – Cardiac Sub-study

For patients taking part in the cardiac sub-study cardiac assessment is required at baseline (pre chemotherapy& radiotherapy), post chemotherapy & prior radiotherapy (of given), Post radiotherapy/6 month FU, 12 month FU, 60 month FU, 120 month FU, At any recurrence.

An anonymised copy of the ECG performed at each visit should be provided along with an anonymised copy of the ECHO report and DVD if the centre is performing repeat ECHO's.

Cardiac History

- A Y/N response is required for each of; Aspirin, Statin, ACE inhibitors, Betablockers and Other cardiovascular drugs. Please do not tick or cross boxes as this will result in a query.

Clinical Examination

- Clinical signs of heart failure should be initialled and dated by a clinician.
- Refer to cardiac CRF page 1 for NYHA classifications.

ECG requested/ECHO requested

- If and ECG or ECHO has not been performed leave this box blank. Only check the box is the ECG or ECHO has been performed and a copy of any reports can be provided.

Query Handling

Data Queries will be raised where;

1. Forms are incomplete, unsigned and/or undated
2. Patient initials, randomisation centre, date of birth and SUPREMO Trial Number do not exactly math those given at randomisation
3. Forms are completed before treatment has been completed
4. Questions have not been answered and/or left blank – All questions should be answered unless clearly stated to be skipped on the CRF.
   Time periods do not match.

SCTRU will issue all data queries, and /or requests for outstanding Case Report Forms, via a spreadsheet and send it to the site by email on a 3-4 monthly basis. Query responses should be **written on the spreadsheet response field and new copies/amended copies of CRFs should not be submitted as responses.**

The completed spreadsheet, signed and dated 'sign off sheet' should be sent to the SUPREMO inbox at **phs.supremo@phs.scot**

Sign off Sheet – *To ensure compliance with GCP, please print, sign and scan 'Sign off sheet' and return with query responses.*

When responding to queries;

1. Queries should be answered by an authorised individual as per the delegation log.
2. The original CRF page **should not** be amended, when answering a query.
3. Photocopies of the CRF are not acceptable and are not required.

SECTION 4 - Serious Adverse Events

Purpose

To explain how to proceed in the event of a serious adverse event.

Scope

All patients consenting to the MRC SUPREMO trial and its sub-studies.

Procedure

The SCTRU SAE/SUSAR report form (UK- Version 4, October 2020 and EORTC-Version 3, August 2006) to be used for reporting any SAE.

Centres should;

- Use this form (Appendix 5 for UK and International) and (Appendix 6 for EORTC) to report all serious adverse events, within 24 hours of the PI/site becoming aware of the event.
- Complete 'Report type box' by ticking; 'Initial'/'Follow up' on page 1 of the SAE Report Form.
- These must be completed, signed and dated by the investigator responsible for the patient. The forms must be sent by email to **phs.sctru@phs.scot**
- Event outcome information, once known, should be completed on the original SAE form and emailed to **phs.sctru@phs.scot**. Please sign and date any amendments to the original SAE form.
- SAE reporting should not be delayed because of missing signatures and/or final diagnosis.

Please note that Centres should NOT;

1. **Send SAE Reports/Forms/correspondence by POST.**
2. **Send Reports/Forms/correspondence by fax as the SCTRU Fax machine has now been decommissioned.**

The trials office will;

- Email the site to acknowledge receipt of the SAE.

- Allocate an SAE number. If the PI at site assesses the SAE to be unexpected then the SAE will be forwarded to the CI for his assessment.
- Email the reporting centre with a request for additional information (if required).
- Inform the Principal Investigator if an SAE is evaluated as a SUSAR.
- Comply with Regulatory guidelines on reporting of SAEs.
- All SAEs will be reported to the SUPREMO Trial DMEC and relevant ethics committee on an annual basis as a line listing.

Definition Of SAEs

ICH GCP defines an SAE as any untoward medical occurrence as shown in Box 1:

BOX 1

- Results in death
- Is life-threatening *
- Requires in-patient hospitalisation ** or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in offspring of patient regardless of time to diagnosis)
- Is an important medical event (an event that jeopardizes the patient or may require intervention to prevent one of the other outcomes listed above)

** The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.*

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

Other important medical events that may not result in death, are not life threatening, or do not require hospitalisation may be considered as serious adverse events when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed in Box 1.

The SUPREMO trial uses standard radiotherapy schedules and unexpected serious adverse events are unlikely to occur. However, all SAEs will be reported to the Data Monitoring and Ethical Committee. Expected adverse events from radiotherapy include skin reactions leading to chest wall tenderness and itching. Skin reactions are usually mild but are occasionally severe. Chest wall pain, usually mild and intermittent can occur. Rarely, osteoradionecrosis of the ribs can occur. Radiation pneumonitis can occur in 1% of patients if treated with tangential fields to the chest wall only. Cardiac damage may occur as a late effect.

SAEs should be reported if they occur during radiotherapy or within 30 days of the last radiotherapy session (fraction), whether or not they are related to the randomised treatment. They should also be reported if they occur at an equivalent time point in patients who are randomised to receive no radiotherapy.

In addition, any toxicity assessed as a Grade 4 or 5 Acute or Late Morbidity Score (see section 9 of the protocol) must be reported on a SAE/SUSAR report form. This applies for the entire follow-up period for the trial.

Patients who are consented and randomised before chemotherapy may experience adverse events related to their chemotherapy. Any chemotherapy related SAEs that may, in the judgement of the responsible clinician, impact upon the delivery of the randomised treatment in SUPREMO should also be reported using the appropriate SAE/SUSAR form.

Table 1 lists the expected adverse events from chemotherapy which should not be reported as SAEs within the SUPREMO trial.

Table 1:

Chemotherapy related SAEs that require reporting	Chemotherapy related SAEs that do not require reporting on SAE/SUSAR form (unless they impact on delivery of the randomised treatment)
1. Wound infections 2. Necrosis of the mastectomy skin flaps 3. Any cardiac event 4. Development of any other serious medical condition between date of consent and planned start of radiotherapy (or equivalent period for those patients randomised to not receive radiotherapy)	Hospitalisation due to: 1. Neutropenia 2. Febrile neutropenia 3. Diarrhoea 4. Infections, including those to Hickman line, catheter 5. Pyrexia 6. Sore throat 7. Nausea or vomiting 8. Cellulitis

SECTION 5 – TRANS-SUPREMO study, Cardiac study and Pathology audit

This section applies only to the centres taking part in the TRANS-SUPREMO study, cardiac study and pathology audit.

Purpose

To clarify the procedure to be followed for blood and tissue block collection.

Scope

All patients taking part in TRANS-SUPREMO, cardiac sub-study and pathology audit.

Procedure

Please refer to MRC SUPREMO (BIG2-04) TransSupremo only Laboratory Manual Version 5, 20/04/2016, TransSupremo and Cardiac Sub Study Lab Manual V6, 20/04/2016 or the EORTC Lab Manual V5, 20/04/2016 in the first instance. These manuals detail all procedures for processing blood and tissue block collection. For any further questions please direct these to; **phs.supremo@phs.scot** or Telephone number 0131 275 7085/7074.

<u>Pathology block, ECG and ECHO payments</u>

Payment of £15 will be issued for retrieval of one representative tumour block from primary/recurrence invasive tumour for each patient. Please only send one representative tumour block for each patient. A surgical resection specimen is required do not send core biopsy.
Payment of £100 will be paid for every ECHO and £10will be paid for every ECG sent to SCTRU for patients who have consented to the Cardiac Sub Study.

SCTRU will request finance details from each centre. PO's will be raised in batches (approx every 6 – 12 months) for any pathology blocks, ECHO and ECG that have been received. Invoices are then requested quoting PO ref at which point payment will be issued.
If you are aware that no finance details have been given for your centre yet please email **phs.supremo@phs.scot** and we will inform you of the information required to set up on our financial systems. Please do not invoice directly as this will not be processed unless sent to the correct address which will be given on PO when raised.
For any invoicing queries please contact **phs.supremo@phs.scot**.

SECTION 6 - Quality of Life

This section applies only to the centres taking part in the Quality of Life (QoL) study.

Information Given To Patients Completing the Questionnaires

Purpose

To clarify information the patient should receive in order to complete the QoL questionnaires.

Scope

All patients receiving the QoL questionnaires.

Procedure

- All patients should have a verbal explanation of the QoL questionnaire; this includes an explanation about how and when the booklets are to be completed.
- It should be explained to the patient that the first booklet will be completed at clinic prior to being told their study treatment.
- It should be explained to the patient that subsequent booklets at 1, 2, 5 and 10 years will be sent to the patient directly from the Centre for Population Health Sciences following confirmation of the patient's suitability to receive the booklet and confirmation of patient address from their GP.
- It should be explained to the patient that the subsequent booklets should be returned to the QoL co-ordinator using the prepaid envelope provided, the booklet should be returned promptly and the necessary part of the demographic form completed if they change address or GP.
- The patients should be encouraged to ask questions and told where to go for help if this is needed with subsequent booklets (member of staff at the hospital or the QoL co-ordinator).
- It should be explained to the patient that:
    - They should not think too long over the questions.
    - There are no right or wrong answers.
    - Their own personal answers should be given.
    - If there are no tick boxes beside the questions the patient should circle the most appropriate answer.
    - All questions should be answered.
    - To please be aware of the timescales of the questions, some refer to the last week and some to the last month.
- It should be reiterated to the patient that the information will be kept and analysed anonymously with the exception that a particularly high score on the anxiety and depression scale (HADS) will result in their GP being informed.

Completing the Baseline Booklet

Purpose

To describe how the Quality of Life Baseline Booklet should be administered and completed.

Scope

All sites taking part in SUPREMO Quality of Life.

Procedure

- The baseline booklet will be given to the patient once they have had a verbal explanation of the QoL study, time to read the patient information leaflet and complete the consent form.
- The baseline booklet will be given to the patient once they have consented to the study but before they are randomised.
- The patient will be given adequate time and privacy to complete the baseline booklet within the centre's grounds.
- Any relative or companion should be discouraged from answering on the patient's behalf.
- An appropriate member of staff should be on hand to offer assistance with completing the form but not to help with the answers.
- If required the questionnaires can be read to the patient in an interview style but the questions must be read verbatim.
- At no point should the member of staff administering the questionnaire:
    - Rephrase or modify any of the questions.
    - Suggest answers to the patients.
    - Ask the patient to amend an answer that perhaps looks wrong (i.e. if two answers are circled).
    - Discuss any issues raised by the patient as a result of completing the questionnaire, before the questionnaire has been completed and handed back.
    - Allow the patient to remove the booklet to complete at a later date.
- The appropriate member of staff will then check the baseline booklet for completeness. Some questions are of a sensitive nature and patients may prefer not to answer, please do not ask the patient to complete an individual question left blank, however, do check (for example) that two pages have not been turned over together etc.
- The demographic form should be checked to ensure all information has been completed as far as possible, it is important that the patient writes their full name (including marital status) and as much of their GP's name, address and phone number as they know.

- The baseline booklet once completed will be returned to the Centre for Population Health Sciences at the University of Edinburgh.

  SUPREMO Trial administrator
  Edinburgh University- Medical School
  Teviot Place
  Edinburgh
  EH8 9AG

- The patient's unique trial number must be added to the booklet following randomisation.

Demographic form and Change of Contact Details form

Demographic and change of address forms are included in the QoL booklets for patients to complete if their details have changed since the last time they received a QoL booklet. It is important that the QoL coordinator is informed of any changes to the patient or GP contact details.

Clinical feedback

Patients who obtain statistically significant scores on the combined anxiety and depression scale (HADS) should be clinically assessed to identify whether or not they exhibit case level disturbance, warranting intervention. When patients are first asked to take part in the QoL study they should be asked to consent to information about high HADS scores being passed to their doctor. High scores on the HADS will be notified to the patient's GP by letter from the Centre for Population Health Sciences.

SECTION 7 - Health Economics Sub-study

This section applies only to the centres taking part in the Health Economics sub-studv.

CRF completion guidelines

Purpose

- To ensure correct coloured Health Economics patient diary is given to
- To ensure correct completion of SUPREMO Health Economics sub-study CRFs at the required time points.

Scope

- All patients consented to the Health Economics sub-study and receiving

Procedure

- The Health Economics patient diary should be given to the patient on date of randomisation, to take away and complete.
- All patients should have a verbal explanation of the Health Economics patient diary; this includes an explanation about how and when the patient diary is to be completed.
- It should be explained to the patient that the patient diary should be completed based on visits the patient makes to a health professional within the specified timelines.
- Patient should be given a freepost envelope and coloured patient diary based on the following criteria:
    - If the patient is randomised to receive radiotherapy and received post-operative chemotherapy, they will receive a red booklet
    - If the patient is randomised to receive radiotherapy and received surgery and hormonal therapy alone OR neoadjuvant systemic therapy and surgery +/- postoperative hormonal therapy, they will receive an orange booklet
    - If they are randomised to not receive radiotherapy, but did receive post-operative chemotherapy, they will receive a blue booklet
    - If they are randomised to not receive radiotherapy and received surgery and hormonal therapy alone OR neoadjuvant systemic therapy and surgery +/- postoperative hormonal therapy, they will receive a green booklet
- The patients should be encouraged to ask questions and told where to go for help if this is needed with subsequent booklets (member of staff at the hospital or the QoL co-ordinator).
- It might be beneficial to take the Health Economics patient diary to any health professional visit within the specified timelines for recording visits.
- All visits to a health professional (including GPs and nurses) should be recorded.
- Outline the timelines for that patient diary;
    - Red booklet - they will be asked to record information about their radiotherapy appointments and details of any visits to a health professional during the period following their post-operative chemotherapy and the start

of their radiotherapy, during their course of radiotherapy and during the period up to 8 weeks after the completion of radiotherapy.
    - Orange booklet - they will be asked to record information about radiotherapy appointments and details of any visits to a health professional during the period following the date of last surgery and the start of radiotherapy, during their course of radiotherapy and during the period up to 8 weeks after the completion of radiotherapy.
    - Blue booklet - they will be asked to record any visits to a health professional during the first five months following the completion of their post-operative chemotherapy.
    - Green booklet - they will be asked to record any visits to a health professional during the first five months following the date of last surgery (either mastectomy or axillary clearance).
- Explain to the patient that the diary can be returned to the Research Nurse or clinic health professional or returned in the freepost envelope provided once completed.
- Booklets should be returned to;

SUPREMO Trial administrator
Edinburgh University- Medical School
Teviot Place
Edinburgh
EH8 9AG

SECTION 8 – Radiotherapy QA Programme

Purpose

To ensure required documentation is sent to the QA coordinator at Mount Vernon Hospital for the trial Radiotherapy QA programme.

Scope

All patients entered into MRC SUPREMO trial.

Procedure

- The Radiotherapy QA coordinator will request copies of plans, together with verification images, for the first 5 patients randomised to receive radiotherapy, from each centre (radiotherapy treatment centre). Before any copies of treatment records are sent for central QA review, any personal identifiers (patient name, medical record/hospital ID) must have been removed and replaced with the patient's SUPREMO Trial Number and initials.

- The QA team will then collect 1 in 10 plans, selected at random, to make sure the protocol is being followed. These must be anonymised prior to sending to the QA team and will be required to undergo TLD measurements, probably using TLD supplied by the UK RT QA team.

APPENDIX 1

MRC SUPREMO (BIG2-04) Trial Duties Delegation Log – Version 4

Principal Investigator:	……..	**Centre Number:**	
Hospital:	……	**MREC Number:**	05/S0501/106
Radiotherapy Treatment Centre:	……	**ISRCTN Number**	61145589

Responsibility key

1.	Read current version of protocol (version 29.1 June 2019)	9.	Enter data into CRFs & resolve data queries
2.	Explain SUPREMO trial to subject	10.	Record serious adverse events
3.	Obtain informed consent	11.	Inform pathologist when patient consents to TRANS-SUPREMO for release of block
4.	Record medical history	12.	Other, (*Specify*)……
5.	Send copy of signed Consent Forms to phs.supremo@phs.scot at SCTRU	13.	Other, (*Specify*)……
6.	Perform physical examination in accordance with protocol for SUPREMO cardiac sub study	14.	Other, (*Specify*)……
7.	Take blood samples	15.	Other, (*Specify*)……
8.	Process laboratory samples	16.	Other, (*Specify*)……

Authorised Signatory	Signature	Initials	Responsibilities (enter relevant numbers from table above)	Dates	PI Signature
Name: Position: Principal Investigator				From:. …/…./…. To:. …/…./….	

MRC SUPREMO (BIG2-04) Trial Duties Delegation Log

Authorised Signatory	Signature	Initials	Responsibilities (enter relevant numbers from table above)	Dates	PI Signature
Name: Position				From:. …/…./…. To:. …/…./….	
Name: Position				From:. …/…./…. To:. …/…./….	
Name: Position				From:. …/…./…. To:. …/…./….	
Name: Position				From:. …/…./…. To:. …/…./….	
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MRC SUPREMO (BIG2-04) Trial Duties Delegation Log

Authorised Signatory	Signature	Initials	Responsibilities (enter relevant numbers from table above)	Dates	PI Signature
Name: Position				From:. …/…./…. To:. …/…./….	
Name: Position				From:. …/…./…. To:. …/…./….	
Name: Position				From:. …/…./…. To:. …/…./….	
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MRC SUPREMO (BIG2-04) Trial Duties Delegation Log

Name: Position				From:. …/…./…. To:. …/…./….
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Principal Investigator to sign at close of trial Date

APPENDIX 2
SUPREMO Trial Schedule –Protocol Version 29.1

Visits (a)	Patients involved	Screening	Post (+/-) chemo pre (+/-) RT	Post (+/-) RT	1 yr	2 yr	3 yr	4 yr	5 yr	6 yr	7 yr	8 yr	9 yr	10 yr	Recurrence[2]
Investigations		Baseline 1	2	3	4	5	6	7	8	9	10	11	12	13	
Informed consent	All	X													
Medical history & examination (b)	All	X		X	X	X	X	X	X	X	X	X	X	X	X
Staging tests	All	X													
Contralateral mammography	All	X			A mammogram of the opposite breast, if appropriate, is recommended at least in alternate years for 10 years from the date of mastectomy										
Blood sampling	If consented to TRANS-SUPREMO	X													X
Tumour paraffin block from primary tumour[1]	All	X													
Tumour paraffin block at recurrence if available[2]	All														X
Acute/ Late morbidity[3]	All			X	X	X	X	X	X	X	X	X	X	X	
Cardiac symptoms and examination	If consented to cardiac sub study	X	X[4]	X	X				X					X	X
Blood sampling for BNP	If consented to cardiac sub study	X	X[4]	X	X				X					X	X
Electrocardiogram	If consented to cardiac sub study	X			X[5]				X[5]					X	X[5]
Echocardiogram (c)	If consented to cardiac sub study	X			X[5]				X[5]					X	X[5]
QOL and EQ5D economic assessment (d)	If consented to QOL sub study	X			X	X			X					X	

(a) Patients in the control arm MUST follow the same follow up schedule as irradiated patients.

(i) The only exception are patients in the cardiac substudy who receive chemotherapy. This is the only group of patients who must attend a post chemotherapy visit.

(ii) For patients receiving chemotherapy, follow up will be on completion of radiotherapy or at 3 months after chemotherapy in non-irradiated patients.
For patients not receiving chemotherapy follow up will be on completion of radiotherapy or at 3 months after surgery in non-irradiated patients.

(b) Questioning for symptoms of recurrent breast cancer, examination of loco-regional area and other relevant clinical areas for evidence of recurrence depending on clinical features.

(c) In centres where isotope ventriculography is the standard examination for patients requiring anthracycline containing chemotherapy, an echocardiogram will also be required at baseline. Echocardiography will be used for all subsequent time points in the study.

(d) Baseline (pre randomisation) quality of life assessment will be conducted in the clinic. All subsequent quality of life assessment questionnaires will be mailed to the patient.

[1] Tumour blocks required from all patients for purpose of audit. Tissue microarrays only constructed if patient consented to TRANS-SUPREMO.
[2]Recurrence defined as local and/or distant relapse and/or development of a contralateral breast primary. Blood and tissue samples should be obtained prior to any subsequent treatment commencing.
[3]Morbidity will be measured using the RTOG/EORTC Radiation morbidity scoring system in all patients regardless of whether they are allocated radiotherapy or not. Any toxicity assessed as a Grade 4 or 5 Acute or Late Morbidity Score must be reported on a SAE/SUSAR report form.
[4]For patients in the cardiac substudy not receiving chemotherapy, the post chemo/pre RT visit will not be required.
[5]Echocardiogram and ECG repeated if B type natriuretic peptide (BNP) exceeds threshold value or clinical features warrant it.

MRC SUPREMO (BIG 2-04)

Selective **U**se of **P**ostoperative **R**adiotherapy Aft**E**r **M**astect**O**my)

NOTIFICATION OF PROTOCOL DEVIATIONS

Patient Initials: ……

Patient Trial No: ☐☐☐☐☐☐☐ **EORTC Centre No (if applicable):** ☐☐☐☐

Protocol Deviations

1. ……

2. ……

3. ……

4. ……

5. ……

6. ……

7. ……

8. ……

9. ……

10. ……

Signature of Principal Investigator …… **Date ……**

Printed Name of Principal Investigator ……

Date form completed: *Signed:*……

Please return top copy to ISD CCTT (see front of booklet) *Printed Name (Capitals)*……

APPENDIX 4

MRC SUPREMO (BIG 2-04)

Selective **U**se of **P**ostoperative **R**adiotherapy Aft**E**r **M**astect**O**my)

NOTIFICATION OF TERMINATION

Patient Initials: ……

Patient Trial No: ☐☐☐☐☐☐☐ **EORTC Centre No (if applicable):** ☐☐☐☐

1) Has patient withdrawn early from the study? Yes* ☐ No ☐

2) * If **YES,** please state reason that the patient withdrew early:

Withdrew consent ☐

Death ☐

Other ☐ Please state reason……..

I confirm that all recorded data for this patient is correct.

Signature of Principal Investigator …… Date ……

Printed Name of Principal Investigator ……

Date form completed: *Signed:*_____

Please return top copy to ISD CCTT (see front of booklet) *Printed Name (Capitals)*_____