UKCCRG
UK Critical Care Research Group

Newcastle University

NHS
The Newcastle upon Tyne Hospitals
NHS Foundation Trust

Statins for Improving orGaN outcomE in Transplantation

SUPPORTED BY
NIHR | National Institute for Health Research

UKODTRN
organ donation and transplantation research network

NHS
Blood and Transplant

Study Leads

Professor John Dark

Dr Dan Harvey

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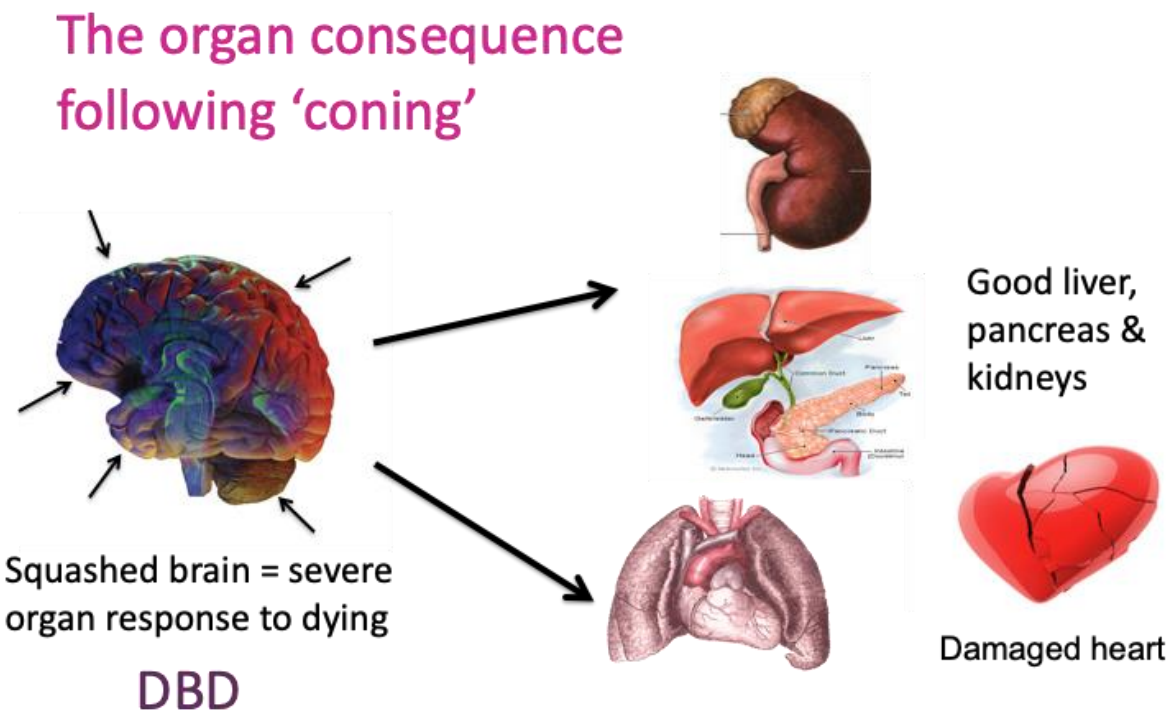
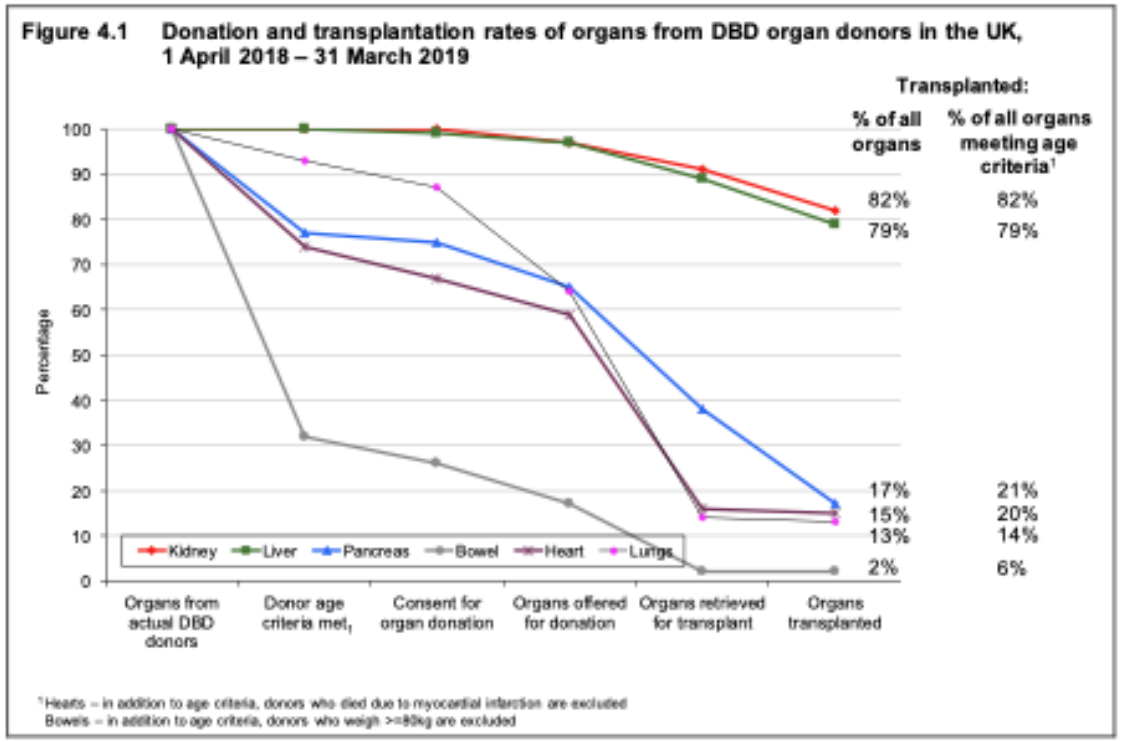
Effects of Brain Stem Death

Damage caused to organs as a result of critical illness, dying process and retrieval and transplantation process





Effects of Statins – in addition to cholesterol lowering

- Retrospective studies - Numerous positive
- Prospective studies
  - No overall value in ARDS
    - But benefit in a hyper-inflammatory phenotype sub-group
  - Benefit across a number of pathways
    - e.g Protective against contrast induced nephropathy

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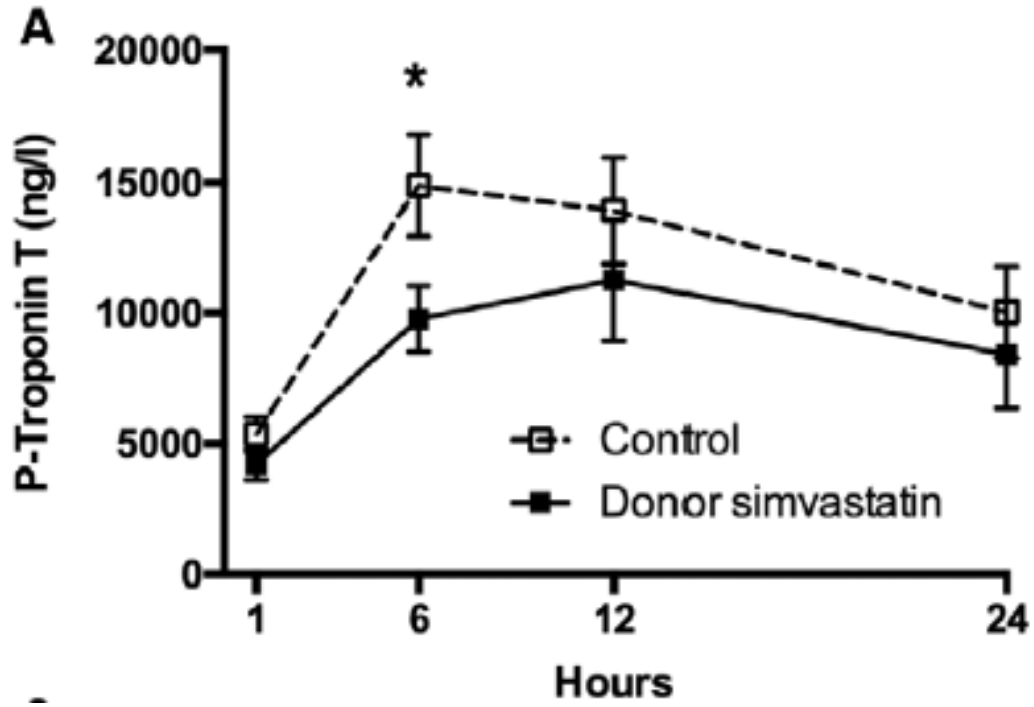
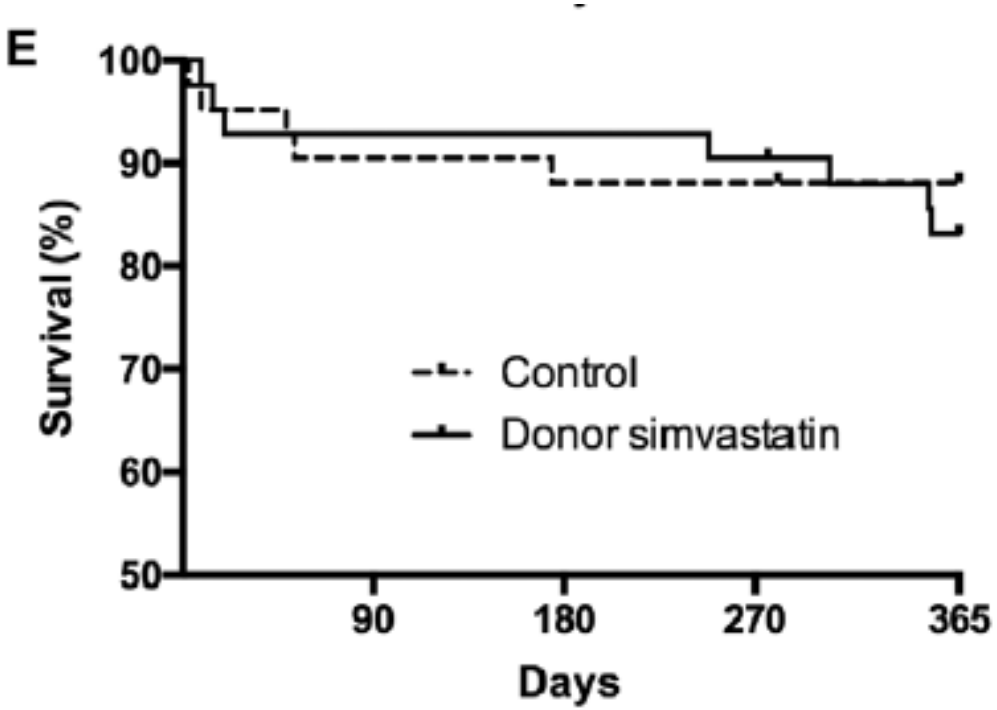
Results of the Helsinki Study





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Summary of the Helsinki Study

Cardiac

- Significant reduction of cardiac injury and heart-failure markers
- Small reduction of early acute rejection
- No effect on recipient mortality at one year

Other Organs

- No benefit or harm for Kidney
- Small, Non-significant Benefit for Lung
- Reduction of ALT at 1 week in Liver recipients

How can we do better ?

- Much bigger population
  - But only if a large number of donors are involved
- Opportunity to look at effects in all organs
  - Unique potential of donation and transplantation data in the UK

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SIGNET Study Objectives

Does treatment of potential organ donors with simvastatin during protocolised care after diagnosis of death using neurological criteria improve outcomes in patients undergoing transplantation?

a) To determine if simvastatin given to the donor confers an improvement in clinical outcomes in cardiac transplant recipients

b) To determine if simvastatin in the donor has a beneficial effect on other solid organs, particularly the liver and lung

c) To determine if simvastatin is safe in all organ transplant recipients (cardiac, renal, lung, liver and pancreas)

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SIGNET Study Design

- 2600 **Adult donors after diagnosis of death by neurological criteria, randomised:**
  - after consent for donation **and** research, to receive
  - **Simvastatin 80mg** as a single dose in addition to standard protocolized care or
  - Standard protocolized care alone
- Main focus of the study will be complications and survival in heart transplant recipients
- Outcomes in all organs from these donors followed from data collected in UK Transplant Registry
- Recipient and transplant teams are blinded to the intervention

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Study Outcomes

Primary Outcome

Composite of death, cardiac mechanical circulatory support or renal replacement therapy within the first 30 days post heart transplant

Secondary outcomes

- Organ utilisation rate for all organs
- 30-day, 3-month and 12-month graft survival for all organs
- 30-day, 3-month and 12-month patient survival for all organs
- Length of ITU and hospital stay
- Other organ specific outcomes

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Donor

Timepoint*	Enrolment	Allocation	Post-Allocation			
	T_{-1}	T_0	T_1	T_2	T_3	T_4
ENROLMENT						
Eligibility Screen	X					
Informed Consent	X					
Randomisation/Allocation		X				
INTERVENTIONS						
Simvastatin 80mg in addition to standard donor management protocol		X				
Standard donor management protocol only		X				
ASSESSMENTS						
Donor Demographics	X					
Donor Medical History	X					
Intervention Data		X	X			
Organ Utilisation			X			

T_{-1} – Screening

T_0 - Baseline

T_1 - At organ retrieval / transplantation

T_2 – 30 days following transplant

T_3 – 3 months following transplant

T_4 12 months following transplant

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Recipient

Timepoint*	Enrolment	Allocation	Post-Allocation			
	T_{-1}	T_0	T_1	T_2	T_3	T_4
ENROLMENT						
All patients on organ waiting list given recipient information	X					
INTERVENTIONS						
Organ transplant		X				
ASSESSMENTS						
Recipient Clinical Outcome				X	X	X

T_{-1} – Screening

T_0 - Baseline

T_1 - At organ retrieval / transplantation

T_2 – 30 days following transplant

T_3 – 3 months following transplant

T_4 - 12 months following transplant

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Study Setting

All Level 1 and 2 donating hospitals in the UK

Site teams :

- Consultant Research Lead (PI)
- CLOD (may be PI if appropriate)
- Trainee Associate PI
- Research Nurse
- SNOD

SIGNET

Roles

Assess Eligibility and Consent

Randomisation

Consent/authorisation for organ donation and research

Check that the patient meets eligibility criteria for SIGNET

Take consent from family and document this. Stick study sticker on the additional information page of the organ donation consent/authorisation form

Log onto Sealed Envelope and Randomise the patient – document this on the Source Data Form and add generic statement of SIGNET randomisation to DonorPath

Specialist Nurses

Roles

Eligibility and Prescription

Administering the intervention

Find an ICU prescribing doctor

Check the eligibility and countersign the Source data form.

Prescribe 80mg simvastatin on the ICU drug chart

Administer the 80mg Simvastatin via the NG tube and document this on the source data form

Specialist Nurses

ICU prescribing doctor

Bedside Nurse

Roles

Data Entry

Email a copy of source data form to central study team and leave for the local research team. The organ donation process should continue as normal.

Specialist Nurses

The local research team will need add the patient and all data to the study specific MACRO database.

Store the Source data form in the site file.

Local research team

Inclusion/ Exclusion Criteria

The SNODs will screen patients for eligibility (*reconfirmed by prescribing doctor)*

Inclusion Criteria

- Within a recruiting ICU
- Patient confirmed dead by neurological criteria (DBD)
- Consent for organ donation in place
- Study specific consent

Exclusion Criteria

- Aged <18 years
- Planned donation after cessation of circulation (DCD)
- Known allergic hypersensitivity to Simvastatin

No screening logs need to be completed.

NB: Enrolling a patient onto the trial who does not meet the inclusion/exclusion criteria is considered a protocol waiver. Protocol waivers are not permitted.

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Consent/ Authorisation

- The SNODs will consent the donor family within the consent /authorisation conversation for organ donation
  - Consent for randomisation, administration of statin and data collection
  - Information sheet for the family to read
  - Sticker to be stuck in the additional information section of the organ donation consent/authorisation form

- Recipients will not be consented
  - Unknown at time of randomisation
  - Donor intervention
  - Potential recipients will be sent a letter and information sh

Consent for Organ and/or Tissue Donation

NHS Blood and Transplant

Unique Tissue Number K | | | | | | | | | | ODT Donor number | | | | | | |

Additional Information

SIGNET Patient Consent Form Sticker (Version 1.0 dated 12.04.2021)

Study: Statins for Improving orGaN outcomE in Transplantation (NHSBT Study Ref no: 109)

REC No: IRAS: 288722 Sponsor Reference: 9691

Chief Investigators: Professor John Dark and Dr Dan Harvey

I have received a relative information leaflet regarding the SIGNET study (version 1.0 dated 12.04.2021) and had an opportunity to discuss it with a qualified member of staff. I give consent/authorisation to my relative's participation in SIGNET and I give permission for the researchers and individuals from the Sponsor and NHS organisation to accesses my relative's records.

I understand that:

- Participation is voluntary and that I am free to withdraw my relative at any time, without giving any reason, without my relative's medical care or legal rights being affected.
- All information will be anonymised by the allocation of codes and the information will remain confidential and only be used for research.
- Relevant sections of my relative's medical notes and data collected during the trial may be looked at by the trial researchers and individuals from the Sponsor or from the NHS organisation, where it is relevant to my taking part in this research.
- My relative's data will be stored on a password protected secure database accessible only by the research team and independent statistician for 5 years following the trial closure.
- Information about my relative's organ donation, which is already provided to NHS Blood and Transplant, will be used for this study.
- Information collected about my relative could also be used to support other research in the future.

Randomisation

- Randomisation by the SNOD via SealedEnvelope
  - Information needed – Donor ID, medication at admission
- Allocation and Randomisation number (RXXXX) revealed
- Donor team will know allocation but this will be blinded to the retrieval teams, theatre teams and recipient teams

Randomisation in 1:1 ratio, stratified for statin therapy

The PI and research nurse will receive a randomisation notification whenever a patient is randomised at your site.

The Intervention

- SNOD should ask ICU doctor to:
  - Reconfirm eligibility (sign Source data form)
  - Prescribe 80mg Simvastatin tablet
    - Simvastatin from ward stock – no formal drug accountability
    - Prescribed on medication chart as per local hospital policy
      - Eg "Simvastatin 80mg once NG, SIGNET study intervention"

- Bedside nurse administers Simvastatin via NG tube
  - NG tube will need to be sited if not already in place (standard care)
  - 80mg Simvastatin tablet crushed and mixed 20mls sterile water
  - Follow local policy for administering medication via NG tube
  - Flush NG tube 10ml sterile water following administration

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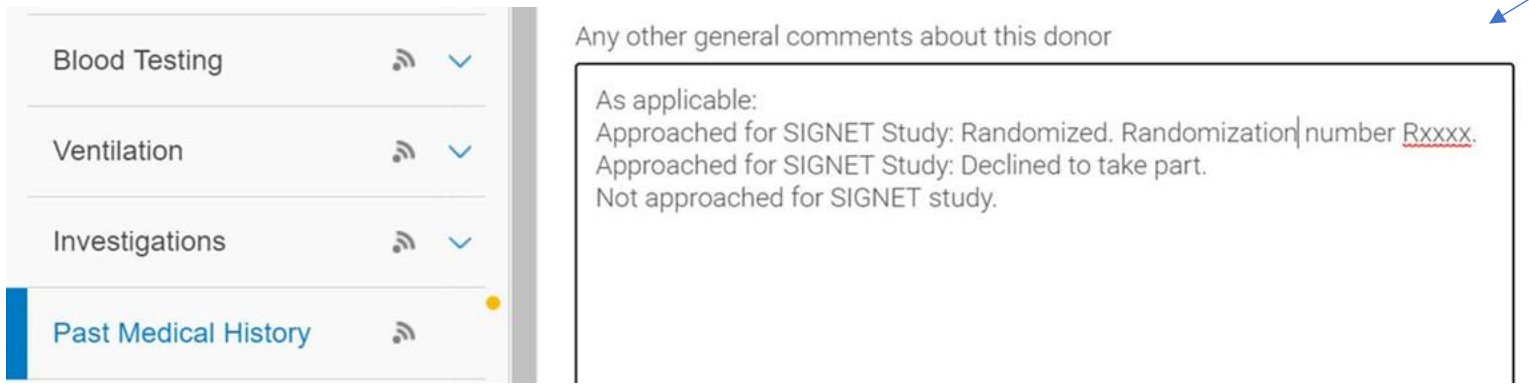
Study Documentation

Source Data Form	Medical Notes	DonorPath	Study Database
Completed by the SNODs, the prescribing doctor and bedside nurse may be asked to complete some sections. Completed forms: - uploaded DonorPath - emailed to SIGNET - left on site in agreed location	ICU doctor **Do not document allocation in notes** e.g “allocation as per SIGNET study randomisation”	SNODs Past Medical History Section: “Approached for SIGNET Study: randomised, randomisation number RXXXX” “Approached for SIGNET study: Declined to take part” “Not approached for SIGNET study”	Completed by the site research team (there will be training for this)



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Source Data From - All of the first page is completed by the SNOD

Site number and Randomisation number will be generated by SealedEnvelope – transcribe from SealedEnvelope

SIGNET

Randomisation number: R

NHS Blood and Transplant

SOURCE DATA FORM

Study site: ..... Site number: Name of Specialist Nurse completing form: .....

Date of Organ Donation: 2 0 (D D M M Y Y Y Y) ODT Donor ID number:

CONSENT/AUTHORISATION

Date of consent/authorisation for organ donation: 2 0 (D D M M Y Y Y Y)

Date of study specific consent/authorisation: 2 0 (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

Date and time of randomisation:

2 0 (D D M M Y Y Y Y)

Randomisation number: R

Randomisation allocation:

- Standard Care ONLY
- 80mg Simvastatin in addition to all standard care

SCREENING: 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 hypersensitivity to simvastatin		

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

Name of person confirming eligibility: .....

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

SIGNET

Randomisation number: R

NHS Blood and Transplant

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

D D M M Y Y Y Y (2 0) — 24 hour clock H H : M M

Name of prescriber: .....

Has 80mg Simvastatin been administered? YES ☐ NO ☐

If Yes, Date and time of Simvastatin administration

D D M M Y Y Y Y (2 0) — 24 hour clock 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 D D M M Y Y Y Y (2 0)

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/ALTER TREATMENT

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

If Yes, date of request D D M M Y Y Y Y (2 0)

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 ☐

Usually completed by prescribing doctor and the bedside nurse administering Simvastatin

Completed by SNOD

only completed if needed, completed by SNOD but amended by research team

only completed if needed, completed by SNOD but amended by research team

Safety Reporting

There is no safety reporting in recipients (secondary outcomes), SAEs will only be reported in donors.

Serious Adverse Events should be discussed with and then assessed by the PI.

Serious Adverse Events are assessed by PI and should be reported to the central study team if they are:

- Related to research procedure
- Unexpected (not listed in the protocol section 9 as an expected event)
- Loss of capacity to donate as a result of research procedures will be recorded as an SAE on the study database

SAEs should be recorded on the study database within 24 hours of becoming aware

The central study team take responsibility for reporting any SAEs to the REC if required

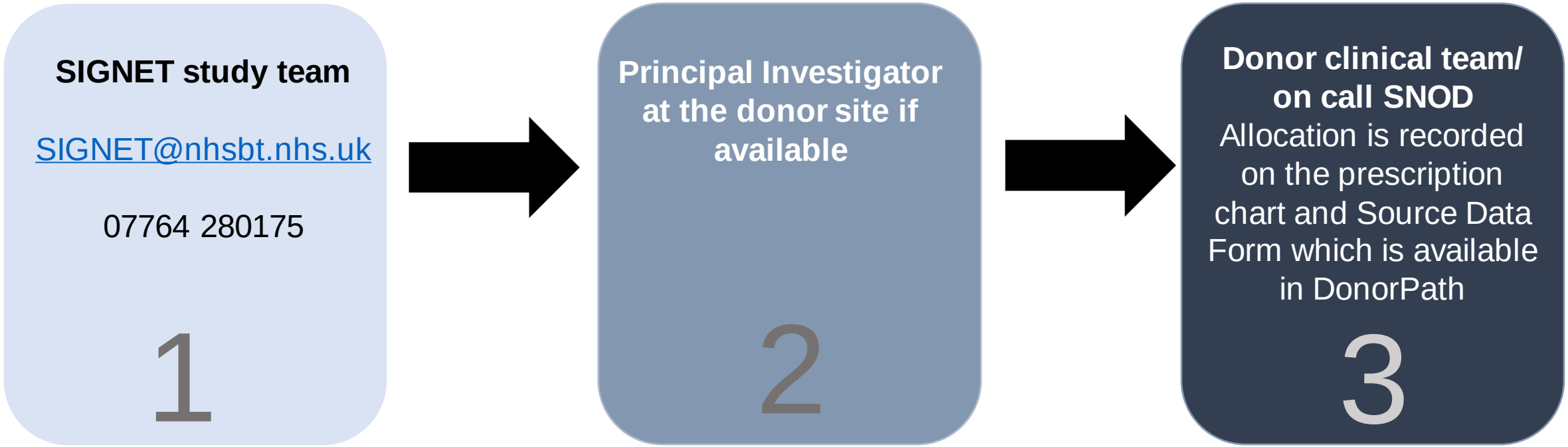
Unblinding

- Donor care team (ICU & SNODs) are not blinded
- Recipient, retrieval and theatre teams **are blinded** to the intervention
- Care is needed not to accidentally unblind retrieval teams!

- A request to unblind the recipient can be made by transplanting team if:
  - The recipient has/would be predicted to come to **harm**
  - Recipient's **treatment would be altered** if allocation was known

Unblinding

Requests to unblind should be made by the potential recipients treating consultant. There are 3 available mechanisms to unblind.



This should be documented on the Source Data Form and the trial database

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Protocol Deviations

- Please notify NHSBT CTU of deviations from the protocol or GCP within 24 hours of becoming aware
- Please document this on a protocol deviation file note and send it to SIGNET@nhsbt.nhs.uk
- Please contact NHSBT CTU if in any doubt as to whether a certain situation constitutes a protocol deviation
- SNODs and ICU teams should report incidents via their clinical governance pathway – they will alert the research team if there are any related incidents

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Serious Breaches

A '**serious breach**' is a breach *of either GCP or the protocol* that is likely to affect to a significant degree: the safety or physical or mental integrity of the participants; or the scientific value of the trial.

- Report immediately of becoming aware to CTU by phone AND email (SIGNET@nhsbt.nhs.uk , 01223 588 016 / 07764 280175)
- Do not wait for local investigations to be complete
- Examples include drug errors, inappropriate breaking of the blind or incorrect consent procedures (use of deemed consent)
- CTU will work with sites to resolve issues

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PI Role

As PI you are responsible for the conduct of research at your site. As such, it is your responsibility to:

- Ensure tasks are delegated and signed off on the delegation of duties log
- Ensure that the ICU team are aware of the study and have had the training cascaded
- Assess SAEs and sign them off on the study database
- Sign off the 'end of study' form on the study database for each patient to ensure that all data collected is accurate
- Have oversight of the study

Sponsors and Funders

Sponsor	NHS The Newcastle upon Tyne Hospitals NHS Foundation Trust
Funder	SUPPORTED BY NIHR | National Institute for Health Research
Study Management	CTU and OTDT research team NHS Blood and Transplant

Trial Oversight

- Trial Steering Committee
- Trial Management Group
- Data Monitoring Committee

Regular progress reports to

- Sponsor
- Funders (NIHR HTA Programme)
- Research Ethics Committees

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Monitoring

- TMG will review and monitor data centrally
- Consent monitored remotely (NHSBT)
- Remote monitoring with sites
  - Site file checklist
  - Monitoring checklist
  - Call to discuss progress and any issues
- If needed, further monitoring

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Investigator Site File

- Site file will be maintained by the local site research team
- We will send you all documents electronically (also available to download on the website)
- Site file will be monitored

End of Study

- Close out / final monitoring call
- Archiving

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Training

- Please confirm your SIV attendance by emailing SIGNET@nhsbt.nhs.uk

- SNODs will be asking ICU doctors if they have received cascaded study training
- Training can be cascaded – use the video or slides on the website
  - Document this on your site training log
  - Please send updated training logs to SIGNET@nhsbt.nhs.uk

- Key documents available here: www.nhsbt.nhs.uk/SIGNET

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What next?

- We will send a prepopulated training log when PI and research team have attended training
  - You will need to cascade training to the ICU team and send us back the updated training log
  - MACRO Training for anyone entering data (PI and research team)
- Delegation log, PI Statement and site agreement
- R&D confirmation of capability and capacity
- We'll check that everything is in place and then send the green light email
  - Activate sites on SealedEnvelope

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Any Questions?

Phone 01223 588016

Email SIGNET@nhsbt.nhs.uk

Website www.nhsbt.nhs.uk/SIGNET

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Contacts

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