

Desmopressin for reversal of Antiplatelet drugs in Stroke due to Haemorrhage (DASH)

EudraCT:2018-001904-12

PHARMACY MANUAL

Version 1.0, 8th January 2019

Chief Investigator: Professor Nikola Sprigg
 Sponsor: University of Nottingham
 Sponsor Reference:18040

Written by: (Print & sign)	Bernie Cook		Date:
Title	Lead Pharmacy Technician – Clinical Trials (NUH NHS Trust)		

Approved by: (Print & sign)	Sheila Hodgson		Date:
Title	Lead Pharmacist – Clinical Trials (NUH NHS Trust)		

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Chief Investigator**

Applicability

This procedure applies to all pharmacy personnel at participating sites. Its purpose is to ensure that the processes of storing, labelling, ordering, dispensing accounting for and destroying IMP are carried out to the standard required for DASH and in accordance with the applicable ICH-GCP principles.

Responsibilities

All personnel carrying out study related activities should be listed on the DASH Authorised Personnel Log and be appropriately trained and familiar with the trial, its protocol and procedures.

For each site a lead pharmacist should be identified. This person will have overall responsibility for the study and will be required to sign a lead pharmacist declaration form and return this to the STU prior to the IMP being received at site

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2. Abbreviations

ICH-GCP	International Conference on harmonisation – Good Clinical Practice
IMP	Investigational Medicinal Product
MA	Marketing Authorisation
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
STU	Stroke Trials Unit
PI	Principal Investigator
PSF	Pharmacy Site File

3. Study Contacts

Chief Investigator:

Professor Nikola Sprigg

Tel:0115 8231765

Email:nikola.sprigg@nottingham.ac.uk

Deputy Chief Investigator:

Dr Michael Desborough

Tel:01865 447900

Email:Michael.desborough@ouh.nhs.uk

DASH Trial Manager & Coordinator:

Diane Havard

Tel:0115 8231775 Fax:0115 8231771

Email: ms-dash@nottingham.ac.uk

Trial Pharmacist:

Sheila Hodgson

Tel:0115 9194450 or 0115 9691169 Ext. 55280

Email:sheila.hodgson@nuh.nhs.uk

Emergency Contact details (including unblinding)

Tel:07736 843 592

Tel:07725 580 092

Tel:07943 470 427

Tel:07798 670 726

DASH Website (login details provided to each site separately)

<http://dash-1.ac.uk>

DASH documents

<http://dash-1.ac.uk/docs>

4. Introduction

The study will recruit patients for 12 months. The participant's involvement in the trial will last for 90 days, from randomisation (day 1) until final follow-up at 90 days.

Trial treatment is administered as desmopressin 20µg (5 x 4mcg/ml) in 50ml sodium chloride 0.9% (total infusion volume of 55mls). Placebo treatment replaces desmopressin with sodium chloride 0.9%, 3 x 2ml in 50ml sodium chloride 0.9% (total infusion volume of 56ml). Doses are administered through a venous cannula over 20 minutes.

5. Study Medication

Nottingham University Hospital pharmacy (MIA IMP 19162) will prepare individual blinded treatment packs containing 5 x 1ml glass ampoules desmopressin 4mcg/ml or 3 x 2ml sodium chloride 0.9%. These will be non-identical. The ampoules and the outer carton will be labelled in accordance with Annex 13 of Volume 4 of The Rules Governing Medicinal Products in the EU: Good Manufacturing Practices, assuming that the primary and secondary packaging remain together throughout the trial. To facilitate identification, the carton and the ampoules contained within it will be labelled with the same unique pack ID number. Additional labels to identify the trial and subject randomisation number will be provided for attachment to intravenous infusion bags, case report forms and participant's medical records.

Personnel preparing the injection for administration will not be masked to the treatment allocation as the ampoules of active and placebo injections are of different sizes and the number of ampoules in the cartons is different for active and placebo treatments. The ampoules are labelled only as trial medication so the researchers and patient will remain blinded to treatment allocation. Detailed prescribing and administration instructions will be provided in the treatment pack.

Desmopressin

Intravenous desmopressin (DDAVP) 4µg/ml 1ml glass ampoules are a licensed product (Ferring Pharmaceuticals). A SmPC is available.

Placebo

Intravenous Sodium Chloride 0.9% will be used as the placebo in this study. Sodium Chloride 0.9% 2ml ampoules are a licensed product. A SmPC is available.

6. Storage

IMP packs must be stored in a refrigerator between 2°C and 8°C.

To ensure stability and quality are maintained, the product must be stored correctly upon receipt and for the duration of the study under the conditions specified above. IMP should be stored in a controlled environment, in a trial specific area separated from the general NHS stock. Access should be controlled and limited only to authorised personnel

Temperature Monitoring

Records of the actual storage conditions during the period of the study must be maintained.

Pharmacy staff should ensure that the location of temperature logs for the area(s) where the trial medication is stored is referenced in the PSF. (Appendix 1 or PSF section 4). A minimum and maximum temperature must be recorded every weekday as a minimum (excluding bank holidays), with a calibrated temperature monitoring device. Temperature logs must be available for review during monitoring visits, if requested.

Temperature Excursions

In the event of a temperature excursion, all affected IMP should be quarantined immediately. A temperature excursion form (Appendix 2 or PSF section 4) should be completed and sent to the DASH Trial Manager Tel:0115 8231775 Fax:0115 8231771 Email: ms-dash@nottingham.ac.uk and NUH Pharmacy Clinical Trials (gmc.pharmacyclinicaltrial@nuh.nhs.uk or fax:0115 9194450).

7. Labelling

In line with sites local policy, additional labels are permitted.

All IMP's provided will be labelled in accordance with Annex 13, plus additional site specific information on the outer carton.

Sample Ampoule Label:

<p>Store in a refrigerator at 2-8°C For Intravenous use only</p> <p>Desmopressin 4 micrograms per 1ml or Placebo Injection</p> <p>Subject Name _____ Subject ID Number _____</p> <p>Pack ID XXXXX</p> <p>Batch Number: xxxxxx Expiry Date: xx.xx.xx</p> <p>Sponsor: University of Nottingham, Tel: 0115 8231770</p> <p>EudraCT Number 2018-001904-12</p> <p>Packed by NUH Pharmacy MIA(IMP)19162</p>

Sample Outer Carton Label:

<p>For Clinical Trial Use Only Store in a refrigerator at 2-8°C</p> <p>For Intravenous Use Only</p> <p>Desmopressin for reversal of Antiplatelet drugs in Stroke due to Haemorrhage (DASH)</p> <p>Desmopressin 4 microgram per 1ml or Placebo Injections</p> <p>To be used as directed in the trial protocol</p> <p>This pack contains 3 or 5 ampoules of study material</p> <p>Subject Name _____ Subject ID Number _____</p> <p>Date of dispensing _____ Pack ID XXXXX</p> <p>Batch Number: xxxxx Expiry Date: xx/xx/xx</p> <p>Chief Investigator: Prof. Nikola Sprigg, University of Nottingham, Clinical Sciences Building, Hucknall Road, NG5 1PB. Tel: 0115 8231770</p> <p>Sponsor: University of Nottingham</p> <p>EudraCT Number 2018-001904-12</p> <p>Keep out of reach and sight of children</p> <p>Packed by NUH Pharmacy MIA(IMP)19162</p>

Label content will remain as shown above, however the formatting of final versions may vary.

8. Ordering & Receipt

Initial Order & Resupply

Ordering and resupply will be under the control of the STU.

Sites will receive notification of pending shipments via email.

Participating sites will be allocated a batch of trial treatment. The container numbers for the batch are tracked by the web-based system to the participating site. When receipt at site is confirmed and temperature records for the transit period have been received and reviewed, containers are released for use in the trial. When the supplies at the participating site reach a pre-determined level a re-order is triggered and a further supply of trial treatment is sent to the participating site.

The study medication will be distributed by Clinical Trials Pharmacy, Nottingham University Hospitals NHS Trust Queens Medical Centre Campus, Derby Road, Nottingham, UK, NG7 2UH.

Sites will receive the shipment within a maximum of two working weeks. A copy of the QP Release Certificate will be included in each shipment.

Receipt

Upon receipt of a shipment, it is the pharmacy staff responsibility to:

- Check study drug received against the Acknowledgement of Receipt Form (Appendix 3).
- Check that supplies are received undamaged
- Sign the Acknowledgement of Receipt form and fax or email to the DASH Trial Manager
Tel:0115 8231775 or Fax:0115 8231771, Email: ms-dash@nottingham.ac.uk
and
NUH Pharmacy Clinical Trials (qmc.pharmacyclintrial@nuh.nhs.uk or Fax:0115 91954450).
- Quarantine supplies and await confirmation of suitability for use/further instruction from DASH Trial Manager .
- Record all supplies on the Pharmacy – IMP Site Inventory Log (Appendix 5 or PSF Section 1).
- Login to the DASH website (<http://dash-1.ac.uk>) and mark packs as received.
- File the Acknowledgement of Receipt forms in the PSF Section 3.

Any complaints related to product quality must be submitted via email to the DASH Trial Manager Tel:0115 8231775 Fax:0115 8231771 Email: ms-dash@nottingham.ac.uk who will forward to NUH Pharmacy Clinical Trials as appropriate.

9. Randomisation

All participants eligible for inclusion will be randomised centrally using a secure internet in real time.

Randomisation will allocate a number corresponding to a treatment pack and the participant will receive treatment from the allocated numbered pack.

Personnel preparing the injection for administration will not be blinded to the treatment allocation as the ampoules of active and placebo injections are of different sizes and the number of ampoules in each carton is different for active and placebo treatments.

In the event of computer failure (for example: server failure), investigators will follow the working practice document for computer system disaster recovery, which will allow the participant to be randomised following standardised operating procedure. This document will be given to the PI at participating sites.

10. Prescribing

Only the PI or qualified medical doctors delegated with the responsibility of prescribing by the PI should prescribe medication for study patients.

Refer to Prescribing and Administration Guide included in each treatment pack (Appendix 9)

Additional labels to identify the trial title and subject randomisation number will be provided for attachment to intravenous infusion bags, case report forms and participants medical records.

Sample Label

This patient has been recruited into the DASH trial. Desmopressin for the reversal of Antiplatelet drugs in Stroke due to Haemorrhage

Randomisation No:

Sponsor: The University of Nottingham. Ref: 18040

Please call the DASH Office if you have any queries.
(+44) 115 82 31672

Please retain these notes until 31/12/2028 v1.0 20181220

11. Dispensing & Accountability

The local site investigator is responsible for ensuring trial treatment accountability, including reconciliation of trial treatment and maintenance of trial treatment records, throughout the course of the study in accordance with UK regulatory requirements. Responsibility can be delegated to the site pharmacy clinical trials staff.

Pharmacy

The site pharmacy will be responsible for issuing the IMP to the Stroke Unit at site. A DASH IMP Transfer Request Form (Appendix 4) must be completed.

The pharmacy clinical trials staff will check that the person completing the Transfer Request Form has delegated responsibility by the PI by reference to the study delegation log.

All IMP issued by Pharmacy to the Stroke Unit must be recorded on the Pharmacy IMP Inventory Log (Appendix 5) and details completed on the DASH IMP Transfer Request Form.

Stroke Unit

The Research Team on the Stroke Unit will be responsible for dispensing the IMP to subjects.

Upon receipt of IMP from the site Pharmacy, allocation of IMP to a subject or return of used/unused packs to the site Pharmacy, the details should be recorded on the Stroke Unit IMP Accountability Log (Appendix 6).

Following randomisation, the participant will be allocated a treatment pack number. Specifically authorised personnel on the delegation log will retrieve the appropriate pack number and complete the participant name, date of randomisation and participant number. Pack number allocation will be checked and countersigned by the research staff and the nursing staff administering the treatment. The empty IMP boxes do not need to be returned to pharmacy. They can be disposed of on the Stroke Unit once the accountability log has been completed. Refer to Appendix 9, DASH Prescribing & Administration Guide)

If returning IMP to the site Pharmacy from the Stroke Unit (e.g. unused or expired pack) a DASH Return of Clinical Supplies form (Appendix 7 or PSF Section 3) must be completed to accompany the packs. The Stroke Unit IMP Accountability Log should be completed, documenting return to the site Pharmacy. Any unused ampoules must be recorded on the Stroke Unit IMP Accountability Log, using the 'comments' section for the Pack Number returned.

In the event a treatment pack is damaged, the site should inform the DASH Trial Manager in order that the website can be updated.

If any packs are lost, the site investigator should complete a non-participant protocol violation CRF or, if unable to do this, they should contact the DASH Trial Manager.

12. Replacement IMP Packs

If the allocated IMP pack is lost or damaged prior to administration, the IMP pack should be replaced. The site team should contact the DASH Trial Manager (or an emergency study contact if out of hours)

13. Code break & Unblinding

Clinicians, patients and outcome assessors (clinical, radiological and haematological assessors) will be blinded to treatment allocation.

In general there should be no need to unblind the allocated treatment. If a contraindication to desmopressin develops after randomisation (e.g. clinical evidence of thrombosis), the trial treatment should simply be stopped. Unblinding should be done only in those rare cases when the doctor believes that clinical management depends importantly upon knowledge of whether the patient received desmopressin or placebo. In those few cases when urgent unblinding is considered necessary, the emergency telephone number should be telephoned, giving the name of the doctor authorising unblinding and the treatment pack number. The caller will then be told whether the patient received desmopressin or placebo. The rate of unblinding will be monitored and audited. The emergency contact details will be given to the investigators at participating sites.

Emergency Out of Hours contacts
 Nikola Sprigg – Tel: 07725 580092
 Mike Desborough – Tel:07736 843592
 Philip Bath – 07798 670726

14. Destruction

Retain all returned unused ampoules in pharmacy until permission is given to destroy

Destruction should be carried out by the site Pharmacy according to local SOPs, only after any discrepancies have been investigated and satisfactorily explained. Reconciliation will be accepted and confirmed in writing by the sponsor/representative prior to any destruction taking place. Destruction will be documented on the DASH IMP Destruction Log (Appendix 8 or PSF Section 3), which should be filed in the PSF.

Destruction of any study medication that is unused at the end of the study or has expired should only be completed following written approval from the sponsor.

Once destruction of packs is completed the site pharmacy staff should login to the DASH website and mark the appropriate pack(s) as destroyed.

15. Version Control

Version Number	Amended By	Amendment Date	Changes implemented by this amendment

Appendix 1

TEMPERATURE LOG

Temperature Range 2°C to 8°C

DASH (EudraCT:2018-001904-12)

Investigator:..... Site:.....

Month:..... Year:.....

Thermometer Location/Thermometer Number:

.....

Inform DASH Trial Manager if temperature is outside permitted range (Tel:0115 8231775 Fax:0115 8231771
Email: ms-dash@nottingham.ac.uk)

Date	Time	Temperature °C			Recorded by	Comments
	24 hour clock	Current	Minimum	Maximum		
01						
02						
03						
04						
05						
06						
07						
08						
09						
10						
11						
12						
13						
14						
15						
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31						

Appendix 2

Temperature Excursion Reporting Form

Desmopressin For Reversal Of Antiplatelet Drugs In Strike Due To Haemorrhage (DASH)

Sponsor: University of Nottingham

EudraCT: 2018-001904-12

Investigator: _____

Site: _____

Site No: _____

Start Date & Time of Temperature Excursion:	___/___/___ ____:____	End Date & Time of Temperature Excursion:	___/___/___ ____:____
Duration of Temperature Excursion (hours/days):		Minimum Temperature Recorded:	
		Maximum Temperature Recorded:	
Reason for temperature excursion:			
Pack numbers affected by excursion			
Date DASH Trial Manager informed:	___/___/___		
Action taken by Site / Pharmacy:			
Reported By: Name:		Signature:	Date: ___/___/___
Reviewed By: Trial Manager:		Signature:	Date: ___/___/___
Outcome:			

Appendix 3

**Nottingham University Hospitals
Pharmacy Clinical Trials Department**

Desmopressin for reversal of Antiplatelet drugs in Stroke due to haemorrhage (DASH)

RECEIPT OF CLINICAL TRIAL SUPPLIES

Despatched To:

Despatched from:

**S Hodgson/S Hodgkinson/B Cook
Pharmacy Clinical Trials
Queens Medical Centre Campus
Nottingham University Hospitals NHS Trust
Derby Road
Nottingham, NG7 2UH**

Date dispatched:

Investigational Medicinal Products enclosed as listed below: -

Description	Batch Number & Expiry Date	Number of packs supplied	Individual Pack Number(s) supplied
Treatment Packs containing: Desmopressin 4microgram/ml injection or Sodium Chloride 0.9% injection (placebo)	BN: Exp:		

Please complete information below and fax or email to the DASH Trial Manager
(Tel:0115 8231775, Fax:0115 8231771 Email: ms-dash@nottingham.ac.uk) **and NUH Pharmacy Clinical Trials** (qmc.pharmacyclinicaltrial@nuh.nhs.uk or Fax:0115 91954450)

Drugs received: (Date & time): ____ / ____ / ____ at ____ am/pm

- All received as described and undamaged? YES / NO (Circle as applicable)
- Quarantined and awaiting confirmation that all packs received within the specified temperature range? YES / NO (Circle as applicable)

Please comment on any discrepancies:.....
.....

Received By: _____

(Signature + Print Name)

Designation: _____

(Print Position)

Appendix 4

CLINICAL TRIALS TRANSFER REQUEST FORM

Desmopressin for reversal of Antiplatelet drugs in Stroke due to Haemorrhage
(DASH)

EudraCT:2018-001904-12

Chief Investigator: Professor N Sprigg/Dr Michael Desborough

Local Investigator:.....

Please Supply:

Treatment packs containing:

3 x 2ml ampoules Desmopressin 4microgram/ml

or

5 x 1ml ampoules Sodium Chloride 0.9%

Date Required:

Ordered by (sign): Bleep/Ext No:

Name in Block Capitals: Date:

FOR PHARMACY USE ONLY

Issued by: Date:

Number of packs issued:.....

Pack Numbers Issued:.....

.....

Checked by: Date:

Collected by: Date:

Appendix 5

Nottingham University Hospitals NHS Trust Pharmacy Department Clinical Trials Service		
Pharmacy - Site IMP Inventory Log		
Protocol Name: Desmopressin for reversal of Antiplatelet drugs in Stroke due to Haemorrhage (DASH)	Protocol/EudraCT Number: 2018-001904-12	
IMP (form and strength): Desmopressin 4microgram/ml or Placebo Injection	Chief Investigator: Professor Nikola Sprigg/ Dr Michael Desborough	Site number:
	Principle Investigator:	

Date dd/mmm/yy	Pack Number	Batch number	Expiry	Quantity R : Received D: Dispensed E: Expired DES: Destroyed R D E /DES	Issued To	Balance	Received / Disp By	Checked By	Additional Comments	Checked By Sponsor

Appendix 6

Nottingham University Hospitals NHS Trust Pharmacy Department Clinical Trials Service		
<u>Stroke Unit</u> – IMP Accountability Log		
Protocol Name: Desmopressin for reversal of Antiplatelet drugs in Stroke due to Haemorrhage (DASH)	Protocol/ EudraCT Number: 2018-001904-12	
IMP (form and strength): Desmopressin 4microgram/ml or Placebo Injection	Chief Investigator: Professor Nikola Sprigg/ Dr Michael Desborough Principal Investigator:	Site number:

Receipt				Issued to Subject						Return to Pharmacy			Comments
Date Received (dd/mmm/yy)	Pack ID Number	Expiry Date	Received By	Date Issued (dd/mmm/yy)	Subject Trial ID Number	Subject Name	Subject Hospital Number	Issued By	Check By	Date Returned to Pharmacy (dd/mmm/yy)	Quantity Returned	Returned By	

Appendix 7

Desmopressin for reversal of Antiplatelet drugs in Stroke due to Haemorrhage (DASH)

EudraCT Number: 2018-001904-12

Local Investigator: Site:.....

The following clinical trial supplies have been returned to pharmacy

Description	Used or Unused Pack(s)	Number of Packs Returned	Pack ID Number(s)
Pack(s) containing: Desmopressin 4µg/ml ampoules or Sodium Chloride 0.9% ampoules			

Stroke Unit Staff		Date	Pharmacy Staff		Date
Returned by			Checked & Received by		
Print Name			Print Name		

For Pharmacy Use Only

Action	Signature & Date	Outcome	Signature & Date
To be quarantined in pharmacy			
To be sent for destruction			

1 copy to investigator file 1 copy to pharmacy file

Appendix 8

RECORD OF IMP DESTRUCTION

At the request of:

Sponsor: University of Nottingham

Sponsor Representative:

Address: East Atrium, Jubilee Conference Centre, Triumph Road, Nottingham. NG8 1DH

(Attach a copy of the authorisation email/correspondence)

The following IMP have been sent for destruction by pharmacy according to local SOPs for destruction of pharmaceutical waste

Study Title: Desmopressin For Reversal Of Antiplatelet Drugs In Strike Due To Haemorrhage (DASH)
EudraCT Number:2018-001904-12

Pack ID Number	Patient Number (if applicable)	Description	Quantity (number of ampoules)	Batch Number	Expiry Date
		Pack containing Desmopressin 4µg/ml 1ml amps or Sodium Chloride 0.9% 2ml amps			
		Pack containing Desmopressin 4µg/ml 1ml amps or Sodium Chloride 0.9% 2ml amps			
		Pack containing Desmopressin 4µg/ml 1ml amps or Sodium Chloride 0.9% 2ml amps			
		Pack containing Desmopressin 4µg/ml 1ml amps or Sodium Chloride 0.9% 2ml amps			
		Pack containing Desmopressin 4µg/ml 1ml amps or Sodium Chloride 0.9% 2ml amps			

Documented for destruction by:.....Date:.....

Name (PRINT):Title:.....

Verified and sent for destruction by:.....Date:.....

Name (PRINT):.....Title:.....

Completed forms to be filed in the Pharmacy File.

Appendix 9

Study Title	Desmopressin for reversal of Antiplatelet drugs in Stroke due to Haemorrhage (DASH)
Protocol No	EudraCT Number 2018-001904-12

Prescribing and administration guide

At randomisation a subject is allocated a subject ID number and a corresponding treatment pack ID number from the stock available at site

Investigational medicinal product (IMP) is prescribed on the participants inpatient treatment chart by a medically qualified individual **who is authorised to prescribe for this study** (refer to trial delegation log for sample signatures.)

In the ONCE ONLY/PRE-OPERATIVE MEDICINES AND PGDS section of the chart prescribe:

DASH STUDY Subject ID Number XXX Pack ID XXX
Total contents of pack: 3 or 5 ampoules (containing Desmopressin 20micrograms or 0.9% sodium chloride) added to 50ml Sodium Chloride 0.9% administered as an IV infusion over 20 minutes .

An additive label for use on each infusion bag is included in the IMP pack provided by pharmacy.

Dispensing and Administration

- select the pack labelled **with the required pack ID** from the stock held in the trials cupboard
- add subject name subject ID number and date of dispensing to the label on the outer packaging
- add subject name and subject ID number to each ampoule label.
- enter subject details in the accountability log against the allocated pack ID

Administer in accordance with the prescription.

Empty packaging and used ampoules can be disposed of on the ward after completion of accountability log. Unused IMP should be returned to clinical trials pharmacy.

Temperature excursions below 2°C and above 8°C should be reported to the clinical trials pharmacy and the trial office as soon as possible