DASH

Statistical Analysis Plan – Appendix: Dummy tables and figures

Version 1.0
26 July 2022

Based on Protocol version 2.1 5 May 2022

Trial registration: ISRCTN67038373

The following people have reviewed the SAP Dummy tables and are in agreement with the contents				
Name	**Job Title**	**Trial role**	**Signature**	**Date**
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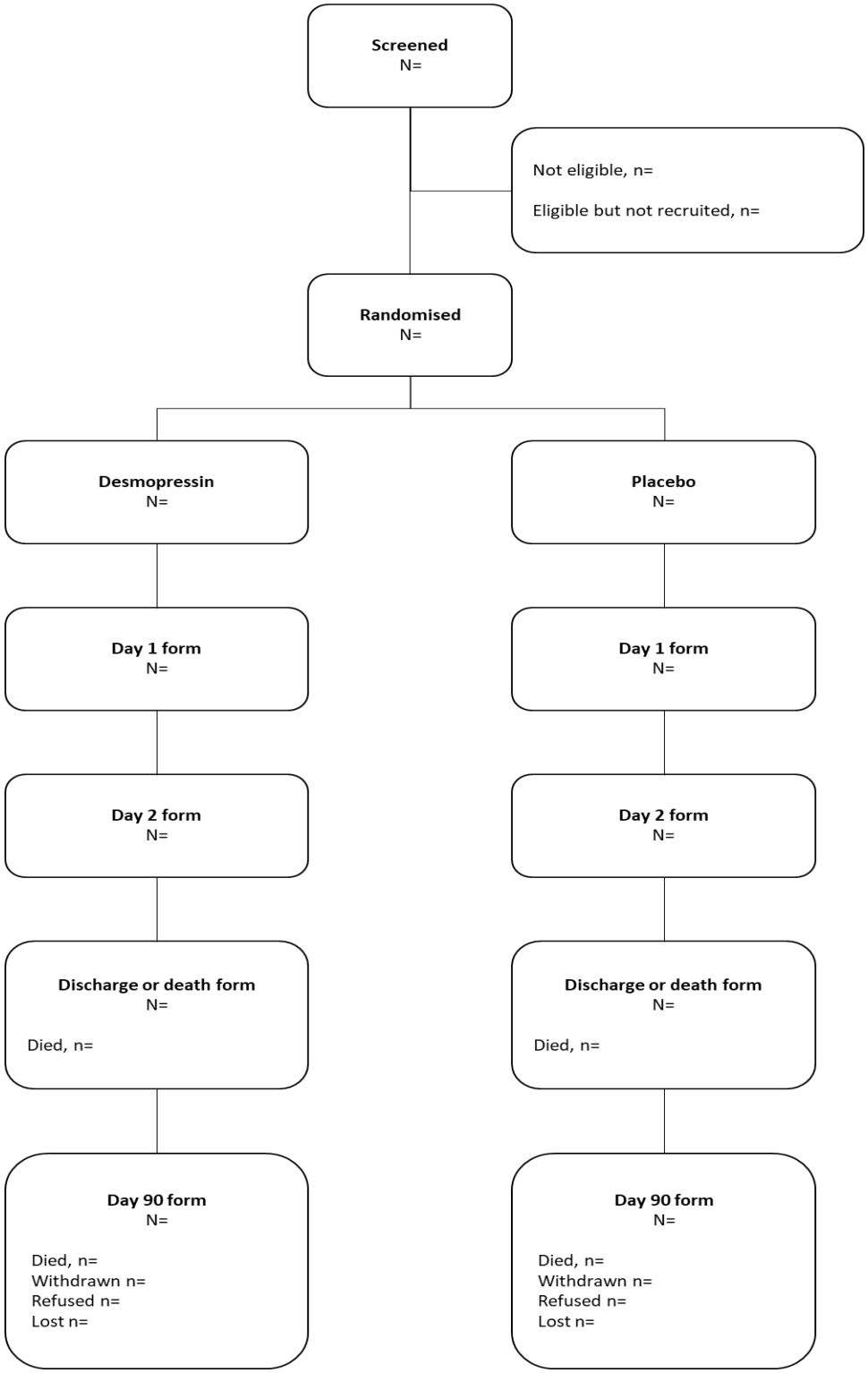
1 Study recruitment

1.1 Participant flow diagram



1.2 Screening and enrolment

Table 1: Recruitment by site

Site name	Date site opened	Date of first recruitment	Date site closed	Months open	Total recruited	Monthly recruitment
Nottingham University Hospital						
St George's Hospital, London						
Leicester Royal Infirmary						
Royal Stoke University Hospital						
Royal Derby Hospital						
Royal Victoria Infirmary						
Royal Devon and Exeter Hospital						
University College London Hospital						
Aberdeen Royal Infirmary						
Royal Infirmary of Edinburgh						
All sites						

Table 2: Screening log overview by site

Site	Screened	Eligible	Recruited	Eligible but not recruited	Excluded
Nottingham					
St Georges					
Leicester					
Stoke					
Derby					
Newcastle					
Devon and Exeter					
UCLH					
Aberdeen					
Edinburgh					
All sites					

Table 3: Reasons for exclusion

Site	All	Not meeting inclusion criteria						Further reasons for non-recruitment						Patient declined
		No prior APTs	Out of time	End of Life	On ACT	mRS 5	Other†	Out of hours	Unknown onset time	No Dr available	Traumatic bleed	Recruit-ment on hold	Other¥	
Nottingham														
St Georges														
Leicester														
Stoke														
Derby														
Newcastle														
Devon and Exeter														
UCLH														
Aberdeen														
Edinburgh														
All sites														

1.3 Baseline data

Table 4: Randomisation characteristics

Variable		**All**	**Desmopressin**	**Placebo**
Number of patients randomised	**N**			
Age, years	Mean (SD) {range}			
	>=70 years (%)			
Sex	Male (%)			
Time from onset to randomisation (hours)	Median [IQR] {range}			
	>=12 hours (%)			
Pre-stroke mRS	Median [IQR] {range}			
	>2 (%)			
Glasgow Coma Scale	Median [IQR] {range}			
	<8 (%)			
Systolic blood pressure (mmHg)	Mean (SD) {range}			
	>=170 mmHg (%)			
Diastolic blood pressure (mmHg)	Mean (SD) {range}			
Intra-ventricular haemorrhage	Yes (%)			
Haemorrhage Volume (mL) [SAS]	Median [IQR] {range}			
History of antiplatelet therapy on admission	Yes (%)			
If yes, what	Aspirin alone (%)			
	Clopidogrel alone (%)			
	Aspirin + Dipyridamole (%)			
	Aspirin + Clopidogrel (%)			

Table 5: Day 1 and Day 2 Characteristics

Variable		All	Desmopressin	Placebo
Day 1				
Number of patients	**n**			
Dominant hand	Right (%)			
Ethnicity	Non-white (%)			
Location of stroke	Lobar (%)			
	Deep (%)			
	Infratentorial (%)			
Haemorrhage volume (ABC/2)	Mean (SD) {range}			
Haemodynamics				
Taken during infusion				
- Systolic BP (mmHg)	Mean (SD) {range}			
- Diastolic BP (mmHg)	Mean (SD) {range}			
- Heart rate (bpm)	Mean (SD) {range}			
Taken after infusion				
- Systolic BP (mmHg)	Mean (SD) {range}			
- Diastolic BP (mmHg)	Mean (SD) {range}			
- Heart rate (bpm)	Mean (SD) {range}			
Medical history				
History of Ischaemic stroke or TIA	Yes (%)			
History of IHD	Yes (%)			
History of hypertension	Yes (%)			
History of diabetes	Yes (%)			
History of atrial fibrillation	Yes (%)			
History of haemorrhagic stroke	Yes (%)			
History of hyperlipidaemia	Yes (%)			
History of statin use	Yes (%)			
History of peripheral arterial disease	Yes (%)			
Smoking, Current	Yes (%)			
Alcohol intake	> 21 units per week (%)			
Investigations				

Variable		All	Desmopressin	Placebo
ECG	AF (%)			
Sodium (mmol/L)	Mean (SD) {range}			
Potassium (mmol/L)	Mean (SD) {range}			
Urea (mmol/L)	Mean (SD) {range}			
Creatinine (mmol/L)	Mean (SD) {range}			
Pre-treatment study samples				
P-selectin sample taken	Yes (%)			
FVIII and vWF sample taken and frozen	Yes (%)			
Assessments				
NIHSS	Median [IQR] {range}			
Day 2				
Number of patients	**n**			
Weight (Kg)	Mean (SD) {range}			
Do Not Attempt Resuscitation	Yes (%)			
Haemodynamics				
Systolic BP (mmHg)	Mean (SD) {range}			
Diastolic BP (mmHg)	Mean (SD) {range}			
Heart rate (bpm)	Mean (SD) {range}			
Investigations				
Sodium (mmol/L)	Mean (SD) {range}			
Sodium <135 mmol/L	n/N (%)			
Sodium <125 mmol/L	n/N (%)			
Potassium (mmol/L)	Mean (SD) {range}			
Urea (mmol/L)	Mean (SD) {range}			
Creatinine (mmol/L)	Mean (SD) {range}			
Assessments				
NIHSS	Median [IQR] {range}			
Change in NIHSS (Day 2 - Day 1)	Median [IQR] {range}			
Neurological deterioration*	Yes (%)			
Glasgow Coma scale	Median [IQR] {range}			

2 Adherence

Table 6: Compliance with allocated treatment

Variable		All	Desmopressin	Placebo
Number of patients	**n**			
All randomised treatment received	Yes (%)			
None or not all randomised treatment received*	Yes (%)			

3 In-hospital outcomes

Table 7: Final Diagnosis of the qualifying event

Variable		All	Desmopressin	Placebo
Number of patients	**n**			
Final diagnosis				
Intracerebral haemorrhage with no known underlying cause	Yes (%)			
Intracerebral haemorrhage with underlying cause*	Yes (%)			
Ischaemic stroke with haemorrhagic transformation	Yes (%)			
Ischaemic stroke without haemorrhagic transformation	Yes (%)			
Non-stroke/other	Yes (%)			
***Underlying cause**				
Amyloid angiopathy	Yes (%)			
AVM	Yes (%)			
Tumour	Yes (%)			
Aneurysm	Yes (%)			
Venous infarct	Yes (%)			
Coagulopathy	Yes (%)			
Hypertension	Yes (%)			
Other	Yes (%)			

Table 8: Outcomes at discharge

Variable		**All**	**Desmopressin**	**Placebo**
Number of patients	**n**			
Length of stay in hospital (days)	Median [IQR] {range}			
Discharge disposition				
Home - Independent	n (%)			
Home - Needing care	n (%)			
Rehabilitation hospital	n (%)			
Transfer to another hospital - ICU/ITU	n (%)			
Died	n (%)			
Events in hospital				
Seizures	Yes (%)			
SAEs	Yes (%)			
Do Not Attempt Resuscitation	Yes (%)			
COVID-19 diagnosis	Definite (%)			

4 Outcomes at final follow-up

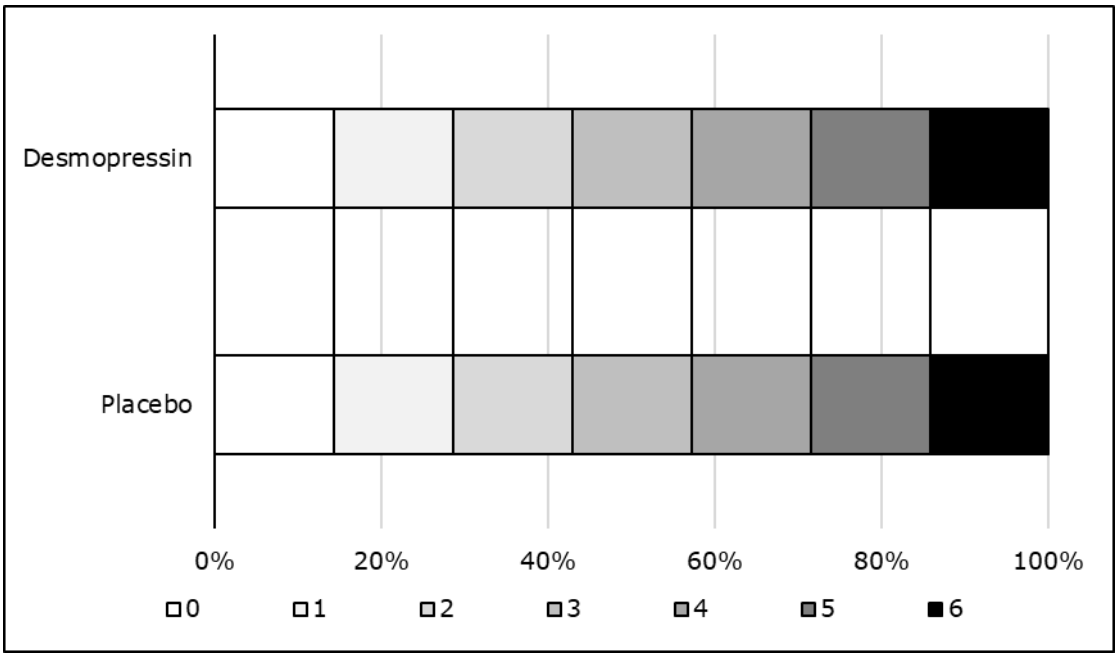
Table 9: Outcomes at Day 90

Variable		**All**	**Desmopressin**	**Placebo**
Number of patients	**n**			
Disposition				
Home - Independent	n (%)			
Home - needing care	n (%)			
Rehabilitation hospital	n (%)			
In hospital with readmission	n (%)			
Still in hospital	n (%)			
Other	n (%)			
Assessments				
mRS	Median [IQR] {range}			
...0	n (%)			
...1	n (%)			
...2	n (%)			
...3	n (%)			
...4	n (%)			
...5	n (%)			
...6	n (%)			
Death or dependency (modified Rankin scale 5 or more)	n (%)			
Barthel Index	Mean (SD) {range}			
Euroqol-5D HSUV	Mean (SD) {range}			
EQ-VAS	Mean (SD) {range}			
TICS-m	Mean (SD) {range}			
Verbal fluency	Mean (SD) {range}			
Zung depression scale	Mean (SD) {range}			
Events				

Variable		All	Desmopressin	Placebo
Death	By day 2 (%)			
	By day 7 (%)			
	By day 28 (%)			
	By day 90 (%)			

EQ-VAS: EuroQol visual analogue scale; Euroqol-5D HSUV: Euroqol 5D-derived health status utility values; mRS: modified Rankin Scale; TICS-m: Telephone Interview for Cognitive Status-modified.

Figure 2: Shift diagram of the modified Rankin Scale distribution at day 90, by treatment



NB: Example diagram only

5 Safety

Table 10: Adverse events recorded at day 2

Variable		All	Desmopressin	Placebo
Number of patients	**n**			
Any adverse event by day 2	Yes (%)			
Diarrhoea	Yes (%)			
Fever/pyrexia	Yes (%)			
Headache	Yes (%)			
Seizure/convulsions	Yes (%)			
Skin reaction	Yes (%)			
Thromboembolic event	Yes (%)			
Dizziness	Yes (%)			
Nausea	Yes (%)			
Vomiting	Yes (%)			
Other	Yes (%)			

Table 11: Safety outcome and serious adverse event information

	All	Desmopressin	Placebo
Number of Safety outcomes			
Fatal SAEs			
Fluid overload			
Hyponatraemia (any)			
Number of SAEs			
Time related to treatment			
Before			
During			
After			
Number of SAEs thought to be related to treatment			
Possibly			
Probably			
Definitely			
Final adjudication			
SUSAR			
SAR			
SAE			
Not an SAE			

Table 12: Serious adverse events by type

	All			Desmopressin			Placebo		
	n	**N**	**%**	**n**	**N**	**%**	**n**	**N**	**%**
Total number of SAEs									
By type									
Cardiovascular									
Nervous system									
Respiratory									
Gastro-intestinal									
Genito-urinary									
Haematological/immunological									
Metabolic/endocrine									
Musculoskeletal/cutaneous									

	All			Desmopressin			Placebo		
	n	**N**	**%**	**n**	**N**	**%**	**n**	**N**	**%**
Miscellaneous									

6 Exploratory analyses

Table 13. Scan adjudications – haemorrhage volume and haematoma expansion

Variable		All	Desmopressin	Placebo
Number of patients with first scan	**n**			
Time from onset to scan (hours)	Median [IQR] {range}			
ICH Location	BG-Thalamus (%)			
	Frontal (%)			
	Parietal (%)			
	Occipital (%)			
	Temporal (%)			
	Midbrain (%)			
	Pontine (%)			
	Cerebellar (%)			
Side of brain affected	Left (%)			
	Right (%)			
	Both (%)			
Cause of ICH	No cause identified (%)			
	CAA (%)			
	Other (%)			
FLP	Yes (%)			
SAH	Yes (%)			
Blend sign	Yes (%)			
Island sign	Yes (%)			
Black hole sign	Yes (%)			
Hypodensity	Yes (%)			
Barras Shape	1 (%)			
	2 (%)			
	3 (%)			
	4 (%)			
	5 (%)			
Barras Density	1 (%)			

Variable		All	Desmopressin	Placebo
	2 (%)			
	3 (%)			
	4 (%)			
	5 (%)			
IVH	Yes (%)			
Graeb	Median [IQR] {range}			
modified Graeb	Median [IQR] {range}			
Atrophy	Yes (%)			
Periventricular lucency	Yes (%)			
Old vascular lesions	Yes (%)			
Haemorrhage volume (ml)				
SAS	Median [IQR] {range}			
ABC/2	Median [IQR] {range}			
IVH volume (ml)	Median [IQR] {range}			
PHE volume (ml)	Median [IQR] {range}			
Midline Shift (mm)	Median [IQR] {range}			
Number of patients with second scan	**n**			
Time from randomisation to second scan (hours)	Median [IQR] {range}			
Haemorrhage volume (ml)				
SAS	Median [IQR] {range}			
ABC/2	Median [IQR] {range}			
IVH volume (ml)	Median [IQR] {range}			
PHE volume (ml)	Median [IQR] {range}			
Midline Shift (mm)	Median [IQR] {range}			
Number of patients with both scans	**n**			
Evidence of expansion†				
SAS comparison	Yes (%)			
ABC/2 comparison	Yes (%)			

CAA: Cerebral Amyloid Angiopathy; FLP: Finger-like projections; IVH: Intraventricular haemorrhage; PHE: Perihaematomal edema; SAH: Subarachnoid haemorrhage SAS: Semi-automated segmentation;

†Haematoma expansion will be determined as follows: ICH haematoma volume (HV), expressed in millilitres, will be calculated on the CT scans performed at baseline (pre-enrolment) and at 24 hours post-randomisation using the ABC/2 method and semi-automated segmentation (SAS) methods (ITK-SNAP 3.4.0). The measurements derived from the semi-automated segmentation method will be used for analysis of the haematoma expansion outcome. This is to ensure uniformity with intraventricular haemorrhage and perihaematomal oedema volumes, which are measured using semi-automated segmentation only. Absolute growth of haematoma will be calculated as $HV_{24hours}$ - $HV_{baseline}$. Relative growth will be calculated as ($HV_{24hours}$ - $HV_{baseline}$) / $HV_{baseline}$, and will be expressed as a percentage. Haematoma expansion will be defined as an absolute growth of >6 ml or a relative growth of >33%

Table 14: P-selectin and Blood results

Variable		All	Desmopressin	Placebo
P-selectin	n/N (%)			
Proportion of patients taking aspirin with impaired baseline platelet function[1]				
Proportion of patients taking $P2Y_{12}$ inhibitors with impaired baseline platelet function[2]				
Blood results	Mean (SD) {range}			
Von Willebrand Factor Antigen (iu/mL)	Pre-IMP			
	One hour post-IMP			
Change	(Post-Pre)			
Von Willebrand Factor Activity: GP1bM (iu/mL)	Pre-IMP			
	One hour post-IMP			
Change	(Post-Pre)			
Factor VIII:C (iu/mL)	Pre-IMP			
	One hour post-IMP			
Change	(Post-Pre)			

1. Defined as P-selectin mean fluorescence less than or equal to 500 in response to arachidonic acid 0.5 mM
2. Defined as P-selectin mean fluorescence less than or equal to 860 in response to adenosine diphosphate (ADP) 10 µM

7 Trial conduct

Table 15: Protocol Violations

Violation	All	Desmopressin	Placebo
Total number of patients with violations			
Total number of violations			
--- Baseline characteristics ---			
Randomisation over 12 hours from onset of symptoms			
Participant less than 18 years of age			
Pre-morbid dependency (mRS of 5)			
Aneurysmal subarachnoid haemorrhage known at time of randomisation			
Haemorrhage suspected to be due to transformation of ischaemic stroke			
Haemorrhage known to be due to thrombolytic drug			
Haemorrhage known to be due to venous thrombosis			
Clinically significant risk(s) of fluid retention associated with desmopressin			
Significant hypotension prior to randomisation (systolic BP under 90 mmHg)			
Known drug-eluting coronary artery stent in previous three months			
Randomising event was secondary to trauma			
Glasgow Coma Scale less than 5			
Known probable life expectancy of less than 4 hours, or planned for palliative care only			
Female patient pregnant or breastfeeding			
Not a primary intracerebral haemorrhage, known at time of randomisation			
Existing contra-indication to desmopressin known at time of randomisation			
--- Practice during the trial ---			
Participant does not receive all of the randomised treatment as per protocol			
Failure to complete SAEs where appropriate			

Violation	All	Desmopressin	Placebo
Failure to complete outcomes where appropriate			
Failure to check serum sodium 24±8 hours after infusion of IMP			
--- Consent and re-consent ---			
Failure to obtain any consent - neither brief information sheet/assent nor fully informed consent			
Failure to obtain appropriate, fully informed consent (following brief or independent physician consent)			
Individual taking consent not authorised to take consent on delegation log			
Wrong consent form used to obtain fully informed consent			
--- Management of IMP (non-participant records) ---			
Treatment pack lost			
Treatment pack exposed to a temperature excursion			
--- Miscellaneous ---			
Any other major violation of the trial protocol			

NB: Only submitted violations will be included in the publication. Information regarding protocol deviations will also be listed with details.

Table 16: Temperature excursions by site

Site	No. temperature excursions				Total excursion duration (hrs)	Mean excursion duration (hrs)	No. IMP packs allocated/unallocated	No. IMP packs exposed to excursions	No. IMP packs quarantined	No. IMP packs destroyed	No. participants receiving IMP previously exposed to both <2°C and >8°C ≤ 25°C	No. participants receiving IMP previously exposed to >8°C ≤ 25°C
	<2°C	>8°C ≤ 25°C	>25°C	Total								
Nottingham												
St Georges												
Leicester												
Stoke												
Derby												
Newcastle												
Devon & Exeter												
UCLH												
Aberdeen												
Edinburgh												
Unallocated*												
Overall												

*IMP stored in NUH pharmacy