



Study Manual

V1.0

10th September 2021

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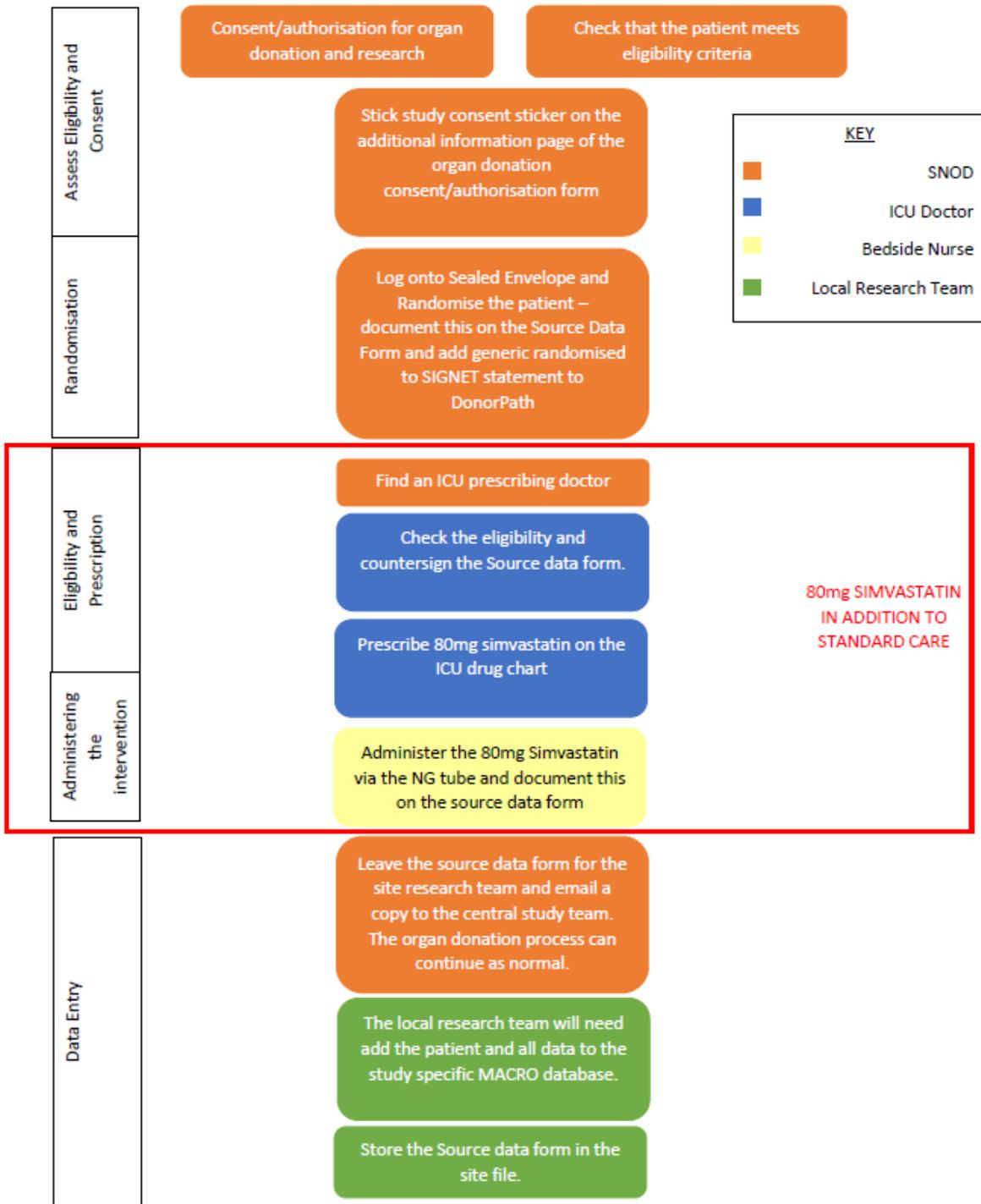
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Abbreviations and Glossary

CI	Chief Investigator
CLOD	Clinical Lead for Organ Donation
COM	Clinical Operations Manager
eCRF	Electronic Case Report Form
CTU	NHSBT Clinical Trials Unit
DBD	Donation after Brainstem Death
DCD	Donation after Circulatory Death
DCF	Data Clarification Form
DFCS	Donor Family Care Services
DM	Data Manager
DMC	Data Monitoring Committee
DRD	Donor Records Department
GCP	Good Clinical Practice
GP	General Practitioner
ICU	Intensive Care Unit
ISRCTN	International standard randomised controlled trial number
IRAS	Integrated Research Application System
ITU	Intensive Therapy Unit
MHRA	Medicines and Healthcare Regulatory Authority
NG	NG
NHS	National Health Service
NHSBT	NHS Blood and Transplant
NIHR	National Institute for Health Research
OTDT	Organ and Tissue Donation and Transplantation
PALS	Patient Advice and Liaison Service
PI	Principal Investigator
PIS	Patient Information Sheet
PPIE	Patient and Public Involvement and Engagement
QA	Quality Assurance
R&D	Research and Development
RCT	Randomised Controlled Trial
RN	Research Nurse
SAE	Serious adverse event
SDF	Source Data Form
SNOD	Specialist Nurse for Organ Donation
SOP	Standard operating procedure
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

1 ROLES AND RESPONSIBILITIES

<p>NHBST Specialist Nurse for Organ Donation (SNOD)</p>	<ul style="list-style-type: none"> - Ensure SOP5945 is followed - Confirm if the patient meets the eligibility criteria - Discuss SIGNET with the donor family and obtain consent/authorisation - Randomise the patient - Ensure adherence to the donor care bundle and request an NG tube to be placed if there isn't one. - Ask an ICU doctor to prescribe and complete the Source Data Form (SDF) - Ensure that the Simvastatin is prescribed and administered - If contacted by recipient medical team to reveal donor allocation, reveal this and document that the patient was unblinded. Document this on the sequence of events. - Documentation of study participation in medical record and DonorPath - Complete the SDF and hand this over to local research team - Email completed Source Data Form to SIGNET@nhsbt.nhs.uk
<p>Principal Investigator (PI)</p>	<ul style="list-style-type: none"> - Support site set up, team members and development - Cascade training to ICU medical staff and sign training log and delegation log - Assess whether SAEs are deemed unexpected and related to research procedures - Report any SAEs - If contacted to reveal donor allocation, reveal this if appropriate and document that the patient was unblinded - Re-confirm if patient meets eligibility - Prescribe 80mg Simvastatin - Troubleshoot study procedures - Sign off 'End of study' form on study database
<p>Associate PI</p>	<ul style="list-style-type: none"> - Cascade training to ICU medical staff and sign training log
<p>Site Research Team</p>	<ul style="list-style-type: none"> - Help with study set up, liaising with R&D departments - Enter study data onto MACRO database - Maintain the site file - Help with study close out
<p>ICU Doctors</p>	<ul style="list-style-type: none"> - Re-confirm if patient meets eligibility - Prescribe 80mg Simvastatin - Documentation of study participation (but not allocation) in medical record
<p>ICU Nurses</p>	<ul style="list-style-type: none"> - Administer 80mg Simvastatin as per study manual - Document administration of Simvastatin on Source Data Form with accurate timings - Deliver donor bundle care as per standard treatment



2 SCREENING POTENTIAL PATIENTS FOR RANDOMISATION

Deemed consent does not apply to research therefore explicit consent/authorisation must be taken for research and the SIGNET study.

The timing of an approach to the donor family for consideration of the SIGNET study is at the discretion of the Specialist Nurses.

All adult DBD donors at participating sites (see DAT3936) should be checked by the Specialist Nurses to see if they meet all the following inclusion criteria and none of the following exclusion criteria.

There is an eligibility checklist for randomisation on the source data form, which is included within the NHSBT donor pack. This must be completed to ensure that the patient meets all inclusion criteria and none of the exclusion criteria prior to randomisation. The SNOD checking eligibility should also record their name below to show who has confirmed that the donor was eligible.

Site teams do not need to complete screening logs.

Inclusion Criteria

- *Within a recruiting Intensive Care unit*
- *Patients confirmed dead using neurological criteria*
- *Consent/Authorisation for organ donation in place, as defined by the Human Tissue Act and accompanying legislation and Codes of Practice.*
- *Study specific consent from donor family*

Exclusion Criteria

- *Aged < 18*
- *Planned donation after cessation of circulation (DCD)*
- *Known donor allergic hypersensitivity to simvastatin*

Please note that if the donor has already received a statin, they are still eligible for SIGNET.

3 OBTAINING INFORMED CONSENT FOR SIGNET

There is an information sheet for relatives and an additional study consent sticker in the donor pack. All study documents are also available on the study website (www.nhsbt.nhs.uk/SIGNET). The SNOD should give the relatives information sheet to the relatives and ask them to read this for full information.

In the event of families being unable to read the information/ understand English, local translation services can be used for organ donation consent/authorisation and to discuss SIGNET and consent/authorisation for the study.

If consent/authorisation is taken over the phone/video:

- Direct the family to the website where they can find a copy of the information sheet.

- Record on the SNOD/ Donor Family Care Services (DFCS) handover form that the study information sheet needs to be sent out to the family unless the family have specified that they do not wish to receive any information.

The study should not be discussed with the family prior to the organ donation discussion with the SN. The Specialist Nurses (SNs) should approach the donor family for participation in the SIGNET study at the point they feel most appropriate. This could be following consent/authorisation for organ donation or within the organ donation consent conversation.

Key messages for relatives:

- The study aims to investigate whether a statin tablet could improve the condition and function of organs which have been donated for transplantation.
- This tablet is commonly used for people with high cholesterol, but it has other possible effects in transplantation.
- The tablet is crushed up and given via the nasal tube that is already in place for the purposes of organ donation. This happens after death is confirmed.
- Patients in the study will still receive all their usual standard donor care
- We don't think there are any risks to the donor by taking part in the study
- This research could benefit transplant recipients now and, in the future

The SNOD should record relative consent/authorisation for SIGNET study by initialling other/scheduled purposes question 3b and putting the study sticker in the additional notes of the consent/authorisation form. This should also be documented in the medical notes.

The consent/authorisation form will be sent to DFCS by the SNOD, following standard procedure.

The date of consent/authorisation for organ donation and date of study specific consent should be documented on the source data form by the SNOD. Please also document if consent was taken over the phone/ video conferencing on the source data form.

Should the family decline to participate, please record this on the SN/DRD handover form and the reason why in the sequence of events section on DonorPath.

4 RANDOMISATION

Randomisation and if required, intervention administration, should occur as soon as possible after study consent and neurological death confirmation.

Randomisation will be conducted by the SNODs via the Sealed Envelope website (www.sealedenvelope.com/access). Randomisation should take place after consent/authorisation for both organ donation and study specific consent/authorisation. As randomisation will be stratified by the computer system according to whether the donor was receiving statin therapy at ICU admission, you will need knowledge of known prescribed medications at ICU admission at the time of randomisation.

Prior to randomisation you will need:

- Consent/authorisation for organ donation
- Study specific consent/authorisation

- A Source Data Form to document the participant’s randomisation number and allocation (this can be found in the donor pack)
- You will need to know:
 - o Your Sealed Envelope log on details (please contact the central research team if this is not known or follow the instructions below if you have forgotten your password)
 - o If the donor was receiving statin therapy on admission to ICU
 - See list of statin names in appendix 2
 - If you cannot see a statin in their medication please select ‘no’
 - o OTDT Donor ID number

Log onto Sealed Envelope. To do this you will need to enter your login details and select ‘login’.

Please make sure you are in the ‘Live’ system.

You will then need to select SIGNET, by selecting ‘Access with role...’. The SN’s will have an ‘investigator’ role.

In the top toolbar you will then need to select ‘randomise’ to take you to the randomisation form.

SIGNET

Statins for Improving orGaN outcomE in Transplantation

You will then need to answer a few simple questions to randomise the patient.

Randomisation

Complete this form to add a new subject to Red Pill. No other forms will be accessible until this form has been entered.

Subject registration

Randomisation number:

Automatically generated

ODT Donor ID: *

A 8 digit number

Date of informed consent/authorisation from donor family: *

Stratification variables

Was the donor receiving statin therapy at ICU admission? *

Yes

No

[reset]

Inclusion Criteria

Does the donor meet all inclusion criteria? *

Yes

No

[reset]

Has informed consent/authorisation been obtained from the donor family? *

Yes

No

[reset]

Exclusion Criteria

Do any of the exclusion criteria apply? *

Yes

No

[reset]

Site

Site region *

Site *

[Enter manual randomisation details](#)

* required

If the ODT donor ID has already been entered or the date of consent/authorisation entered is in the future, a warning will appear. You will also get a warning if the donor does not meet the inclusion criteria or meets any of the exclusion criteria.

Date of informed consent/authorisation from donor family: *

 Date must not be in the future



This question must be answered yes to proceed

Once you have completed the randomisation form, you will need to click the blue 'Randomise' box, at the bottom of the page, and sealed envelope will ask you to check the data entered and enter your password to confirm that you wish to randomise the patient.

Investigator's declaration

By entering my password below I declare that the information presented in this form accurately reflects the medical records and that I wish to proceed with randomisation

Name
Amy Evans (ID 12951 - Administrator)

Date
6 Aug 2021 12:33 (UTC)

Password *

Once you have entered your password and clicked 'confirm' you will be notified that the randomisation was successful.



Success

Randomised to **Simvastatin 80 mg administered by NG tube in addition to protocolised standard care** on
22 Jul 2021 10:42 (BST)

This will then take you to the page where you can see the donor's Randomisation number, the site number and the donor's allocation.

Randomisation number: R0039 164 Nottingham, Nottingham University Hospitals Qmc Campus, United Kingdom

Return to subject Visit: Randomisation Create a query

Randomisation

Complete this form to add a new subject to Red Pill. No other forms will be accessible until this form has been entered.

The subject was successfully randomised.

Randomised to **Simvastatin 80 mg administered by NG tube in addition to protocolised standard care**

Donor's Allocation

Once randomised, you will be given the patient's allocation and randomisation number. The SNOD should document this on the Source Data Form (found in the donor pack). An electronic notification will be sent automatically to the person randomising the patient, the central research team, and the local research team and PI for that site.

The patient's randomisation number should be recorded on DonorPath by the SNOD but do not record the patient's treatment allocation. This should be documented as "SIGNET: Consent RXXXX" in the free text box in the past medical history section of DonorPath.

If you have any problems accessing or using Sealed Envelope, please contact the SIGNET team (SIGNET@nhsbt.nhs.uk or 07764 280175). If outside of working hours, please try accessing Sealed Envelope using a mobile device or using an alternative user account.

If you forget your password, please contact SIGNET@nhsbt.nhs.uk or if it is out of hours you can select 'Forgot your password?' (shown below), however for this option you will have needed to add another email or phone number when you set up your account. You will need to enter your email address after following the 'Forgot your password' link and an email will be sent with instructions and a link to reset your password. A security code will also be sent to your back-up email or mobile phone. You will need this code to reset your password.

Please log in

To log in you must enter your registered email address and password.

Email address:

Password:

5 INTERVENTION

5.1 STOCK

For the purposes of this study, it is expected that ward stock of Simvastatin tablets to the total of 80mg will be used.

5.2 STORAGE

Storage of Simvastatin is expected to be in line with normal clinical practice and therefore temperature monitoring records will not be collected specifically for the study.

5.3 LABELLING

The intervention requires no specific trial related labelling.

5.4 DRUG ACCOUNTABILITY

Usual standard practices for documenting administration of medications will be utilised at investigating sites, no formal trial specific accountability of medication will be expected to be completed.

5.5 REQUESTING THE INTERVENTION

An ICU prescribing doctor, who is aware of the study, will need to prescribe the intervention as per the protocol. Before prescribing the 80mg Simvastatin they should reaffirm that the patient meets all the eligibility criteria and none of the exclusion criteria; this check should be documented on the source data form.

The 80mg Simvastatin should be prescribed as per local hospital procedure (I.e paper or electronic medication chart) eg “Simvastatin 80mg once NG, SIGNET study intervention”

5.6 DOCUMENTATION

5.6.1 DONORPATH

Documentation of the organ donation process is electronic within NHSBT’s DonorPath system. The approach, subsequent randomisation and study intervention should be documented by the SNOD in the past medical history section as:

- “SIGNET: consent RXXXX”
- “SIGNET: Decline”
- “SIGNET: Not approached”

For an example please see the image below:



5.6.2 PATIENT MEDICAL RECORD

A similar entry in the medical record can be by the ICU Dr and / or the SNOD, which should not include the study allocation to maintain the blinding of recipient teams.

5.6.3 SOURCE DATA FORM

The SNOD should fill in the Source Data Form which needs only limited information on the allocation, date and time of prescription and administration. If for any reason the intervention is not given following randomisation, this will also need to be documented on the Source Data Form.

The SNOD should scan the completed source data form to DonorPath and also send a scan to the central study team (SIGNET@nhsbt.nhs.uk) with 'Confidential SIGNET Source Data Form' as the email subject. The completed source data form should then be stored locally for the local research team to collect as per local arrangements (see DAT3936 for locations).

5.6.4 STUDY DATABASE

The site research team will need to pick up the completed source data forms and enter this data onto the study MACRO database. There are training slides and guidance below on how to use MACRO.

5.7 ADMINISTERING THE INTERVENTION

The Simvastatin should be administered by the bedside nurse via NG tube. An NG tube is part of standard donor care and should be in place when considering organ donation in patients after neurological death.

Before administering the suspension stop external feed and flush the NG tube with 20-30ml of water.

- The 80mg Simvastatin tablet(s) should be crushed well and mixed with 20mls sterile water from hospital stock supply.
- Draw the study medication into an appropriate size and type of syringe as per local policy. The tablets should disperse (when agitated) to form a fine dispersion which should not block a Nasogastric (NG) tube.
- The suspension should be administered via NG tube. The NG tube should be in place as part of the donor care bundle. To administer the Simvastatin, flush the study medication down the NG tube.
- Following administration, flush the NG tube with 10ml water to ensure that the total dose is administered.

6.0 UNBLINDING

The ICU team and SNOD team caring for donor and family will not be blinded to the intervention.

Retrieval teams, Theatre teams and Recipient Transplant teams should be blinded to the study intervention.

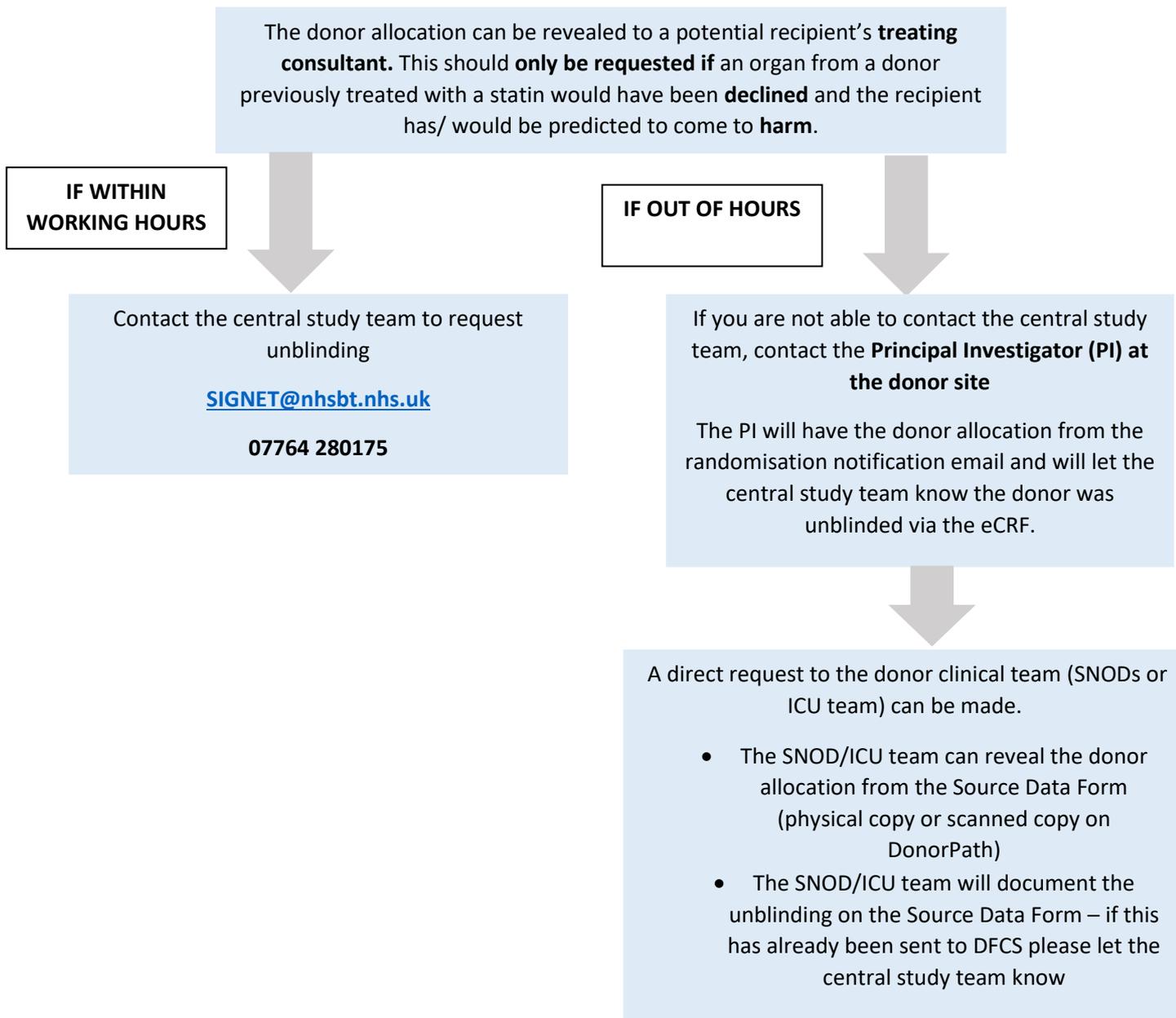
Care must be taken not to accidentally unblind the retrieval teams, for example by discussing the study intervention in conversations, or sharing study documentation with the donor records. Documentation will record participation in SIGNET but not whether they received the Simvastatin.

The circumstances where the donor's allocation may be deliberately unblinded are:

- Where a recipient has/would be predicted to come to harm
- If a recipient's treatment would be altered if the study allocation were not known, for example a known severe hypersensitivity to simvastatin

6.1 THE UNBLINDING PROCESS

A request to reveal the donor intervention allocation can be made through three mechanisms. The request should be made by the potential recipient's treating consultant (surgical or medical).



If within working hours a request can be made by direct communication with the central study team (SIGNET@nhsbt.nhs.uk / 07764 280175). The recipient treating consultant will need to know the donor's trial ID (this should be documented in their medical notes and on DonorPath in the past medical history section).

If you are not able to contact the central study team, the donor allocation can be unblinded by direct communication with the donor site Principal Investigator. The PI will have received a randomisation notification with the donor allocation on and should document the unblinding request using the eCRF. The PI should decide if the request to unblind meets the criteria to unblind and if so, let the recipient treating consultant know the donor allocation.

If either are unavailable, or it is out of hours, a direct request to reveal the treatment allocation may be made to the donor clinical team. If a SNOD receives a request to unblind they can use the prescription chart or source data form (which will also be uploaded to DonorPath) to see if the donor received the intervention. The SNODs will need to document any requests for unblinding on the Source Data Form. The date of the request, the person requesting and their role and their reasons for requesting unblinding will need to be documented. The SNOD will also need to document if, following the request, the donor allocation was unblinded. If the request comes through to the SNODs or NHSBT operational team after the source data form has been sent to DFCS, please send this information to SIGNET@nhsbt.nhs.uk.

If you need to contact Hub Operations to see if a donor was in the study, the contact number is 0117 975 7580.

Only the recipient treating consultant will be informed of the treatment allocation, who will then determine if this impacts on the decision of transplant. Transplanting teams accepting organs from the same donor, or subsequent teams considering the same organ, will not be informed unless they have also requested unblinding using the same process. The treatment allocation will remain blinded within the DonorPath documentation.

7 ORGAN DONATION

Following randomisation and administration of the intervention, the organ retrieval and transplantation process should continue as normal. However, the following steps should be made:

- When the SNOD registers the donor with Hub Operations, please **include** that they have consented for SIGNET study number 109.
- During the SNOD/NORS handover, advise that they have been randomised to the SIGNET study but do not inform them if they received the intervention.
- Upload a copy of the source data form to DonorPath, email to SIGNET central team (SIGNET@nhsbt.nhs.uk) with 'Confidential SIGNET Source Data Form' as the subject. Leave the original in the agreed location for local site teams to upload data to study system (this will be documented on DAT3936)
- When completing the post donation notes in the hospital record, include SIGNET participation and trial ID (randomisation number).

8 STUDY DATA

8.1 SOURCE DATA FORMS

The Source Data form needs to be completed by all SNs for all patients randomised to SIGNET (those randomised to both the intervention and to standard care). This is shown below and contains:

- Eligibility, consent, randomisation and end of study sections which need to be completed for **all** patients randomised to SIGNET by the SN
- The intervention section will need to be completed for patients randomised to receive 80mg Simvastatin in addition to standard care **only**. The SN will hand this to the ICU doctor to reconfirm eligibility and prescribe the Simvastatin and then to the bedside nurse to document when the simvastatin was administered.
- **Only** the first question in the withdrawal section needs to be completed unless there is a request to withdraw a patient.
- **Only** the first question in the unblinding section should be completed unless there is a request to unblind a patient.

SOURCE DATA FORM

Site:

Site Code:

Name of Specialist Nurse completing form:

Date of Organ Donation:

D D M M Y Y Y Y

ODT Donor ID number:

ELIGIBILITY CHECKLIST
INCLUSION CRITERIA

YES

NO

Is the patient within a recruiting Intensive Care Unit?

Has the patient been confirmed dead using neurological criteria?

Is consent/authorisation for organ donation in place?

Is study specific consent/authorisation, from the donor family, in place?

IF ANY "NO" BOX IS TICKED THEN THE PATIENT IS NOT ELIGIBLE FOR THIS TRIAL
EXCLUSION CRITERIA

YES

NO

Is the patient aged < 18

Planned donation after cessation of circulation (DCD)

Known donor allergic hypersensitivity to Simvastatin

IF ANY "YES" BOX IS TICKED THEN THE PATIENT IS NOT ELIGIBLE FOR THIS TRIAL

Name of person confirming eligibility:

Date and time of eligibility confirmation:

D D M M Y Y Y Y

24 hour clock

H H : M M

CONSENT/AUTHORISATION

Date of consent/authorisation for organ donation:

D D M M Y Y Y Y

Date of study specific consent/authorisation:

D D M M Y Y Y Y

Name of person taking study specific consent:

Has the study specific sticker been stuck to the organ donation consent/ authorisation form?

YES

NO

Has consent/authorisation been taken via phone or video?

YES

NO

RANDOMISATION

Name of person performing randomisation:

Was the donor previously receiving statin therapy at ICU admission?

YES

NO

(If unknown, please select 'No')

Date and time of randomisation:

24 hour clock

D D M M Y Y Y Y

H H : M M

Randomisation number:

Randomisation allocation:

Protocolised Standard Care ONLY

Simvastatin 80 mg administered by NG tube in addition to protocolised standard care

THE DONOR'S ALLOCATION SHOULD REMAIN BLINDED TO THE RETRIEVAL AND RECIPIENT TEAM
PLEASE DOCUMENT ON DONORPATH THAT THEY WERE RANDOMISED TO SIGNET, BUT NOT THEIR ALLOCATION

INTERVENTION—Complete for Simvastatin arm only:

Has an ICU doctor reconfirmed that the patient meets all of the inclusion criteria and none of the exclusion criteria prior to prescribing 80mg Simvastatin? YES NO

Name of ICU doctor reconfirming eligibility:

Has 80mg Simvastatin been prescribed? YES NO

If Yes, Date and time of Simvastatin prescription :

20							24 hour clock				
D	D	M	M	Y	Y	Y	Y	H	H	M	M

Name of prescriber:

Has 80mg Simvastatin been administered? YES NO

If Yes, Date and time of Simvastatin administration:

20							24 hour clock				
D	D	M	M	Y	Y	Y	Y	H	H	M	M

If No Simvastatin was prescribed/administered please specify why:

Organ donation did not proceed → Complete End of Study section

Study specific consent revoked → Complete Withdrawal section

Other, please specify

WITHDRAWAL

Has the patient been withdrawn from the study? YES NO

If Yes, Date of withdrawal: 20

Reason for withdrawal: Study specific consent revoked

Other, please specify

Does the patient representative agree for continued data collection? YES NO

END OF STUDY—COMPLETE FOR ALL PATIENTS

Did the organ donation process proceed? YES NO

If No, Reason: Organs/donation process unsuitable
 Consent revoked
 Other, please specify

Has the donor had any reportable Serious Adverse Events (see study manual for guidance)?

Yes → Complete the SAE Form

No

UNBLINDING

THE RETRIEVAL AND RECIPIENT TEAM SHOULD REMAIN BLINDED TO THE DONORS ALLOCATION UNLESS UNBLINDING WILL STOP HARM OR ALTER TREATMENT

Has there been a request to unblind the donor allocation? YES NO

If Yes, Date of request: 20

Name of requestor:

Requestors team:

Reason for request to unblind:

Recipient has known hypersensitivity to Simvastatin

Recipient has had an anaphylactoid reaction

Other, please specify

Was the donor allocation revealed? YES NO

Ensure that the randomisation number is documented on all pages of the Source Data Form once this is known.

The site code is the 3 digit number used to identify each hospital. If, for example, your site code shows up on Sealed Envelope as 1 this would be entered on the source data form as 001. If your site code showed up as 24, this would be entered on the source data form as 024.

If there was any deviation from the randomised treatment allocation, please document the reason for this.

Once completed the Source Data Form needs in an agreed local location (See DAT 3936) for the site research team to enter onto the study MACRO database (please see appendix 1 for guidance on using MACRO).

If there are any changes required after the SDF has been left at site:

- NHSBT Specialist nurses should contact the SIGNET team (SIGNET@nhsbt.nhs.uk) to inform them of the changes
- The site team can document this on the eCRF (see guidance on using MACRO below)

8.2 CASE REPORT FORMS (*COMPLETED ON MACRO DATABASE*)

The completed Source Data Form will be handed over by the SNs for the site research team to enter onto the MACRO database (left in agreed location as per DAT3936). For generic database guidance see appendix 1. Each member of the research team will be given a password protected MACRO login, following training.

It is the PI's responsibility to sign off data entered on MACRO.

9 STAFF TRAINING REQUIREMENTS

SNOD training will be carried out by NHSBT. This will be documented on the NHSBT training record.

A Site Initiation Visit will be scheduled before each site is opened to recruitment; these will be via Zoom/Teams. The PI, associate PI and research team **must** attend a training session and will be required to log their attendance on the local training log. It is recommended that as many of the ICU team attend as possible, however the PI or Associate PI is responsible for ensuring that training is cascaded to the local team and that training is signed off on the training log. The completed training logs should be sent to SIGNET@nhsbt.nhs.uk.

Training requirements for prescribing medical staff are minimal but important. It is important that all prescribing doctors on the ICU are aware of the study. This can be via attending a training session or via the cascaded training.

The table below outlines the training requirements for each staff group; however, anyone is welcome to join training sessions:

Role	GCP Training Required	Other Requirements
PI	Yes	Provide CV/GCP certificate. Cascade training and sign training log.
Associate PI (eg. a senior trainee in critical care with an interest in organ donation and / or research)	Yes	Provide CV/GCP certificate. Cascade training and sign training log.
Local Lead Research Nurse	Yes	Provide CV/GCP certificate
ICU staff/ prescribing doctor	No	
Specialist Nurses	No	Proportionate GCP training and training in SOP5945, documented on NHBST training record
Pharmacy	No	

10 SAFETY REPORTING

10.1 SAES THAT NEED RECORDING

Safety reporting refers only to the donor; all clinical outcomes in recipients are secondary outcomes for the study.

SAEs should be reported by the research team from the point of randomisation up to organ retrieval.

It is the PI's responsibility to assess whether any serious adverse events need recording. SAEs that need recording include:

- Those deemed **unexpected** and **related** to the research procedures
- Those that lead to the loss of capacity to donate any organ as a result of the study procedures – The PI will need to assess whether the failure to proceed to retrieval for any organ was as a result of the study procedures.

10.2 EVENTS THAT DO NOT NEED RECORDING

Section 9.2 of the protocol gives examples of anticipated adverse events which do not need recording. These include:

- a. Cardiovascular instability, including tachyarrhythmia, bradycardia, hypotension, hypertension, cardiac failure.
- b. Respiratory failure including hypoxia, hypercapnia, pulmonary oedema.
- c. Renal failure including central or renal diabetes insipidus
- d. Metabolic / hormonal disturbance including diabetes insipidus, hypo or hyperglycaemia requiring intervention.
- e. Hepatic impairment including transaminitis or biliary stasis

For further guidance on Safety Reporting, please see the trial protocol (section 9) or contact SIGNET@nhsbt.nhs.uk.

Blood and Transplant SAE Narrative Form

Randomisation Number

R				
---	--	--	--	--

Site: _____

Site code:

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SERIOUS ADVERSE EVENT (SAE) NARRATIVE FORM

Type of report: *(Please tick one box only)*

Initial

Follow up 1

Follow up 2

1. Serious Adverse Event Name :

2. Date and time of SAE onset:

D	D	M	M	Y	Y	Y	Y

24 hour clock

H	H	: M	M

3. Describe SAE: *(including manifestation and progression of event. Continue on a separate sheet if necessary)*

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.....

.....

.....

4. Treatment / Tests given:

.....

.....

.....

5. Outcome:

.....

.....

.....

Completed SAE Narrative Form must be sent to the NHSBT CTU within 5 working days of identification of the event.

Principal Investigator (PI) Name (print)

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PI Signature:

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Date of Form Completion:

D	D	M	M	Y	Y	Y	Y

Q1. Please ensure that this is the same SAE name as entered on the SAE form.

Q2. Please ensure this matches the data and time on the SAE Form.

Q3 -5. Please describe the event, treatment/tests and outcome. This is vital to provide further details on the event.

The second page of the SAE form is a narrative form. This MUST be completed alongside the SAE form as it provides vital details.

If there are any updates on the SAE, the local site team should overwrite the changes on the SAE form on the study database – NHSBT will maintain an audit trail of changes. Any additional information for the event can be recorded on the SAE narrative form as a new entry.

11 INCIDENT REPORTING

11.1 PROTOCOL DEVIATIONS

Any deviations to the protocol should be reported by the local site team on a file note which can be sent to SIGNET@nhsbt.nhs.uk.

11.2 ODT CLINICAL GOVERNANCE

The SNODs should follow standard procedure for reporting incidents via the OTDT Clinical Governance pathway. If the study is part of the incident, please include the study name. In addition, local sites will require any incidents to be reported via local governance pathways, this should be done following standard procedure.

11.3 SERIOUS BREACHES

If the local site team are aware of any potential serious breaches to the protocol or GCP, these need to be reported by the local research team to the central study team within 24 hours of becoming aware. These should be reported by the site team by phone and email to SIGNET@nhsbt.nhs.uk/07764 280175. Please do not wait for local investigations to be completed before reporting.

If you are unsure if something should be reported, please contact us and we can advise.

12 STUDY WITHDRAWAL

If a participant's family wishes to withdraw the participant from the study prior to the 'End of Study', they must be asked whether they are happy for data which has already been collected to be retained, or whether they wish for this to be destroyed. They should also be asked whether they are happy for continued follow-up data to be collected.

The 'Withdrawal Form' should be completed to record this information. Please also notify the SIGNET Trial Team. Please give as much information as possible as to the reason for withdrawal.

Any withdrawal requests coming through the Hub or DFCS will be passed on to the Team Manager/SN. This can be passed on to the study team at SIGNET@nhsbt.nhs.uk

13 APPENDIX 1 – USER GUIDE: MACRO DATABASE FOR LOCAL SITE TEAM

13.1 Overview

Uploading CRF data to the MACRO database for the SIGNET study is a site research team responsibility.

MACRO™ is the database system we use to collect and store the study data. It is particularly useful for conducting clinical trials because it keeps a detailed audit trail, which shows which user made changes to the database and when. For this reason, it is important to ensure that you do not allow anyone else to log into your MACRO™ account.

Link to MACRO™: <https://www.ctu.nhsbt.nhs.uk>

Compatible Browsers for MACRO™ v4.9.0.8594:

- Microsoft Internet Explorer v11
- Mozilla Firefox v52 ESR

- Google Chrome v53

You will not be able to access MACRO via Apple devices, e.g. iPads/mobile phones, or browsers not on the above list, e.g. Safari. You will get an error message displayed as follows: “The browser you are using is not compatible for this version of the software. Please read the release Notes to see supported browsers”. If you have problems connecting please contact the study data manager (Roshni.Paul@nhsbt.nhs.uk).

Google Chrome seems to work best; Internet Explorer can be very slow. **You need to allow pop-ups.**

You can connect from a laptop running supported software via a wireless network, but you may experience difficulties losing the connection or reconnecting.

13.2 Entering a New Participant

To create a new participant, click the “create a new study subject” button on the toolbar:



Select your site and click OK a pop-up box will confirm that the participant has been successfully registered onto the database. You do not need to record the number in this pop-up. If the participant cannot be registered, then this indicates that a required field has not been completed. Please note all forms will be available for entry once participants are randomised. Each section of the source data form will be a new page on the study database.

13.3 Visits and the Study Schedule

“Visit” refers to a collection of eCRFs that form the schedule for the participant as they progress through the study.

This image shows the Schedule QuickView with the different Visits. The Baseline Visit has been expanded to show the eCRFs inside, in green boxes:

Schedule QuickView

PLUTO/nhsbt280/R1234

- Screening
- Baseline
- Form 2- Eligibility 27/01/2020 (S111-14)
- Form 3- Baseline 28/01/2020

PLUTO/nhsbt280/R1234	Screening	Baseline	Randomisation	Day 1	Day 2	Day 3
Form 1- Screening Log	5111-14 27/01/2020					
Form 2- Eligibility		5111-14 27/01/2020				
Form 3- Baseline		28/01/2020				
Form 4- Randomisation Form			28/01/2020			
Form 5- Transplant Operation			28/01/2020			
Form 6- Day 1				28/01/2020		
Form 7- Day 2						
Form 8- Day 3						
Form 9- Toxicity						
Form 10- Medication and Blood Products						

The “Study Schedule” is a screen which opens when accessing a participant’s records on MACRO, or when an eForm is closed. It is a large grid with each column representing a visit and each row a form name e.g. Each “cell” of the grid contains an icon representing an eForm, if the eForm is present in that visit. Double click on the eForm icon to open the page.

13.4 Entering Dates

Enter dates in the format DDMMYYYY. Do not enter any punctuation when inputting dates, e.g. the 3rd of February 2020 would be entered 03022020. MACRO™ will automatically change this to 03/02/2020.

13.5 Saving and Navigating Between Pages

To open up an eCRF double-click its icon on the study schedule. It can be difficult to navigate the study schedule, so you may prefer to use the Schedule QuickView instead. To do this, open up any page from the study schedule and then click the Schedule QuickView icon on the toolbar. You can then navigate to the exact page you want much more easily. Please note that the QuickView will only be available when an eCRF is open, otherwise it will be blank.



To move from one eCRF to the next, click the “Save and move to next e-form in schedule” button on the toolbar. There is also an option to save and move to the previous e-form.



If you go into a form that you don’t need by accident, or if MACRO™ automatically opens a new repeat of a form that isn’t needed, then please do not save the form. Once a form has been saved it cannot be deleted, and it can cause issues within the database. Instead, use the grey arrows to move between forms or use the red cross to go back to the study schedule without saving.



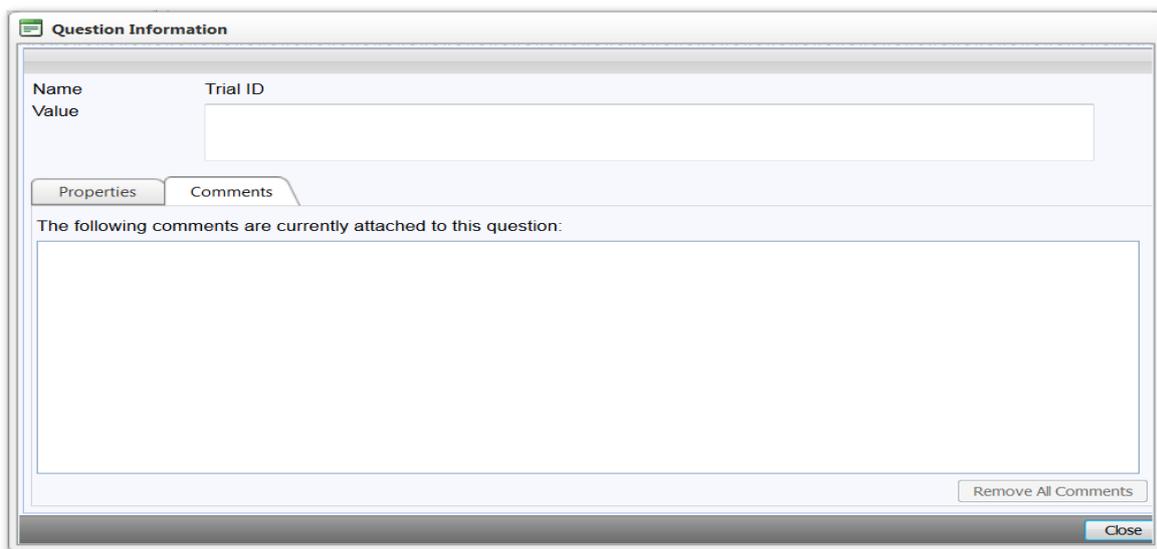
If you do accidentally save a form that should not have anything entered into it, please leave a comment to let the data reviewer know.

13.6 Comments

It is possible to leave a comment attached to a question in MACRO™, and this also reduces the number of queries that sites have to respond to.

It is appropriate to use a comment when, for example, to respond to a warning message asking for clarification, or a piece of information is not available.

To leave a comment, right click on the question and select “Comments” and then “Add...” The following box will pop-up:



Enter your comment and click “Close”.

13.7 Warnings

The database has been programmed to make warnings pop up when the data entered meets certain criteria, for example when a date appears out of chronological order or under the wrong visit, or when further action is required, e.g. another form needs to be completed.

When a warning fires, you can close the window using the close button. Please do not attempt to overrule warnings because data management need to check them.

Question Information

Name: Date sample taken for serum creatine
 Value: 03/01/2020 03:15

Warnings

The following warnings have been generated:

Message	Overrule
⚠ Date entered does not corresponds to day 1, please check.	<input type="text"/>

When a question has triggered a warning, then the question status symbol will look like this: ⚠. Right click this symbol and select “View warning” to check why the warning fired.

If a warning has fired but you can confirm that the data that has been entered is correct, or you have completed the eCRF that the warning is asking for, then please leave a comment on the question to confirm this. A data reviewer will then check this and close the warning if appropriate. This will make the question status look like this: 🗨.

If a warning fires on a date field, please double check that the date is correct and that the form or question answers are being added under the right visit.

13.8 Missing data & finding missing data quickly

If any question has not been answered after the page is saved, then a missing symbol will appear next to the question ☀. When the data has been entered, the missing symbol will disappear.

To quickly search for all of the missing data from your site, click the missing data symbol on the toolbar.



13.9 Changing / updating data and unavailable data

When a form has had data entered into it and has been saved, it is still possible to change the data. Any changes will show on the audit trail. When a data field is changed a box will pop up prompting you to enter an explanation for the change. There are some prepared answers available in the drop down box, but you can also type free text into the box.

At times, data may be unavailable or was not recorded. Leave a comment against this data to say that it is unavailable or was not recorded and a data reviewer will mark it unavailable if appropriate.

Sometimes you will not be able to enter an answer for a question, because it needs to be triggered by answers to previous questions. In that case, there will be this symbol next to the question: 

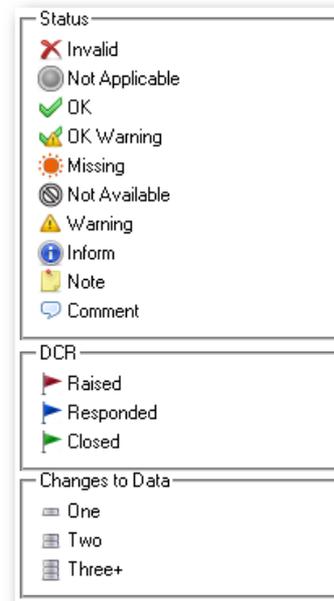
13.10 Symbol Key

The image on the right is a key showing the symbols that you may come across while using MACRO.

A full list of symbols used in MACRO can be accessed at any time by clicking the “Symbols and Function Keys” button on the toolbar.

These symbols may appear individually, or stacked on top of each other if more than one apply.

Each eCRF and visit will also show a status symbol indicating the contents. It will only show one status, which is the one it deems to be most important.



13.11 Searching for a participant

To find a particular participant in the database, open the search panel and select “Subject” in the top left drop down menu. This will change the panel so that only the “General” box is present. Enter the Subject Label into the “Subject” area (include leading zeros), select “Label” and then click the green arrow to execute the search e.g. 001.

It is very important to run this search before entering a new participant on the database to prevent duplicate participants being created.

If you want to view a list of recently accessed participants, you can select the “Open the recent subjects List page” from the toolbar.



13.12 Query Process

Data entered on the database is regularly reviewed by a Data manager. If they come across a problem, they will raise a query (also called a DCR – Data Clarification Request) to resolve the issue. Queries on a piece of data can be identified by a red flag on top of the question status symbol, like this:



To view the query, right click the symbol and select DCR > View.

Priority	Date	Status	Subject	Visit	eForm	Question	Value	User Name
5	2020/01/29 10:58:43	Raised	PLUTO/nhsbt012/R0022	Baseline	Form 3- Baseline Characteristics	Patient ODT Recipient Number	123456	Lisha Gracias

Use the scroll bar across the bottom to navigate to the query question. The query will begin by identifying the form and the question that the query relates to, so that it is easier for you to use if you choose to print the queries out.

When you have found the answer to the query, or you have confirmed that an answer is not and will never be available, then right click the question and select “Respond to DCR”. Enter the response into the box and click OK. If appropriate, you should also edit the data on the eCRF to reflect any required changes.

After responding to a query, the red flag icon will change to blue. The data reviewer will be able to see that you have responded to the query and will check that the answer is appropriate and fully answers the question. If they are satisfied then they will close the query, which will turn the flag green. If they feel that further information is required, then the query will be re-raised, turning the flag red again.

To see a full list of the queries raised for your site, the quickest way is to click the red query flag icon on the toolbar. That will bring up a list like the following:



Priority	Date	Status	Subject	Visit	eForm	Question	Value	User Name	OC Id	Text
5	2020/01/29 11:04:34	Raised	PLUTO/nhsbt012/R0022	Randomisation	Form 4- Randomisation Form	Date & time of randomisation		Lisha Gracias		Form 4- Randomisatic
5	2020/01/29 10:58:43	Raised	PLUTO/nhsbt012/R0022	Baseline	Form 3- Baseline Characteristics	Patient ODT Recipient Number	123456	Lisha Gracias		Form 3- Baseline Char

Double click anywhere on a line to open up the eCRF that contains the query.

14 APPENDIX 2 – STATIN LIST

This may be the proper name, and generic versions will have this name – shown in **Bold**.

But there are also trade-name versions of most of these drugs – shown after hyphen.

The two Combination drugs, Simvastatin plus ezetimibe and Simvastatin plus fenofibrate contain a good dose of the base statin, so are included in the list.

If a donor is recorded as taking *any* of these drugs they are regarded as already on a statin with regard to randomisation.

If *none* of these names appears, they are regarded as not already on a statin

Pravastatin

Atorvastatin

- Lipitor

Fluvastatin

- Dorisin XL
- Lescol XL
- Nandovar XL

Rosuvastatin

- Crestor

Simvastatin

- Simvador
- Zocor

Simvastatin plus ezetimibe

- Inegy

Simvastatin plus fenofibrate

- Cholib

15 APPENDIX 3 – SITE LIST

Trust	Hospital	Region	PI
Cambridge University Hospitals NHS Foundation Trust	Addenbrooke's Hospital	Eastern	TBC
East Suffolk and north Essex NHS foundation trust	Ipswich Hospital	Eastern	Kate Turner
	Colchester General Hospital		
North West Anglia NHS Foundation Trust	Peterborough City Hospital	Eastern	TBC
Barking, Havering and Redbridge University Hospitals NHS Trust	Queens Hospital, Romford	Eastern	Mandeep Phull/Farrel Igielman
	King George Hospital		
Luton and Dunstable University Hospital NHS Foundation Trust	Luton And Dunstable Hospital	Eastern	Stephen Brosnan
Norfolk and Norwich University Hospitals NHS Foundation Trust	Norfolk And Norwich University Hospital	Eastern	Deborah Easby
East and North Hertfordshire NHS Trust	Lister Hospital	Eastern	Pietro Ferranti
West Hertfordshire Hospitals NHS Trust	Watford General Hospital	Eastern	Valerie Page
Royal Free London NHS Foundation Trust	The Royal Free Hospital	London	Kulwant Dhadwal
	Barnet General Hospital		
Royal Brompton & Harefield NHS Foundation Trust	Harefield Hospital	London	Sian Jaggur
	Royal Brompton Hospital		
London North West University Healthcare NHS Trust	Northwick Park Hospital	London	Michael Dean
	Ealing Hospital		
Imperial College Healthcare NHS Trust	Charing Cross Hospital	London	Richard Stumple
	Hammersmith Hospital		
	St Marys Hospital		
King's College Hospital NHS Foundation Trust	Kings College Hospital	London	Shahana Uddin
	Princess Royal University Hospital		
University College London Hospitals NHS Foundation Trust	National Hospital For Neurology And Neurosurgery	London	Niall Maccallum
	University College Hospital		
Barts Health NHS Trust	The Royal London Hospital	London	Dan Kennedy
	Whipps Cross Hospital		
	Newham General Hospital		
	St Batholomew's Hospital		
Guy's and St Thomas' NHS Foundation Trust	St Thomas' Hospital	London	TBC
University Hospitals Birmingham NHS Foundation Trust	Birmingham Heartlands Hospital	Midlands	Robert O'Brien
	Queen Elizabeth Hospital		

	Good Hope District General Hospital		
Sandwell and West Birmingham Hospitals NHS Trust	City Hospital	Midlands	Balaji Ramamurthy
	Sandwell District General Hospital		
The University Hospitals Of Derby and Burton	Queen's Hospital, Burton	Midlands	Gregory Fletcher
	Royal Derby Hospital		
University Hospitals Coventry and Warwickshire NHS Trust	Coventry, University Hospital (Walsgrave)	Midlands	Robert Green
University Hospitals Of Leicester NHS Trust	Glenfield General Hospital	Midlands	Ricky Bell
	Leicester Royal Infirmary		
Nottingham University Hospitals NHS Trust	Queen's Medical Centre	Midlands	Dan Harvey
	City Hospital		
Worcestershire Acute Hospitals NHS Trust	Alexandra Hospital	Midlands	Steven Haynes
	Worcestershire Royal Hospital		
University Hospitals Of North Midlands NHS Trust	Royal Stoke University Hospital	Midlands	Dr. Nageswar Bandla
The Royal Wolverhampton Hospitals NHS Trust	New Cross Hospital	Midlands	Shameer Gopal
Betsi Cadwaladr University Health Board	Ysbyty Gwynedd District General Hospital	North West	David Southern
	Maelor General Hospital		
	Glan Clwyd District General Hospital		
East Lancashire Hospitals NHS Trust	Royal Blackburn Hospital	North West	Carole Pilkington
Blackpool Teaching Hospitals NHS Foundation Trust	Blackpool Victoria Hospital	North West	Jason Cupitt
Bolton NHS Foundation Trust	Royal Bolton Hospital	North West	Hannah Durrant
Pennine Acute Hospitals NHS Trust	Royal Oldham Hospital	North west	Andrew Drummond
	Fairfield General Hospital		
Countess Of Chester Hospital NHS Foundation Trust	Countess Of Chester Hospital	North West	Kathryn Tizard
Lancashire Teaching Hospitals NHS Foundation Trust	Royal Preston Hospital	North West	Catherine Roberts
Liverpool University Hospitals	University Hospital Aintree	North West	Robert Parker
The Walton Centre NHS Foundation Trust	Walton Centre For Neurology And Neurosurgery	North West	Gerald Smith
Manchester University NHS Foundation Trust	Manchester Royal Infirmary	North West	Malachy Columb
	Wythenshawe Hospital		
St Helens and Knowsley Hospitals NHS Trust	Whiston Hospital	North West	Ascanio Tridente
Salford Royal NHS Foundation Trust	Salford Royal	North West	Chris Booth
County Durham and Darlington NHS Foundation Trust	Darlington Memorial Hospital	Northern	Sheshank Jajur
	University Hospital Of North Durham		
South Tees Hospitals NHS Foundation Trust	The James Cook University Hospital	Northern	Stephen Williams
The Newcastle Upon Tyne Hospitals NHS Foundation Trust	Freeman Hospital	Northern	Alan Sweenie
	Royal Victoria Infirmary		

Northumbria Healthcare NHS Foundation Trust	Northumbria, Nsech	Northern	Bryan Yates
Belfast Health and Social Care Trust	Royal Victoria Hospital	Northern Ireland	Dominic Trainor
Western Health and Social Care Trust	South West Acute Hospital	Northern Ireland	Adrian Donnelly
	Altnagelvin Area Hospital		
NHS Grampian	Aberdeen Royal Infirmary	Scotland	Paul Gamble
NHS Lanarkshire	Monklands District General Hospital	Scotland	Nina Tatarowska
	Hairmyres Hospital		
	Wishaw General Hospital		
NHS Ayrshire and Arran	The Ayr Hospital	Scotland	Alistair Meikle
	Crosshouse Hospital		
NHS Tayside	Ninewells Hospital	Scotland	Pauline Austin
NHS Lothian	Royal Infirmary Of Edinburgh	Scotland	Thomas Craven
	Western General Hospital		
NHS Greater Glasgow & Clyde	Queen Elizabeth University Hospital	Scotland	Richard Appleton
	Royal Alexandra Hospital		Kevin Rooney
	Glasgow Royal Infirmary		Kathryn Puxty
Oxford University Hospitals NHS Trust	John Radcliffe Hospital	South Central	Simon Raby
Northampton General Hospital NHS Trust	Northampton General Hospital	South Central	Jonathan Wilkinson
Portsmouth Hospitals NHS Trust	Queen Alexandra Hospital	South Central	Richard Clinton
University Hospital Southampton NHS Foundation Trust	Southampton General Hospital	South Central	Ahilanandan Dushianthan
Great Western Hospitals NHS Foundation Trust	Great Western Hospital	South Central	Malcolm Watters
East Kent Hospitals University NHS Foundation Trust	William Harvey Hospital	South East	Christine Vimalanthan
	The Queen Elizabeth the Queen Mother		Moustafa Shebl Zahra
Brighton and Sussex University Hospitals NHS Trust	Royal Sussex County Hospital	South East	Alex Harrison
Frimley Health NHS Foundation Trust	Frimley Park Hospital	South East	Elaine Hipwell
	Wexham Park Hospital		
Ashford and St Peter's Hospitals NHS Foundation Trust	St Peter's Hospital	South East	Pardeep Gill
Western Sussex Hospitals NHS Foundation Trust		South East	Andrew Hetreed
East Sussex Healthcare NHS Trust		South East	Sinan Bahlool
Medway NHS Foundation Trust	Medway Hospital	South East	Paul Hayden
St George's Healthcare NHS Foundation Trust	St George's Hospital	South East	Argyro Zoumprouli
Lewisham and Greenwich Healthcare NHS Trust	The Queen Elizabeth Hospital	South East	Richard Breeze
	University Hospital Lewisham		
Aneurin Bevan University Health Board	The Grange University Hospital	South Wales	Matthew Carwardine/ Phillipa Jones
Cwm Taf Morgannwg Health Board	Princess Of Wales Hospital	South Wales	Sonia Sathe
	Prince Charles Hospital		TBC
	Royal Glamorgan Hospital		Jayaprakash Singh

Cardiff And Vale University Health Board	University Of Wales Hospital	South Wales	Matt Wise
Royal United Hospital Bath NHS Foundation Trust	Royal United Hospital	South West	Prof Jerry Nolan
University Hospitals Dorset NHS Foundation Trust	Royal Bourenmouth Hospital	South West	Michelle Scott
	Dorset Hospital		
University Hospitals Bristol NHS Foundation Trust	Bristol Royal Infirmary	South West	Fran O'Higgins
North Bristol NHS Trust	Southmead Hospital	South West	Ian Thomas
University Hospitals Plymouth NHS Trust	Derriford Hospital	South West	Colin Bigham
United Lincolnshire Hospitals NHS Trust	Lincoln County Hospital	Yorkshire	Edward Pogodaev
	Pilgrim Hospital		
Hull and East Yorkshire Hospitals NHS Trust	The Hull Royal Infirmary	Yorkshire	Harish Lad
	Castle Hill Hospital		
Northern Lincolnshire and Goole NHS Foundation Trust	Scunthorpe General Hospital	Yorkshire	Shan Dharmarajah
	Diana Princess Of Wales Hospital		
Calderdale and Huddersfield NHS Foundation Trust	Calderdale Royal Hospital	Yorkshire	Paul Knight
	Huddersfield Royal Infirmary		
Leeds Teaching Hospitals NHS Trust	Leeds General Infirmary	Yorkshire	David Moir
	St James's University Hospital		Mike Adlam
York Teaching Hospital NHS Foundation Trust	Scarborough Hospital	Yorkshire	Robert Ferguson
	York District Hospital		
Sheffield Teaching Hospitals NHS Foundation Trust	Northern General Hospital	Yorkshire	Jim Hoyle
	Royal Hallamshire Hospital		