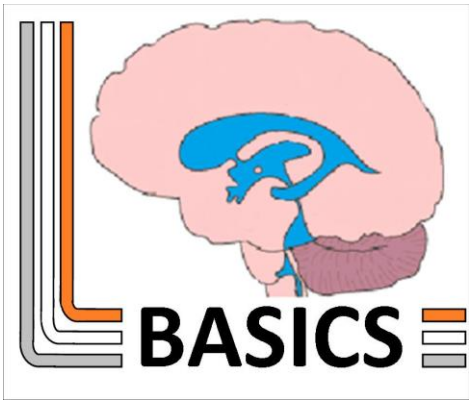

The BASICS trial

The British Antibiotic and Silver Impregnated Catheters for ventriculoperitoneal Shunts multi-centre randomised controlled trial

Version 9.0
10th August 2016

Study Sponsor(s):
Alder Hey Children's NHS Foundation Trust
Alder Road
L12 2AP

ISRCTN number: ISRCTN49474281

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Sponsor Ref: 10/29/RE

MC CTU is a division of CTRC

Protocol Approval

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Signature: _____ Date: 10/8/2016

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General Information

This document describes the BASICS trial and provides information about procedures for entering patients into it. The protocol should not be used as an aide-memoir or guide for the treatment of other patients; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but centres entering patients for the first time are advised to contact the coordinating centre (Medicines for Children Clinical Trials Unit) to confirm they have the most up to date version. Clinical problems relating to this trial should be referred to the relevant Chief Investigator via the CTU.

This protocol defines the participant characteristics required for study entry and the schedule of treatment and follow-up. Participant recruitment will be undertaken in compliance with this document and applicable regulatory and governance requirements and waivers to authorise non-compliance are not permitted.
Incidence of protocol non-compliance, whether reported prospectively (e.g. where the intervention cannot be administered as allocated or retrospectively noted (e.g. as a result of central monitoring) are recorded as protocol deviations, the incidence of which are monitored and reported to trial oversight committees.

Statement of Compliance

This study will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996) amendments and will be conducted in compliance with the protocol, CTU Standard Operating Procedures and Good Clinical Practice (GCP) as published by the European Medicines Agency “Note for Guidance on Good Clinical Practice” (CPMP/ICH/135/95) (Approval 17 July 1996).

The trial involves the use of CE-marked medical devices employed for their intended purpose, therefore this trial is not considered to be a clinical investigation under the Medical Devices Regulations 2002,.

Relationship Statements

The UK Clinical Research Collaboration (UKCRC; www.ukcrc.org) is a partnership organisation working to establish the UK as a world leader in clinical research. Following a review by an international panel, the Clinical Trials Research Centre (CTRC) at the University of Liverpool has been assessed as reaching the highest quality standard required by the UKCRC and achieved full UKCRC registration.

The Medicines for Children Research Network Clinical Trials Unit (MC CTU) is a division of CTRC. All CTRC activities are underpinned by methodological rigour, a modern data management system, similar technical requirements and a common set of standard operating procedures.

The NIHR Medicines for Children Research Network is part of the National Institute for Health Research Clinical Research Network.

Contact Details: Institutions

Sponsor:	Trial Management and Monitoring:	Clinical Laboratory: **(central facilities for storage of CSF and serum samples)**
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The contact details of other individuals involved in the trial are detailed in the Trial Oversight Committee Membership document.

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Glossary

VPS	Ventriculoperitoneal shunt
AE	Adverse Event
CI	Chief Investigator
CRF	Case Report Form
CTRC	Clinical Trials Research Centre
CTU	Clinical Trials Unit
GP	General Practitioner
IDSMC	Independent Data and Safety and Monitoring Committee
IEC	Independent Ethical Committee
MC CTU	Medicines for Children Clinical Trials Unit
MREC	Multi-centre Research Ethics Committee
NIHR CRN	National Institute for Health Research Clinical Research Network
PI	Principal Investigator
R&D	Research & Development
REC	Research Ethics Committee
RN	Research Nurse When RN is referred to in this protocol it means either the research nurse or someone who has been delegated that duty
SAE	Serious Adverse Event
SDV	Source Data Verification
TMG	Trial Management Group
TSC	Trial Steering Committee

1 PROTOCOL SUMMARY

Title:	National three-arm, double blind multi-centre randomised controlled trial comparing Bactiseal (antibiotic-impregnated), Silverline (silver-impregnated) and standard (non-impregnated) VPS in patients with hydrocephalus undergoing insertion of their first permanent shunt.
Phase:	IV
Population:	The trial population is up to 1650 patients (children and adults) with Hydrocephalus of any aetiology (including IIH) requiring first VPS. These patients will be recruited from 19 neurosurgical wards across the United Kingdom & Ireland
Study Centres and Distribution:	The trial will take place in neurosurgical units in the UK & Ireland, which have access to microbiology laboratories with Clinical Pathology Accreditation. Most of the sites that will participate in the trial fall within the Medicines for Children Local Research Networks.
Study Duration:	Utilising a recruitment period of 4 years, 2 months, the minimum follow-up will be 6 months and the maximum 2years per patient.
Description of Intervention:	We will randomly allocate patients to a standard non impregnated ventriculoperitoneal shunt (VPS), a Silverline***** (Silver impregnated) VPS or a Bactiseal***** (antiobiotic impregnated) VPS on a ratio of 1:1:1. All VPS used for the trial are CE marked medical devices being used for their intended purpose. ***SEE PAGE 14**
Primary Objective:	To determine whether antibiotic or silver impregnated VPS reduce infection compared to standard VPS in hydrocephalus following insertion of de novo VPS.
Secondary Objective/s:	1) To determine the proportion of first VPS infections occurring more than 6 months after insertion of de novo VPS 2) To determine whether antibiotic or silver impregnated VPS reduce shunt failure of any cause compared to standard VPS in hydrocephalus following insertion of de novo VPS 3) To assess whether the reason for shunt failure is different across the three different types of VPS 4) To determine which organisms and their resistance/sensitivities, subsequently infect three alternative VPS 5) To determine whether antibiotic or silver

impregnated VPS reduce infection, following first (non-infected) clean VPS revision for mechanical failure, compared to standard VPS in hydrocephalus following insertion of de novo VPS

6) To assess the impact of VPS infection on the patient in terms of Quality of Life
7) To assess the cost-effectiveness and health economics of antibiotic and silver impregnated VPS compared to standard VPS

1.1 *Impregnated VPS CE Marked Devices for use within the trial

This trial will be comparing silver impregnated and Antibiotic impregnated VPS. All VPS used for this trial are CE marked medical devices being used for their intended purpose.

The table below, lists all the devices currently being used within the study. Any future devices with equivalent specification will be considered for inclusion by the TMG.

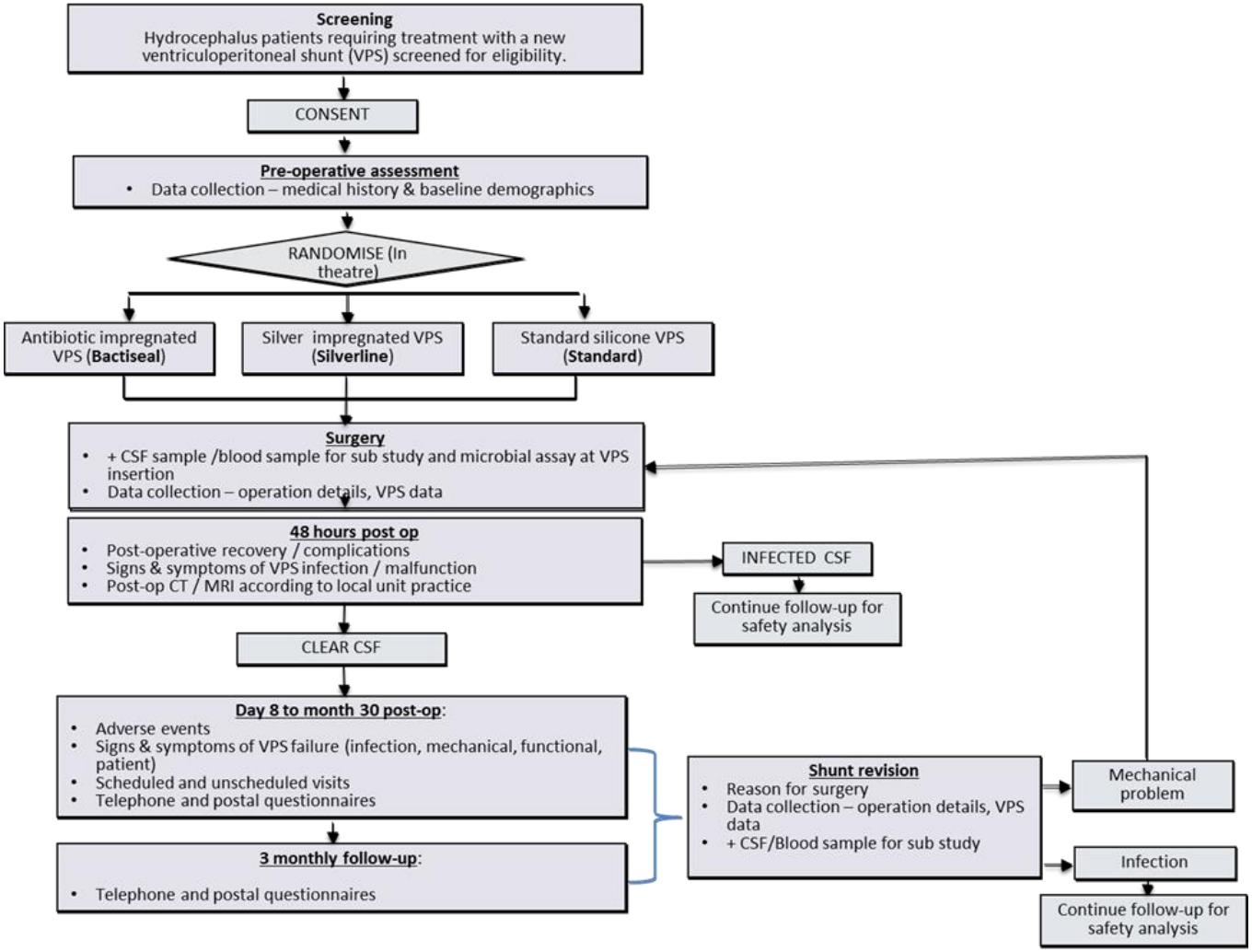
Silicone VPS are also used within this trial and are referred to as 'standard VPS'.

Antibiotic Impregnated VPS	**Silver Impregnated VPS**
Bactiseal (Codman)	Silverline (Fannin)
ARES (Medtronic)	

Where a particular brand of VPS is mentioned throughout this protocol (Bactiseal or Silverline) this refers to any equivalent CE marked device as listed in this table.

Protocol Summary - continued

Schematic of Study Design:



2 BACKGROUND INFORMATION

2.1 Introduction

Current Practice

Hydrocephalus affects one in every five hundred births, and is thus one of the most common developmental disabilities in children. The condition also affects older children and adults of all ages and can be secondary to a variety of causes including intracranial tumours, haemorrhage and infection. In the late 1950s, the development of treatment with cerebral shunts revolutionised the management of these patients.

Standard treatment for Hydrocephalus remains the ventriculoperitoneal shunt (VPS). A ventriculoperitoneal shunt is composed of silicone tubing and a valve. The tubing passes from the brain fluid cavities (ventricles), under the skin and into the peritoneum (abdominal cavity). The shunt drains cerebrospinal fluid from the ventricles into the peritoneal cavity. Insertion of a ventriculoperitoneal shunt for hydrocephalus is now one of the most common procedures performed in neurosurgical units, and between 3000 and 3500 shunt operations are carried out per year in the UK in adults and children (1). Currently there are three types of shunt catheter available (standard, antibiotic impregnated and silver impregnated). There is no standard practice or guidance in the UK as to which catheter is most effective at reducing infection. Practice is variable across the UK and indeed the world. There are no current NICE guidelines nor is there a position statement from the Society of British Neurological Surgeons (SBNS) regarding the use of any type of VPS.

Clinical questions addressed by the trial

Shunt failure due to infection has plagued this neurosurgical advance ever since it was developed. The incidence of shunt infection varies markedly in the literature from 3-27% (2-6) and is higher in certain groups, e.g. neonates and children under 1 year old, patients treated with a previous temporary external ventricular drain (EVD). Episodes of shunt infection have a significant impact on patients and the NHS and require prolonged inpatient hospitalisation, additional surgery to remove the infected hardware, placement of a temporary EVD, intravenous and intrathecal antibiotics, and further surgery to place a new shunt once the infection has been treated. Other clinical consequences of infection including epilepsy, reduced IQ and loculation have often been reported but never formally studied in the context of a prospective clinical trial. This trial thus addresses the primary question of which shunt catheter is most effective in reducing shunt infection and also has secondary questions addressing the consequences of infection in a clinical and financial context.

2.2 Review of Literature and Rationale for the study

Currently, the type of VPS inserted (standard, Bactiseal or Silverline) is selected according to surgeon preference.

There are currently three main types of VP shunt catheters on the market in the UK:

1. Standard VPS are made of silicone
2. Bactiseal® (Codman™) VPS are made of silicone and impregnated with antibiotics (0.15% Clindamycin and 0.054% Rifampicin). They have been on the market for ~8 years and have been adopted by the neurosurgical community as a means to potentially reduce shunt infection, despite the fact that they are more expensive and class I evidence is lacking.

A recently published systematic review and meta-analysis of Bactiseal VPS identified one RCT and 11 observational studies. The RCT, conducted in a single centre in South Africa, demonstrated a trend favouring impregnated VPS but did not show a statistically significant difference between the two groups (RR: 0.38 CI: 0.11, 1.30; p=0.12), however meta-analysis of the 11 observational studies showed a statistically significant difference favouring Bactiseal VPS (RR: 0.37 CI: 0.23, 0.60; p<0.0001) (7). Research on Bactiseal VPS in Liverpool has shown that over a 2-year period the infection rate reduced in paediatric patients compared to historical controls (8). However continued data collection over 3.5 years and published as part of a Liverpool-led multi-centre observational study with two other UK paediatric neurosurgical units showed no significant reduction in infection in Liverpool (9). Indeed the reduction in infection achieved by Bactiseal VPS in the multi-centre observational study was only seen in neonates and was heavily weighted by the results from one unit. This latter study (9) was not part of the published systematic review (7).

3. Silverline® (Forth Medical™) VPS are made of silicone and impregnated with silver. They were launched in the UK in March 2011 with similar claims. There is little doubt silver ions have antimicrobial effects and they elute from Silverline catheters. However the efficacy of Silverline catheters at preventing VPS infections is not yet proven. In-vitro models have shown varying results and clinical studies are currently limited. (10, 11) There is one observational study of Silverline VPS used to successfully treat seven patients with active CSF infection (12). There are no observational studies comparing Silverline VPS infection rate with either standard or Bactiseal VPS. However, in a randomised controlled trial of external ventricular drains (EVD: a temporary tube placed in the ventricles that is prone to infection) in children and adults, Silverline EVDs have been shown to reduce infection from 21.4% (30/140) to 12.3% (17/138) (P=0.042) (13). Two further observational studies comparing standard to Silverline EVDs also show a reduction in infection rates (14, 15). The comment accompanying the EVD study acknowledges the need for a randomised controlled trial to study the relative benefits of silver impregnated catheters.

Data from the UK shunt registry (to which most neurosurgical units contribute) reports that 15% of shunt revisions are for infection (16). In the largest randomised controlled shunt trial worldwide, the infection rate was 8.4% for primary ventriculoperitoneal shunts (17).

The commonest pathogens detected are staphylococcus species, but in a proportion of patients with suspected infection the organism is never determined, especially if they have already received antimicrobial treatment, or there may be a delay in culturing the organism, hampering microbiological treatment. However newer molecular approaches are increasing the diagnostic rate for a range of CNS infections. Episodes of shunt infection are also responsible for reduced cognitive function and IQ (18). Indeed, the number of shunt infections is an independent predictor of death in patients requiring cerebrospinal fluid (CSF) shunts [HR 1.66, 95% CI: 1.02-2.72] (19).

Whilst a systematic review (7) and our own studies from Liverpool (8, 9) suggests that Bactiseal shunts may be an effective way of reducing the incidence of shunt infections, there is some evidence that Bactiseal VPS that become infected may be more difficult to treat leading to prolonged hospital stay (20). Bactiseal VPS prevent the sensitive organisms causing infection and may leave the rifampicin resistant organisms that subsequently cause VPS failure secondary to infection. A second report following up 500 Bactiseal primary and revision VPS insertions showed sensitive organisms may still cause infection but presentation was significantly delayed compared to standard historical controls (21). It is plausible to suggest that Bactiseal VPS may lead to a delay in presentation allowing increased time for biofilm development on the ventricular surface rather than just the VPS.

This could certainly lead to more difficult to treat, serious, infection through rifampicin resistance and warrants further investigation.

There are no economic evaluations of VP shunts, however four retrospective cost studies from the USA (22-25) which include both adults and children, suggest that cost savings may be possible through reduction in infection with Bactiseal shunts. Approximately 70% of shunt operations in the UK are with Bactiseal® shunts (verified by feasibility screening log) and there is likely to be a significant uptake of Silverline® shunts by neurosurgeons despite the lack of evidence of clinical benefit.

The potential beneficial effect on health status of these impregnated catheters is reduced shunt infection and its negative sequelae. This must be balanced against the possibility of selecting out resistant organisms or rendering infections more difficult to treat with adverse impact on outcome and increased cost for AISs. In our recently published review article on contemporary management of paediatric hydrocephalus in the BMJ, we emphasised and highlighted the need for a multi-centre RCT on impregnated ventriculoperitoneal shunts (26).

A randomised controlled trial is needed urgently to determine whether these impregnated VPS reduce infection, compared with standard VPS, and whether this is cost effective.

2.3 Objectives

2.3.1 Primary objective:

To determine whether antibiotic or silver impregnated VPS reduce infection compared to standard VPS in hydrocephalus following insertion of de novo VPS

2.3.2 Secondary objectives:

8) To determine the proportion of first VPS infections occurring more than 6 months after insertion of de novo VPS
9) To determine whether antibiotic or silver impregnated VPS reduce shunt failure of any cause compared to standard VPS in hydrocephalus following insertion of de novo VPS
10) To assess whether the reason for shunt failure is different across the three different types of VPS
11) To determine which organisms and their resistance/sensitivities, subsequently infect three alternative VPS
12) To determine whether antibiotic or silver impregnated VPS reduce infection, following first (non-infected) clean VPS revision for mechanical failure, compared to standard VPS in hydrocephalus following insertion of de novo VPS
13) To assess the impact of VPS infection on the patient in terms of Quality of Life
14) To assess the cost-effectiveness and health economics of antibiotic and silver impregnated VPS compared to standard VPS

2.4 Potential Risks and Benefits

2.4.1 Potential Risks

VPS infection is a serious complication for patient with treated hydrocephalus. It leads to prolonged hospital stay, multiple operations and reduced IQ. Impregnated VPS (Bactiseal and Silverline) have been developed to reduce the early infection rate, however there is no good class one clinical evidence to support this. As all the VPS used in this trial are CE marked and used in routine clinical practice, there is no additional risk to trial participants over and above standard care.

2.4.2 Known Potential Benefits

The potential beneficial effect on health status of these impregnated catheters is reduced shunt infection and its negative sequelae. This must be balanced against the possibility of selecting out resistant organisms or rendering infections more difficult to treat with adverse impact on outcome. In our recently published review article on contemporary management of paediatric hydrocephalus in the BMJ, we emphasised and highlighted the need for a multi-centre RCT on impregnated ventriculoperitoneal shunts (26).

3 SELECTION OF CENTRES/CLINICIANS

Trial centres will be initiated once all global (e.g. local R&D approval) and trial-specific conditions (e.g. training requirements) have been met, and all necessary documents have been returned to the MC CTU. Training in the protocol requirements and the requirements outlined in CTRC SOPs TM017 and TM018 will be disseminated to personnel at a trial launch meeting and continually on site for all relevant new staff who may be involved in the trial. Site assessment will be undertaken at trial set up and sites will be selected using The BASICS Centre Inclusion Criteria.

Personnel with responsibility for ensuring all staff follow the standardised blood and CSF sampling procedures will be so trained prior to commencing the trial, as will any staff members responsible for carrying out duties outlined in the standardised microbiology lab protocol.

Adherence to the protocol procedures will be monitored throughout the trial by the Trial Coordinator/Data Manager. Participating centres will be expected to each maintain a file of essential trial documentation (Investigator Site File), which will be provided by the MC CTU, and keep copies of all completed CRFs for the trial. Data collection will use a combination of paper CRFs (with no carbon copies) and electronic data collected retrospectively from the Hospital Episodes Statistics database, -(see section 13.2 for details on the data capture methods).

4 TRIAL DESIGN

4.1 Primary Endpoint

Time to failure of the first VPS due to infection (see section 8.2)

4.2 Secondary Endpoint(s)

a. Time to shunt failure of any cause
b. Reason for shunt failure (infection, mechanical, patient, other)
c. Types of bacterial VPS infection (organism, antibiotic resistance)
d. Time to VPS infection following first clean revision
e. Quality of Life
f. Incremental cost per VPS failure
g. Incremental cost per QALY gained

5 STUDY POPULATION

The trial will be open to all patients (children and adults) with hydrocephalus requiring treatment with a first permanent VPS, who meet the eligibility criteria.

5.1 Inclusion Criteria

1. Hydrocephalus of any aetiology (including IIH) requiring first VPS.

Please note the following:

a. Failed primary endoscopic third ventriculostomy allowed
b. Indwelling ventricular access device (e.g. Ommaya or Rickham reservoir or – ventriculo-subgaleal shunt or similar) are allowed
c. Indwelling EVD allowed

5.2 Exclusion Criteria

1. Previous indwelling ventricular or lumbar peritoneal or atrial shunt
2. Active and on-going CSF or peritoneal infection (**previous infected cases allowed once clear of infection)**
3. Multi-loculated hydrocephalus requiring multiple VPS or neuro-endoscopy
4. Ventriculo-atrial or ventriculo-pleural shunt planned
5. Allergy to antibiotics associated with the antibiotic shunt
6. Allergy to silver

5.3 Patient Transfer and Withdrawal

In consenting to the trial, patients are consented to trial intervention, follow-up and data collection. If voluntary withdrawal occurs, the patient (or parent/legal representative) should be asked to allow continuation of scheduled evaluations, complete an end-of-study evaluation if appropriate, and be given appropriate care under clinical supervision until the symptoms of any adverse event resolve or the patient's condition becomes stable.
Follow-up of these patients will be continued through the trial research nurses, the lead investigator at each centre and, where these are unsuccessful, through the child's GP, unless the participant explicitly also withdraws consent for follow-up.

5.3.1 Patient Transfers

For patients moving from the area, every effort should be made for the patient to be followed-up at another participating trial site and for this trial site to take over responsibility for the patient.

A copy of the patient CRFs should be provided to the new site. The patient (or parent/legal representative) will have to sign a new consent form at the new site, and until this occurs, the patient remains the responsibility of the original site. The CTU should be notified in writing of any patient transfers.

If transfer of responsibility is not possible (if the hospital the patient is transferred to is not a participating trial site), the research nurse at the original hospital should liaise with staff at to collect follow up data from the routine clinical records until the appropriate follow-up time as detailed in section 8.1.

The Research Nurse at the recruiting centre will provide written notification using a transfer letter to be given to the staff at the receiving centre

In both cases, resource use and mortality will be obtained at end of study using Hospital Episode Statistics (HES) -

5.3.2 Withdrawal from Trial Completely

Patients are free to withdraw consent at any time without providing a reason. Patients who wish to withdraw consent for the trial will have anonymised data collected up to the point of that withdrawal of consent included in the analyses. The patient will not contribute further data to the study and the CTRC should be informed and a withdrawal CRF should be completed. Data up to the time of withdrawal will be included in the analyses unless the patient explicitly states that this is not their wish.

6 ENROLMENT AND RANDOMISATION

6.1 Screening/ Enrolment

Screening will be performed daily by clinical staff or the designated research nurse in order to identify potentially eligible patients. This can be carried out on the daily ward rounds or at an appropriate time point depending on the clinical setting. A screening log will be maintained at each trial centre, recording all individuals screened for the trial and the eventual outcome. All patients having a first VP shunt for hydrocephalus of any aetiology (including IIH) should be screened for eligibility and recorded on the screening log. Reasons for non-recruitment will be documented (e.g. not eligible, declined consent etc.) and the information will be used for monitoring purposes.

The screening log should be maintained by the research nurse or designated other (recorded on delegation log) and should be faxed to the MC CTU monthly.

If a patient is assessed to be eligible for the trial (i.e. meets the eligibility criteria listed in section 5.1), an appropriate member of the research team who is listed on the delegation log will provide written information in advance in the form of a patient information sheet. In the case of children or adults lacking mental capacity to consent, the research nurse will meet with parents, consultee or legal representative at the earliest time that can be arranged pre-operatively to discuss participation. Where feasible, this may be at a clinic visit prior to admission, but may be during their pre-operative ward admission. The research nurse will allow the family sufficient time to discuss the trial and decide whether to consent to trial entry (see section 11.3 for consent procedures).

If written consent is provided by the patient, parent legal representative or consultee, the patient will be eligible to be randomised to the trial.
Once written consent has been provided by the parent or legal representative, or once a patient representative consultee form has been signed, it is valid for 14 days. If the patient has not been randomised within 14 days of the date written on the consent form re-consent will be required.

In the case of adults lacking capacity, this will be re-evaluated and if they are judged not to have regained capacity, their consultee will be re-approached. If the patient that was previously lacking capacity is found to have regained capacity during this time, they should be asked to provide written consent.

The Research Nurse should ensure that the log for patients lacking capacity is completed at every visit to record whether patient has regained capacity and reconsented.

6.2 Baseline

The research nurse will confirm to the operating team that written informed consent has been provided and that the patient has been confirmed has being fully eligible for trial participation by PI/Co-PI (confirmation of eligibility should only be carried out by physicians) the Baseline Preoperative Assessment CRF- should then be completed

The following data should be recorded on a Baseline Preoperative Assessment CRF:

- Physical examination details
- Admission details
- Relevant medical history

- Risk of infection assessment
- CSF/EVD history
- Reason for shunt
- Quality of Life Questionnaire
- Pregnancy assessment
- Concomitant Medications (from 72 hours)

6.3 Randomisation

Once the Research Nurse has confirmed that written consent has been provided and that patient has been deemed as being fully eligible for trial participation by PI/Co-PI, the designated staff memberwill randomise the patient in surgery and select the appropriate type of VPS to be inserted.

Randomisation should be carried out in theatre by a designated staff member (as specified on the training log) at the time that VPS insertion is required. At randomisation participants will be issued with a unique randomisation number and VPS allocation. Trial entry and randomisation number should be recorded in the patient's medical notes. Details of the trial VPS allocated should **not** be recorded in the medical notes.

The allocated trial number and VPS type will be provided to centres in the form of a series of sequentially numbered randomisation packs. The individual responsible for randomising the participant will select the next sequentially numbered, sealed pack from the supplies provided. Each pack will contain an opaque, pressure-sealed envelope that will give the randomisation allocation. The envelope will be similar to those used for pay slips, which cannot be viewed without fully opening and their construction is resistant to accidental damage or tampering. The pack will also contain an unblinding envelope and a pre-paid envelope. This is so that page 1 of the randomisation envelope containing information on the randomisation process and whether the VPS was inserted can be returned to the MC CTU in the pre-paid envelope, and pages 2 & 3 of the randomisation envelope containing details of the actual VPS type inserted can be stored securely in the unblinding envelope on site in an accessible location. For further details on the administration and recording of the allocated VPS see section 7.3.

The randomisation packs will be securely stored near to the boxes containing VPS for trial use. The VPS boxes (sets) will be labelled as supplied by the manufacturer. Once the patient has been randomised, the operating surgeon will select and insert a device of the type allocated.

An appropriate member of the neurosurgical team (as specified on the delegation log) will check to ensure that the correct number of randomisation packs is present, that they are intact and that the sequential numbering system is maintained. Any discrepancies will be immediately reported to the MC CTU. The research nurse will also ensure that there are adequate stocks of each type of VPS available for the trial, and will liaise with the local procurement department (and the MC CTU) as necessary.

Eligibility & Randomisation CRF should then be completed and the following data recorded:

- Review of inclusion / exclusion criteria
- Details of consent
- Randomisation details
- Operation details CRF (to document the procedure and processes in theatre)
- Pre theatre checks
- Procedures in theatre
- Surgery details
- Surgeon details
- CSF sample details and corresponding microbiology
- Device placement details
- Related adverse events
- Date Eligibility confirmed (must be before randomisation date)

6.4 Early Post Operative Assessment

Early Postoperative Assessment CRF should be completed at discharge or at 72 hours post op whichever is the soonest, and the following data recorded:

- Physical examination
- Microbiology
- Wound check
- Imaging
- CSF Leak
- Related adverse events
- Concomitant medications
- Quality of Life Questionnaires
- Patient transfer details

At this point, the patient should also be given their first health service diary to complete over the next 3 months.

6.5 First Routine Post Op Assessment

First Routine Post Op Assessment CRF should be completed and the following data recorded according to local practice:

- Physical examination
- Imaging
- Wound check
- CSF leak
- Related adverse events
- Concomitant medications
- Pregnancy
- Outcome of visit

We do not specify a timescale for this assessment to be completed but this should be the first time the patient is seen in clinic post operatively according to their usual post operative care pathway.

6.6 Subsequent Post Op Assessment

Subsequent Post Op Assessment CRF should be completed and the following data recorded at the time of the any subsequent routine assessment according to local practice:

- Physical examination
- Imaging
- Wound check
- CSF leak
- Related adverse events
- Concomitant medications
- Pregnancy
- Outcome of visit

6.7 12 Weekly Follow-up Assessment

The Research Nurse will contact patients every 12 weeks from date of insertion to complete the assessments. This could be done by telephone or may coincide with routine appointments. The following data should be recorded:

- Related adverse events
- Concomitant medications
- Pregnancy

During the first 12 weekly assessment the research nurse will complete the relevant quality of life questionnaires with the patient over the phone.

Health service diaries are to be given/posted out to patients every 12 weeks. Patients will complete these and return to sites 12 weeks later. During the 12 weekly assessments the research nurse should remind patients to return these diaries if they have not done so and prompt them to complete the new diaries that they should have received.

6.8 Unscheduled Visit/Admission Assessment

Unscheduled Visit/Admission CRF should be completed for any none routine attendance at the treating Neurosurgical centre and the following data recorded:

- Source of unscheduled visit
- Reason for return
- Physical examination
- Microbiology
- Blood samples
- Imaging
- Wound check

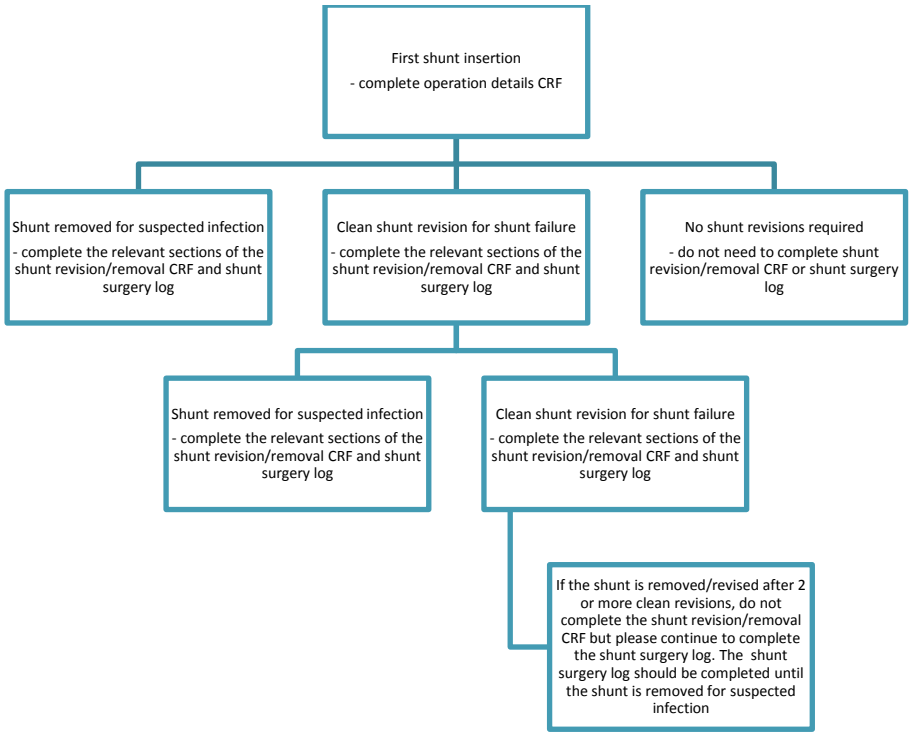
- CSF leak
- Related adverse events
- Concomitant medications
- Pregnancy
- Outcome of visit

6.9 Shunt Revision/Removal

If patient is admitted for a clean VPS revision (for mechanical shunt failure, functional shunt failure or failure due to patient) or removal (for suspected infection), the Shunt Revision/Removal CRF must be completed and the following data must be recorded:

- Surgery details (separate sections for revisions/removals)Surgeon details
- CSF sample details (including samples for substudies if patient is taking part)
- Related adverse events
- Concomitant Medications

See diagram below



In addition, the shunt surgery log should be completed for all surgeries taking place after the initial surgery when the randomised shunt was inserted

In instances were the shunt is removed for suspected infection concomitant medications but be reported up until 14 days after removal and the patient will be reviewed for 48 hours after removal for safety..

6.10 End of Study Phone Call

When the study comes to an end the End of Study Phone Call CRF should be completed, and the following data must be recorded:

- Related adverse events
- Concomitant medications
- Pregnancy
- Quality of Life Questionnaire
- The final health service diary should also be returned.

RN's should endeavour to contact the participant a maximum of three times, at different times of the day and different days of the week. If patient is uncontactable this should be documented on the CRF and returned the CTU.

7 TRIAL INTERVENTIONS

7.1 Introduction

Patients will be randomised to standard VPS, antibiotic impregnated (Bactiseal – Rifampicin and Clindamycin) VPS or silver impregnated VPS (Silverline) in a ratio of 1:1:1. This ratio reflects uncertainty about which of these three types is best in terms of the risk of early shunt infection and cost effectiveness.

7.2 Packaging, Labelling, Storage and Stability

The VPS used in the trial will be sourced via usual NHS procurement arrangements according to local Trust policy.

All variations of VPS allowed in the trial design are CE-marked medical devices used in accordance with the manufacturer's instructions for their intended purpose.

The VPS to be used for the trial should come from normal stocks. All VPS stocks should be stored in accordance with local policy and according to manufacturer requirements. They should be readily accessible to the clinician responsible for randomisation and insertion. The VPS boxes will be labelled as supplied by the manufacturer.

The VPS boxes contain a minimum of 3 labels as standard and they should be used as follows:

- one to be placed on the randomisation envelope to be returned to MC CTU (this is described in further detail in section 7.3),
- one to be placed on the letter to be kept at site (this is described in further detail in section 7.4.1)
- one to be placed in the unblinding envelope and kept at site (this is described in further detail in section 7.4.2).

It will be the responsibility of the participating trial site, in liaison with the local procurement department to ensure the disposal of VPS supplies when the shelf life expires and arrange resupply where appropriate. The appropriate staff member at site will monitor that trial VPS are being used before their expiry date.

7.3 Administration of Trial Interventions

- To administer the randomly allocated VPS:

a. **The member of staff responsible for randomising the patient will select the next sequential randomisation pack to ascertain the treatment allocation**

b. **The operating surgeon** will select and insert the allocated VPS type. Type of valve used is according to operating surgeon and clinical indication. Details of the valve should be recorded on the CRF.*

c. After insertion **the operating surgeon** or **staff member who has randomised the patient** will place the label from the VPS box which carries the VPS type, expiry date and product code on page 1 of the randomisation envelope. Page 1 of the randomisation envelope should then be placed into the prepaid envelope and posted to the MC CTU ideally within 24 hours so that correct allocation can be verified and use prior to expiry can be monitored. The research nurse should liaise with the operating staff to ensure that this is carried out promptly.

   A BASICS trial sticker will be placed in the patient's medical notes, and also on the shunt registry form.

d. Pages 2 & 3 of the randomisation envelope will be placed in the unblinding envelope and stored securely on site in an accessible location.

- The allocated VPS type should not be disclosed to the rest of the clinical team.

e. If the initial attempt at insertion is unsuccessful, the allocated VPS type will be used for the subsequent attempt on the same patient. Should an envelope be opened and the allocation subsequently not used (ie: surgery is abandoned), this will be recorded and page 1 of the randomisation envelope returned to the MC CTU. It will not be used for the next eligible patient.

- If a trial participant requires a subsequent VPS <u>after the trial VPS has been removed for infection</u> the subsequent VPS will not be randomised. The patient will be allocated the default VPS used at that centre.

- If a trial participant requires a subsequent VPS <u>after the trial VPS has been removed for mechanical failure</u> the subsequent VPS should be the same type as the randomised VPS.

<u>Notes</u>

It is accepted that a small proportion of the shunt system between the reservoir and the valve may not be impregnated. For example, unitised reservoir and valve components may still be included as long as the proximal catheter and the catheter distal to the valve is impregnated with the same substance as the allocated VPS.

With frontally placed ventricular catheters and reservoirs, where the valve is inserted elsewhere (e.g. Miethke valve requires placement in vertical position), then intervening extra tubing should be impregnated according to the randomised VPS tubing from the available distal tubing.

7.4 Allocation concealment and unblinding

7.4.1 Maintaining allocation concealment

Ideally, the allocation of VPS type would be completely blinded to all personnel involved in the trial. This is not possible because of differences in appearance that are visible at insertion. Bactiseal VPS are orange in colour, Silverline are grey and standard are white. It is not possible to manufacture all of the products to standardise the colour.

The allocation type (standard, silver or antibiotic) must NOT be recorded in the medical records during the patient's participation in the trial:

- The label from the VPS box should be placed on the letter provided as part of the randomisation pack.
- This letter is then placed in the envelope and stored in a secure location at site.
- The letter will then be placed in the medical notes at the end of trial.

7.4.1.1 Initial insertion of new randomised VPS

At the time of surgery, all staff members present in theatre will be unblinded to the participant's allocation.

Whilst blinding is not possible to the operating surgeon, it is possible to minimise disclosure of allocation following first shunt surgery because the three types of VPS are not visible after insertion. The importance of non disclosure of this information will be stressed during trial training. The operating surgeon and any other staff members present during primary VPS insertion will be requested to not disclose the allocation.

7.4.1.2 First Shunt Revision (includes first infection or mechanical revision)

The decision regarding the requirement for revision surgery will be made on clinical merits by the clinical team responsible for the patients care. This decision making process should not require the VPS allocation to be revealed.

a) Suspected infection

When the shunt is being removed for likely clinical infection and replaced by External ventricular drainage, there is no need for the removed shunt to be unblinded. Standard procedure and treatment for infected VPS will ensue according to local protocol, (see section 8.2 for subsequent follow up).

b) Mechanical failure

When surgery is being performed for presumed clean mechanical malfunction, the operating surgeon will perform surgery as per standard practice and replace components of shunt as required, recording the reason for surgery and failure and part of shunt revised. Where possible, if a component of the tubing is changed (part or all), then the replaced tubing should be replaced like for like (as originally randomised) and the new tubing inserted recorded on the revision/removal CRF. It is accepted that from this point, the surgical team will be unblinded as per the original allocation of VPS.

When the person involved in the first VPS insertion contributes to the subsequent care of the patient, the information will be documented with their involvement in the decision process relating to clinically suspected shunt malfunctions and the decision to revise.

7.4.1.3 Subsequent shunt surgery for clean shunt revisions

It should be noted that the trial is designed to capture first clean shunt revision only, therefore subsequent and multiple shunt revision patients should not need unblinding, and should be treated according to local unit and surgical preference.

7.4.2 Unblinding Procedure

7.4.2.1 Unblinding of Individual Patients During Trial Conduct

If simply removing the VPS is a viable option for the patient's care, it should not be necessary for unblinding to occur.

Unblinding to the clinical team, parent or participant should be considered only when knowledge of the allocation is deemed essential for the participant's ongoing care or to enable treatment of a serious adverse event(s). In general, unblinding during conduct of the clinical trial should only occur when there are compelling medical or safety reasons to do so.

If unblinding is deemed necessary, the following unblinding procedure should be followed:

a. Where possible (during office hours), consent for individual unblinding should be made via the Trial Coordinator at MC CTU who will seek agreement of the Chief Investigator (or nominated delegate).
b. The unblinding envelope prepared by the inserting clinician or trial RN containing pages 2 & 3 of the randomisation envelope and the VPS set cover, which has been stored on site in an accessible location, can be used to obtain the VPS allocation.
c. The research nurse will ensure all necessary CRFs are completed and submitted to MC CTU (if possible, completed before unblinding is performed). N.B. If unblinding has occurred, the participant will still be followed up as described in section 8.
d. All instances of unblinding should be recorded on the Unblinding CRF and returned to the MC CTU within 24 hours including:
    i. Date information requested & date of unblinding
    ii. Detailed explanation of circumstances and reason for unblinding;
    iii. Recipients of the unblinding information;
    iv. If accidental unblinding, action to prevent further occurrence of unblinding.

7.4.2.2 Accidental disclosure to staff and parents and / or patients

If the VPS allocation is accidentally disclosed to staff at any other time during the patient's participation in the trial, an Unblinding CRF should be completed and returned to the MC CTU within 24 hours of the disclosure.

7.5 Accountability Procedures

7.5.1 Trial VPS

The VPS used in the trial will be sourced via usual NHS procurement arrangements. The research nurse will liaise with the local procurement department and the medical device liaison officer to ensure that the centre has the following measures in place and will report any problems to the MC CTU:

a. A system in place that allows for the retrieval of defective products;

b. Ensure that there are enough devices (minimum of 6 of each type) within their shelf life

c. Ensure devices are used in compliance with the protocol requirements and accountability records are maintained as per local policy;

d. Ensure that the VPS are stored where they are readily accessible to the clinician responsible for randomisation and insertion.

7.5.2 Randomisation envelopes

a. Upon receipt of the randomisation envelopes for the trial, the research nurse will be requested to check they are intact and that they are in sequence and send confirmation of this back to the MC CTU.
b. Any discrepancies will be immediately reported to the MC CTU

7.5.3 Unblinding envelopes

a. It is the responsibility of the research nurse at site to ensure that the unblinding envelopes are stored in a location that is easily accessible.
b. Unblinding envelopes should be periodically checked to ensure that they are intact. This check should be documented on the appropriate log and sent to the MC CTU.

7.6 Assessment of Compliance with Study Intervention

The allocated trial VPS will be inserted by the operating surgeon. The MC CTU will monitor compliance of centres sending the randomisation envelopes to the MC CTU and will check the returned randomisation envelopes to assess the level of compliance of the VPS with the randomisation allocation.

See section 13 for further details on monitoring.

7.7 Concomitant Medications/Treatments

The use of the following medications / treatments should be recorded on the concomitant medications CRFs at each visit;

- Antibiotics
- Antifungals
- Immunosuppressants e.g. Corticosteroids
- Anticoagulants

Concomitant medications must be reported throughout the patients participation in the study. In instances where the shunt is removed for suspected infection concomitant medications but be reported up until 14 days after removal.

7.8 Co-enrolment Guidelines

To avoid potential confounding issues, patients should not be recruited into other trials using VPS as the trial intervention. Where recruitment into another trial is considered to be appropriate and without having any detrimental effect on the BASICS trial this must first be discussed with the MC CTU who will contact the Chief Investigator or delegated other.

8 ASSESSMENTS AND PROCEDURES

All paper CRFs should be completed as described in section 13.2 by personnel named on the delegation log as authorised to do so, usually the RN, and returned to the MC CTU within 28 days of visit date, unless stated otherwise.

Eligibility, randomisation details including insertion of the VPS and consent details will be collected as described in section 6 and 7.3. Patient details including initials, date of birth, postcode and NHS number will be reported on the consent form, separate to clinical data. Once written informed consent has been obtained from the parent or legally acceptable representative, the RN will collect baseline data using the baseline preoperative assessment CRF.

8.1 Schedule for Follow-up

	Screening	Baseline[1] (Pre-operative assessment)	Randomisation (First surgery)	Early post -op assessment	First routine post-op Assessment[2]	12 weekly follow up assessment	Subsequent routine post-op Assessment(s)	End of trial phone call	Unscheduled visit/Admission	Shunt revision /removal
Informed consent[3]	X									
Assessment of Eligibility Criteria	X	X	X							
Review of relevant Medical History	X	X								
Collect demographic data	X	X								
Review of Concomitant Medications		X	X	X	X	X	X	X	X	X
Weight		X								
Heart rate		X		X					(X)	
Head circumference		(X)		(X)	(X)		(X)		(X)	
Neurological assessment (GCS)		X		X					(X)	
Temperature				X					(X)	
Randomisation			X							
Study Intervention			X							X
Wound check				X	(X)		(X)		(X)	
CSF sample taken			X[4]						(X)[5]	X[4]
Additional CSF and blood taken for sub study			(X)							(X)
CSF results reviewed				X[6]					(X)	
Health economics questionnaire		X		X		X[7]		X		
Health service diary				X		X		X		
Post op CT/ MRI				(X)	(X)		(X)		(X)	
Assessment of Adverse Events				X	X	X	X	X	X	X

(X) – As indicated/appropriate.

[1] At baseline, all procedures should be done before study intervention.

[2] Schedule of post-operative follow up visits is dependent on the Trust's post-operative follow up procedure, and the participant's clinical condition.

[3] Informed consent should always be sought prior to trial intervention. The exception to this rule is adults lacking capacity to consent (see section 11.1). If an adult lacking capacity should regain capacity at any point during the trial, informed consent should be sought.

[4] CSF sample taken during surgery

[5] CSF sample taken using CSF tap or lumbar puncture

[6] Results must be reviewed (and microbiology form updated) within 72 hours of surgery, even if the patient has been discharged before the results are available. If results indicate a CSF infection patients will only be followed up for safety (until 48 hours after VPS removal)

[7] Health economics questionnaires only completed during **first** 3 monthly follow up phone call.

8.2 Procedures for assessing Efficacy

Patients will be followed up after randomisation as outlined in section 8.1.

Shunt failure is categorised as follows. Details of shunt failure will be captured on the Shunt Revision/Removal CRF:

(i) **Shunt infection**: see below.

(ii) **Mechanical shunt failure**: can occur at the proximal ventricular catheter (commonest), valve or distal peritoneal catheter. In addition, disconnection or damage to the shunt components effectively results in shunt obstruction.

(iii) **Functional shunt failure**: commonly results from excessive drainage of CSF into the peritoneum and causes subdural haematoma formation or slit ventricle syndrome. This is more common in children and may lead to valve revision despite the shunt system being patent and not infected. Likewise functional underdrainage may occur resulting in shunt revision to a more suitable tailored valve.

(iv) **Failure due to patient**: occasionally despite a functional patent VPS a patient will be unable to absorb the CSF deposited into the peritoneum – this may result in a shunt revision to an alternative site e.g. atrium, pleural space

Infections will be defined as all VPS CSF infections, peritoneal and deep incisional infections, arising from the insertion of a shunt. The cause of shunt failure will be determined by the TMG, blinded to the allocated VPS. Every potential infection will be classified in relation to site, certainty of diagnosis and relationship to insertion or later contamination using the following: the clinical symptoms and signs, and the microbiology results will be considered together by the TMG to define a VPS infection as:

1. VPS CSF or peritoneal infection:

1a. Definite - Culture positive (significant culture of organisms from the CSF)

- Organisms grown on primary culture or repeated (> 1) subculture
- with or without clinical signs of infection or malfunction
- AND managed by shunt removal and antibiotic treatment

1b. Probable - Culture uncertain (organisms grown on one subculture only)

- with or without symptoms and signs of CSF infection
- with CSF pleocytosis and / or organisms seen on gram stain
- AND managed by shunt removal and antibiotic treatment

1c. Probable - Culture negative (no organisms grown but)

- with or without symptoms and signs of CSF infection
- with CSF pleocytosis and / or organisms seen on gram stain
- AND managed by shunt removal and antibiotic treatment

1d. Possible - Culture uncertain

- No symptoms or signs, no pleocytosis, no organisms seen on gram
- growth after enrichment in one CSF only
- managed by shunt removal and antibiotic treatment.

2. VPS deep incisional infection:

An infection occurring within 1 year of VPS placement (if appears related to the placement) involving subcutaneous (extracranial or abdominal) shunt tubing without any evidence of CSF infection, but requiring removal and antibiotic treatment.

3. VPS superficial incisional infections (without CSF or tubing involvement):

Infection of the superficial incision (skin and subcutaneous tissue above fascia - without extension to the shunt material) and treated without VPS removal is defined in line with the national Surgical Site Infection Surveillance Service, Healthcare Associated Infection & Antimicrobial Resistance Department, Health Protection Agency: . **-**

8.3 Procedures for Assessing Safety

Adverse events whose causal relationship to the trial intervention (VPS) is assessed and judged by the investigator to be possibly, probably, or almost certainly related to the intervention, which occur from the time of VPS insertion will be reported. An independent Data and Safety Monitoring Committee (IDSMC) will be convened to monitor safety data (see section 16.3 for further details).

8.4 Other Assessments

8.4.1 Quality of Life and Health Economics

Routine Data Collection

Previous studies are cost analyses, retrospective in design, and from a US perspective (22-25). Their relevance to the UK setting is limited, and a *de novo* prospective economic evaluation is therefore warranted. The health economic analysis will adopt the perspective of the NHS and Personal Social Services. Costs will include those of the shunts, duration of intensive care stay and hospital admission, antibiotic treatment, contact with health professionals and social services. Resource use will be based on entries made in designated sections of patients' case report forms which will include questions on use of personal social services (27). This will be complemented with Hospital Episode Statistics data sourced from the NHS Information Centre, which has the benefit of tracking patients according to their NHS number (should they move within the UK) whilst assuring their anonymity. Unit cost data will be obtained from routine hospital data (NHS reference costs) (28) and other resources such as the BNF (29) and Curtis' unit costs of health and social care (30). Given that the economic question under consideration is one of technical efficiency (i.e. which of the three shunts is most cost-effective), we shall approach this as a cost-effectiveness analysis, based on the incremental cost per shunt failure averted. Secondary economic outcomes will include: (i) incremental cost per shunt infection avoided; and (ii) incremental cost per QALY gained, estimated by administering the EuroQol EQ-5D-3L, EQ-5D-Y (youth version) or Hydrocephalus Outcome Questionnaire (HOQ) to patients (or their parents, according to age) at each follow-up visit (see table 1 for details). Costs and benefits occurring after the first year will be discounted at 3.5% per annum. Total costs will be combined with the measures of health outcome to calculate the incremental cost-effectiveness (utility) ratios of each technology. Where appropriate, missing resource use or health outcome data will be imputed. The number of QALYs experienced by each patient will be calculated as the area under the curve, using the trapezoidal rule, and corrected for baseline utility score. Non-parametric bootstrapped 95% confidence intervals will be estimated (10,000 replicates). We will also employ simple parametric approaches for analysing cost and QALY data that assume normal distributions given the large samples where the near-normality of sample means is approximated. Should the data indicate otherwise, we will develop a generalised linear model, to deal with problems such as skewness. Stratified cost-effectiveness analyses will be conducted on important, pre-specified patient subgroups (including neonates, patients under 1 year old, patients with a previous EVD). Estimates of ICERs will be compared with the £20,000 to £30,000 per QALY threshold of cost-effectiveness, and a range of one-way sensitivity analyses will be

conducted to assess the robustness of the analysis. Multivariate sensitivity analyses will be applied where interaction effects are suspected, for instance in the assessment of the combined effect of development of resistant organisms and the costs associated with their management. The joint uncertainty in costs and benefits will be considered through the application of bootstrapping and the estimation of cost-effectiveness acceptability curves (31).

Table 1: Health Economics Questionnaires

	Completed by:	
Age	**Participant**	**Parent / carer**
<5 **(Under age 5)**	None administered	None administered
5 to <8 **(From age 5 to under 8)**	None administered	Hydrocephalus Outcome Questionnaire (parent version) EQ-5D-3L (proxy 1)*
8 to <18 **(From age 8 to under age 18)**	Hydrocephalus Outcome Questionnaire (child version) EQ-5D-Y (Including EQ-VAS -visual analogue scale)	EQ-5D-3L (proxy 1)* (Including EQ-VAS -visual analogue scale)
≥18 **(Age 18 and over)**	EQ-5D-3L (Including EQ-VAS -visual analogue scale)	** EQ-5D-3L (proxy 1) (Including EQ-VAS -visual analogue scale)

*Where the EQ-5D-3L or HOQ is completed by proxy, every effort should be made to ensure that the same parent / caregiver / consultee completes the questionnaire each time.
**In the case of adults lacking capacity to consent for themselves, the EQ-5D-3L (proxy 1) will be completed by the consultee with whom the study was discussed.

Once a child reaches the age of 16 they are normally classified as an adult, however Health Economic Questionnaires classifies adults as being age 18 and above. Participants who reach the age of 16 will continue to complete the EQ-5D-Y and the EQ-5D-3L-Proxy 1. The same applies for any participants who enter the trial between the ages of 16 – 18.

For consistency though throughout the patient's involvement with the trial, and so that we can best track the change in their health state over time using the same questionnaire (and therefore don't have to potentially allow for this in the final analysis), one option would be for the patient to complete the first questionnaire as appropriate for their age on the first occasion (as per the table in your email) and to then stick with this completing this same questionnaire throughout their involvement with the trial, even if they change age classes.

Note: A script will be provided for Researchers administering questionnaires via the telephone.

8.4.2 Routine Data Collection

Subject to agreement with participating site Finance departments and in line with their usual financial data practices, data on trial patient hospital resource use will be collected annually from the PLICS datasets. These datasets include Health Resource Groups (HRG) which detail costs for patient stays and treatments. Responsibility for the data collection and anonymisation will rest with the site RN who will supply their site Finance

departments with the necessary details to ensure only information on consented participating patients is provided. It is the responsibility of the site Finance departments to provide the site RNs with the data in a timely fashion and should the site RN so request, ensure all patient identifying data has been replaced with the patient BASICS trial number.

A secure webpage will be set up for the two-way flow of information between the BASICS team and each site RN. It will be the responsibility of the site RN to keep safe their password and user name, ensure any data uploaded to this site is anonymised and ensure each line of resource use data is marked with the patient trial number. Anonymised PLICS Data will be stored on this secure web page until final analysis.

8.4.3 Special Assays or Procedures

CSF samples taken at insertion of first VPS will be sent for routine microbiology analysis as per the standardised microbiology lab protocol devised for the trial. In addition at selected sites, additional CSF and serum will be sampled at first VPS insertion and at subsequent revision as defined in section 8.5.

Any positive isolates will be transferred to Great Ormond Street Hospital (as per Microbiology protocol) for future analysis. If the sample is clear of infection it will be disposed of.

8.5 Substudies

There are a number of substudies proposed to run alongside BASICS. All proposals for substudies will be reviewed by the Trial Management Group and the Trial Steering Committee and approved as appropriate.

Additional blood and CSF samples to be used for substudies will be taken from patients at trial sites that are able to contribute;. These samples will be stored at the Institute of Infection and Global Health at the University of Liverpool.

Consent will be sought at trial entry for collection of these additional samples and their storage at University of Liverpool. Up to a maximum of 4.5 mls of additional CSF and up to a maximum of 4.5mls of blood (less than a teaspoon) will be taken according to blood volume guidelines. These will be taken at shunt insertion and at first revision for each patient who consents to the substudies.

In view of the nature of out of hours shunt revisions, if the additional samples are not taken at this time then in cases where an EVD is inserted to treat the infection the additional CSF and blood samples can be taken at a later point,

8.6 Loss to Follow-up

Trial follow-up is by the research nurse until the time points specified in section 8.1. If any of the trial patients are lost to follow-up before the relevant timepoint (e.g. lost due to transfer to

another hospital), contact will initially be attempted through the trial research nurses and the lead investigator at each centre. If the lead investigator at the trial centre is not the patient's usual clinician responsible for their speciality care then follow-up will also be attempted through this clinician. Hospital Episode Statistics and Office of National Statistics will still be accessed.

8.7 Trial Closure

The end of the trial is defined to be the date on which data for all participants is frozen and data entry privileges are withdrawn from the trial database. However the trial may be closed prematurely by the Trial Steering Committee, on the recommendation of the Independent Data and Safety Monitoring Committee (IDSMC).

9 STATISTICAL CONSIDERATIONS

9.1 Introduction

A separate and full Statistical Analysis Plan (SAP) will be developed prior to the final analysis of the trial. The SAP will be agreed by the Trial Steering Committee (TSC). The main features of these planned statistical analyses are included here in the main protocol.

9.2 Method of Randomisation

The randomisation code list will be generated by a statistician (who is not involved with the BASICS trial) at the MC CTU. Patients will be randomised to standard, antibiotic impregnated, or silver impregnated VPS in a ratio of 1:1:1. This ratio reflects uncertainty about which of these three types is best in terms of the risk of VPS infection and cost effectiveness.

9.3 Outcome Measures

The primary and secondary outcomes are defined in section 4.

9.4 Sample Size

Approximately 30% of new VPS will fail within the first 6 months of insertion due to shunt complications, which will include infection but also malfunction, and mechanical failure typically secondary to catheter or valve obstruction and peritoneal complications. When a VPS has failed for reasons other than infection then this prevents infection being observed. Infection is the event of interest with all other reasons for shunt failure being competing risks. The trial will compare Bactiseal versus standard VPS, and Silverline versus standard VPS. A Bonferroni adjustment has been made to allow for the multiple comparisons and a statistical significance level of 0.025 will be used accordingly. The sample size calculation is based on Pintilie 2002 (32) assuming time to any type of event (of interest or competing risks) follows an exponential distribution. Using a two year accrual period with six month follow up once accrual has completed and a competing risks event rate of 30% across trial arms with the event rate of interest (infection) being 8% in the standard arm (17) and 4% in the treated arms (hazard ratio of 0.49) then with 5% loss to follow up we would require 989 patients to provide 80% power. The table below shows how the power varies according to changes in the event rate with a fixed total sample size of approximately 1143. Allowing for 5% loss to follow up a sample size of 1200 participants allows a hazard ratio of 0.49 to be detected over a range of baseline event rates (0.05 to 0.1) with good statistical power.

The value of 8% is supported elsewhere (17), in addition, infection rate surveillance over 10 years (1993-2003) at Great Ormond Street Hospital involving over 1500 insertions has demonstrated that while there are fluctuations in monthly infection rates that overall the rate has remained remarkably stable around this level. Observed fluctuations in infection rates within a centre will be influenced by the size of the denominator.

Infection rate: Control arm	Infection rate: Treated arms	Hazard ratio	Power	Total sample size (across three trial arms)
0.1	0.05	0.48	94	1140
0.08	0.04	0.49	80	942
0.08	0.04	0.49	88	1157
0.05	0.025	0.49	67	1144

A feasibility study was conducted for a period of one month during the development of this full application. The feasibility study which involved sites prospectively completing screening logs developed for this study over a 4-week period demonstrated the commitment of sites to the study and the volume of participants meeting the eligibility criteria. The data supports annual eligible participant figures of 1200. Using a conservative estimate of consent of 50% this demonstrates that the sample size is achievable over a two-year recruitment period.

Reduction of infection is a priority and therefore it could be argued that much smaller differences than those the study is powered to detect are still important. However the applicants believe that a strong effect is required to inform clinical practice and establish a first line treatment policy across the NHS. This is in part due to the large differences in cost between the VPS; we need to warrant expenditure on type of VPS as opposed to other infection control activities. This size of effect has also been demonstrated in related studies (7, 13).

The sample size calculation detects a change from 0.08 to 0.04 with a hazard ratio of 0.49 and requires a total of 989 participants, which will take two years of recruitment to achieve. In considering a smaller effect size the impact on the numbers required needs to be considered. Keeping all other parameters in the sample size calculation constant detecting a change from 0.08 to 0.06 (a hazard ratio of 0.74) would require a total sample size of 4866 participants, with a change from 0.08 to 0.05 (a hazard ratio of 0.61) requiring 1973 participants.

The change to be detected by BASICS is considered to be that required to provide convincing evidence to impact clinical practice. The magnitude required is in part related to costs of the shunts but also the size of difference observed in other studies as detailed above.

9.4.1 Sample size calculation revision

In January 2016, the IDSMC reviewed the accumulating primary outcome and safety data. Upon looking at the data, it became apparent that some of the assumptions underlying the original sample size calculation do not hold.

After adjusting the sample size assumptions, recruitment of 1606 patients will provide 80% power to detect a hazard ratio of 0.49. It was decided that the recruitment period should be extended for 12 months. Based on current recruitment figures, the total recruitment after an additional 12 months should be approximately 1650 patients. This will allow some flexibility should the trial run into any unforeseen recruitment problems or if there are any further changes to these assumptions.

9.5 Interim Monitoring and Analyses

The trial will be monitored by an Independent Data and Safety Monitoring Committee (IDSMC) who will assess the trial data and take into account the current world-wide evidence. The IDSMC members will comply with a trial-specific IDSMC charter according to International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines.

The trial statistician at the MC CTU will prepare the report for the IDSMC, the contents of which will be agreed by the IDSMC. The IDSMC will be asked to give advice on whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment of further patients or further follow-up. A decision to discontinue recruitment, in all patients or in selected subgroups will be made only if the result is likely to convince a broad range of clinicians including participants in the trial and the general clinical community. If a decision is made to continue, the IDSMC will advise on the frequency of future reviews of the data on the basis of accrual and event rates. The IDSMC will make recommendations to the Trial Steering Committee (TSC, see section 16) as to the continuation of the trial.

There will be an interim analysis of the primary outcome half way through the trial after approximately 50% of the total events have been observed, using Peto-Haybittle stopping rules (33). A full statistical analysis plan will be written prior to any comparison of the treatment groups.

9.6 Analysis Plan

The trial will be analysed and reported using the 'Consolidated Standard of Reporting Trials' (CONSORT) and the International Conference on Harmonisation E9 guidelines. A full and detailed statistical analysis plan will be developed prior to the final analysis of the trial. The main features of the statistical analysis plan are included here.

The primary analysis will be by intention to treat principle as far as is practically possible. Results will be presented throughout using 97.5% confidence intervals and a 2.5% level of statistical significance. Analysis of the primary outcome will be by cumulative incidence. The Fine & Gray (34) regression method will be used to directly model the cumulative incidence function. In addition two semi-parametric models described in Scheike and Zhang (35) will be used to consider time varying effects. Time to event outcomes where competing risks is not an issue will be analysed using Kaplan Meier curves, log rank tests and Cox Proportional Hazard models. Assumptions of proportional hazards will be investigated. Categorical outcomes will be analysed using Chi-square tests.

Missing data will be monitored and strategies developed to minimise its occurrence, however as much data as possible will be collected about the reasons for missing data and this will be used to inform the handling of missing data.

10 SAFETY REPORTING

10.1 Terms and Definitions

10.1.1 National Research Ethics Service (NRES) Definitions

An **Adverse Event (AE)** is defined as any untoward medical occurrence in a participant to whom a research procedure has been administered, including occurrences which are not necessarily caused by or related to that procedure.

In medical devices research the National Research Ethics Service (NRES) defines a **Serious Adverse Event (SAE)** as an untoward occurrence that:

- Results in death;
- Is life-threatening*;
- Requires in-patient hospitalisation or prolongation of existing hospitalisation**
- Results in persistent or significant disability or incapacity, or;
- Consists of a congenital anomaly or birth defect;
- Other important medical events***.

*'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.
***Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event/experience when, based upon appropriate medical judgment, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

The National Research Ethics Service defines related and unexpected SAEs as follows:

- **'related'** – that is, it resulted from administration of the medical device or any of the research procedures;
- **'unexpected'** – that is, the type of event is not listed in the protocol as an expected occurrence.

NRES require that a SAE occurring to a research participant, where in the opinion of the Chief Investigator the event is related and unexpected, is to be reported to the main Research Ethics Committee (REC).

10.1.2 Medicines and Healthcare products Regulatory Agency (MHRA) Adverse Incident Centre (AIC) Definitions

As the trial involves the use of CE-marked medical devices employed for their intended purpose, adverse incidents are also reportable to the Medicines and Healthcare products Regulatory Agency (MHRA) Adverse Incident Centre (AIC) under the User Devices Vigilance requirement.

The MHRA AIC define an **Adverse Incident (AI)** as:

- An event that causes, or has the potential to cause, **unexpected or unwanted effects** involving the safety of device users (including patients) or other persons.

Causes of AIs involving devices may include:

- Design or manufacturing problems;
- Inadequate servicing and maintenance;
- Inappropriate local modifications;
- Unsuitable storage and use conditions;
- Selection of the incorrect device for the purpose;
- Inappropriate management procedures;
- Poor user instructions or training (which may result in incorrect user practice).

Conditions of use e.g. environmental conditions or location may also give rise to adverse incidents.

Any adverse incident involving a device or its instructions for use should be reported to the MHRA AIC, especially if the incident has led to or, were it to occur again, could lead to all occurrences listed under SAEs in section 10.1.1, as well as:

- Unreliable test results and associated risk of mis-diagnosis or inappropriate treatment;
- Ongoing faults that successive service/maintenance visits have failed to rectify.

The MHRA AIC also request that minor safety or quality problems with the device should also be reported as these can help demonstrate trends or highlight inadequate manufacturing or supply systems. Reports of adverse incidents (i.e. related and unexpected AEs) as that appear to be caused by human error should also be reported because:

- The error may be partly (or wholly) due to deficiencies in the design of the device or instructions for use;
- They may prompt promulgation of advice or device design improvements that will help prevent repetition of mistakes.

By these definitions AIs are the same as related and unexpected AEs and related and unexpected SAEs.

10.2 Severity / Grading of Adverse Events

The assignment of the severity/grading should be made by the investigator responsible for the care of the participant using the definitions below.
Regardless of the classification of an AE as serious or not, its severity must be assessed according to medical criteria alone using the following categories:

Mild: does not interfere with routine activities

Moderate: interferes with routine activities
Severe: impossible to perform routine activities

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity (see above) whereas seriousness is defined using the criteria in section 10.1, hence, a severe AE need not necessarily be a Serious Adverse Event.

10.3 Relationship to Trial Intervention (VPS)

The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in Table 2.
If any doubt about the causality exists the local investigator should inform the study coordination centre who will notify the Chief Investigators. In the case of discrepant views on causality between the investigator and others, NRES and the MHRA AIC will be informed of both points of view.

Table 2: Definitions of Causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship. N.B. An alternative cause for the AE should be given
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after insertion of the VPS). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possibly*	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after insertion of the VPS). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probably*	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Almost certainly*	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

*Possibly, probably, or almost certainly related will be referred to throughout the protocol as 'related'.

10.4 Reporting Procedures

AEs and SAEs will only be reported for patients where consent has been obtained and the causal relationship to the trial intervention (VPS insertion) has been assessed and judged by the investigator to be related to the VPS (see section 10.3), which occurs:

- From the time of VPS insertion until 48 hours after VPS removal or;
- From the time of attempted insertion of the allocated VPS until 48 hours afterwards if the insertion was not successful.

All the events listed in table 3 are expected within the trial population and can be related to the trial intervention (VPS).

Table 3: Expected adverse events associated with VPS

Expected event
Infection, including; - Wound infection - Shunt infection - Wound dehiscence
Injury, including; - Brain injury related to procedure with new neuro deficit - Vascular injury to brain pseudoaneurysm - Tunnelling injury (organ, viscus, lung, vascular)
Seizures (early, post op, delayed)
CSF Leak
Mechanical shunt failure, including; - Disconnection - Migration - Fracture - Misplacement (of ventricular or distal catheter)
Catheter obstruction, including; - Ventricular catheter - Shunt valve - Distal catheter
Overdrainage/Underdrainage - Extraaxial fluid collections - Slit ventricle syndrome - Subdural haematoma from excessive CSF drainage - Sunken fontanelle - Valve change for symptomatic over/underdrainage
Loculation of ventricles
Abdominal complications, including; - Abdominal fistula - Abdominal hernia - Bowel perforation as a result of shunt surgery - Ascites - Abdominal cysts - Pseudocysts - Adhesions - Malabsortion - Independent abdominal infections (such as appendicitis/cholecystitis/diverticulitis/other) -
Intracranial haemorrhage related to shunt placement

Expected events taken from Instructions for Use for HAKIM Ventricular Catheter with BACTISEAL Silicone and HAKIM Peritoneal Catheter with BACTISEAL Silicone 10/09, Instructions for Use for Silverline Antimicrobial Ventricular Shunt Catheter version 8.0, 02/08/2010 and Instructions for Use for Silverline Antimicrobial Peritoneal Shunt Catheter version 5.0 02/08/2010.

Events listed in table 3
All AEs in table 3 should be reported by the RN using the Related Expected Adverse Event CRF and returned to the MC CTU within 7 days of event occurring.

If the AE is a hospital admission with any expected events as stated in table 3 and then graded as **serious** you are **NOT** required to complete an SAE form. This information is captured on other CRFs, so **it is** a requirement to report to the MC CTU but the report will not be expedited.

Events not listed in table 3
If the event is not listed in table 3, it should be reported by the RN using the related adverse event CRF with the expectedness code of **'unexpected'**. The PI or designated other should grade the expectedness of the event as **'not serious' or 'serious'**.

- **Events graded as not serious**
  If the event is graded as **not serious,** it should also be reported as per local reporting procedures. The Related Adverse Event CRF should be returned to the MC CTU within 7 days of event occurring.

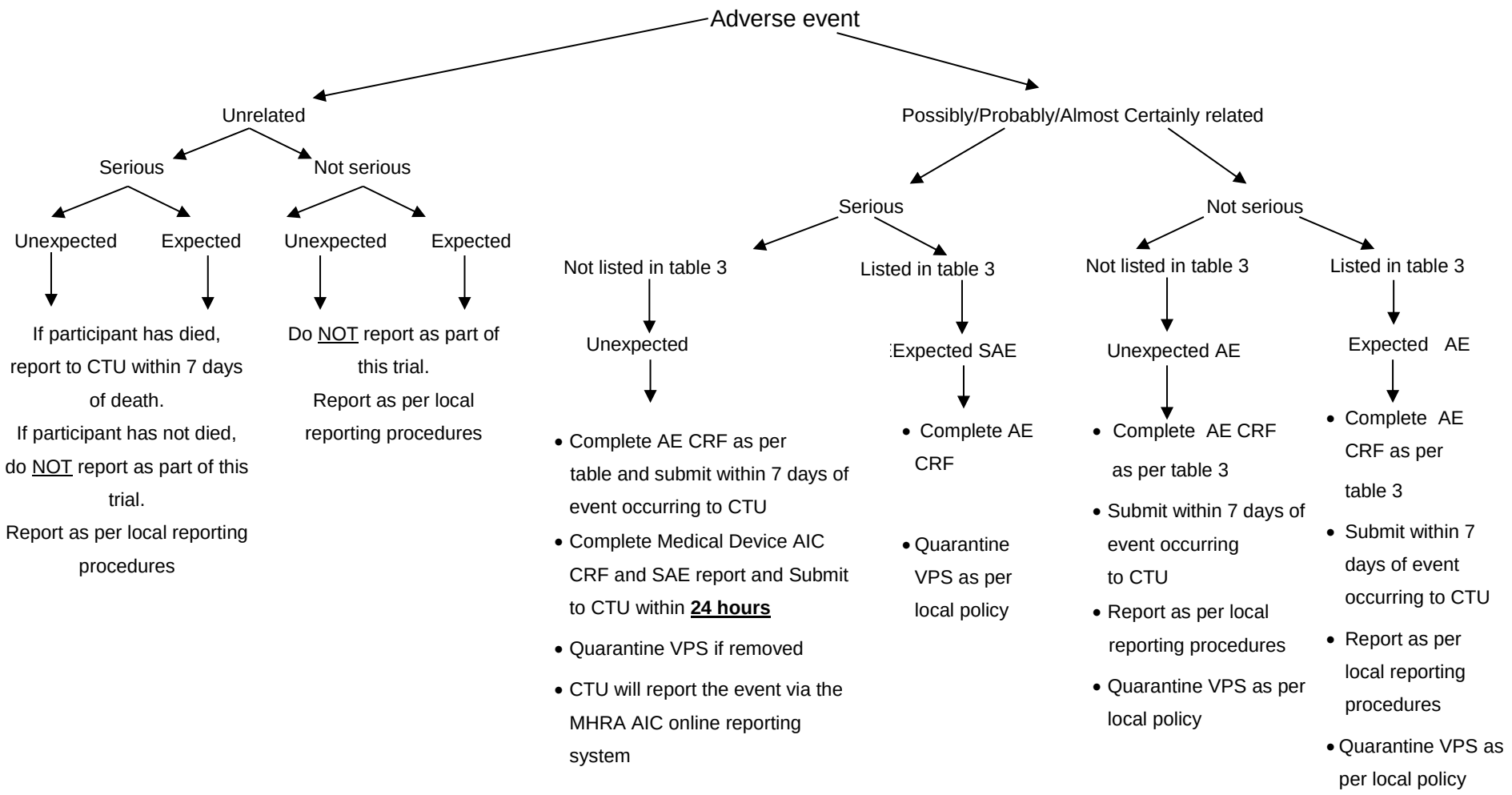
- **Events graded as serious**
  If the event is graded as **serious** (see section 10.1), the RN should also complete the **related serious adverse event CRF and Medical Device Adverse Incident CRF**, and the CRFs **returned to the MC CTU within 24 hours** of the clinical research team becoming aware of the event.

Do Not Include
- Any AEs whose causal relationship to the trial intervention (VPS) is assessed and judged by the investigator to be unrelated or unlikely to be related to the trial intervention (randomised VPS)
- Medical or surgical procedures - the condition which leads to the procedure is the adverse event
- Pre-existing disease or conditions present before treatment that do not worsen
- Situations where an untoward medical occurrence has occurred e.g. cosmetic elective surgery
- The disease being treated or associated symptoms/signs unless more severe than expected for the patient's condition

Include
- An exacerbation of a pre-existing illness
- An increase in frequency or intensity of a pre-existing episodic event/condition
- A condition (even though it may have been present prior to the start of the trial) detected after the insertion of the trial intervention (VPS)
- Continuous persistent disease or symptoms present at baseline that worsens following the insertion of the trial VPS
- Laboratory abnormalities that require clinical intervention or further investigation (unless they are associated with an already reported clinical event or as part of routine follow-up).
- Abnormalities in physiological testing or physical examination that require further investigation or clinical intervention
- Injury or accidents that are not expected.

All deaths occurring after randomisation up until the end of follow-up should be reported to the MC CTU using the death CRF **within 7 days** of the clinical research team becoming aware of the event. If a patient's death has been assessed and judged by the investigator to be related to the intervention (see section 10.3) a related SAE CRF should also be completed. After removal of the VPS any deaths that occur should only be reported to the MC CTU using the death CRF.

The flowchart below is given to aid in determining reporting requirements for adverse events.



10.5 Follow-up After Adverse Events

All adverse events should be followed until satisfactory resolution or until the investigator responsible for the care of the participant deems the event to be chronic or the patient to be stable.

Follow-up information is noted on another AE/SAE form by ticking the box marked 'follow-up' and faxing to the MC CTU as information becomes available. Extra, annotated information and/or copies of test results may be provided separately.

When reporting SAEs the investigator responsible for the care of the participant should apply the following criteria to provide information relating to event outcomes: resolved; resolved with sequelae (specifying with additional narrative); not resolved/ongoing; ongoing at final follow-up; fatal or unknown.

10.6 Quarantine, Labelling & Storage of Devices Involved in an Adverse Incident (i.e. Related Unexpected AE/SAE)

Medical devices that have been involved in an adverse incident (i.e. related and unexpected AE), whether serious or not, should be quarantined as per your local trust policy. Except for serious unexpected adverse incidents which should follow the MHRA guidelines below.

Until the MHRA has been given the opportunity to carry out an investigation, they should not be discarded, repaired or returned to the manufacturer. All material evidence, i.e. devices/parts removed, replaced or withdrawn from use following an incident, instructions for use, records of use, repair and maintenance records, packaging materials, or other means of batch identification must be:

- Clearly identified and labelled;
- Stored securely.

Evidence should not be interfered with in any way except for safety reasons or to prevent its loss. Where appropriate, a record should be made of all readings, settings and positions, together with any photographic evidence and eyewitness reports.

If it is thought that an urgent examination of the device (and/or related items) may be required, upon notification of the incident an MHRA device specialist will decide whether to inspect the item urgently on site (or at other appropriate facilities), or may request that the device is sent to the MHRA. If required, the MHRA will contact the manufacturer (Cook Medical) and, if accompanied by an appropriate person, they may be allowed to inspect the items. To facilitate an investigation, it may be possible to provide the manufacturer with a sample of unused stock from a large batch. However, until advised to the contrary by the MHRA, the manufacturer must not be allowed to exchange, interfere with, or remove any part of the product implicated in the incident as this might prejudice MHRA investigations, or those of other official bodies.

10.7 Responsibilities – Investigator

The Investigator is responsible for reporting all related AEs that are observed or reported during the study.

All related SAEs must be reported immediately by the investigator to the CTU on an SAE form unless the SAE is specified in the protocol as not requiring immediate reporting.

Minimum information required for reporting:

- Study identifier
- Study centre
- Patient number
- A description of the event
- Date of onset
- Current status
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study intervention

i. The Investigator is responsible for reporting all AEs that are observed as possibly, probably, or almost certainly related to the intervention.

ii. The SAEs forms should be completed by a designated investigator, a physician named on the 'signature list and delegation of responsibilities log' as responsible for reporting SAEs and making trial related medical decisions, and submitted to the MC CTU within the timelines specified in section 10.4. The investigator should assess the SAE for the likelihood that it is a response to the intervention. In the absence of the designated investigator, the form should be completed and signed by an alternative member of the research centre trial team and submitted to the MC CTU. As soon as possible thereafter the responsible investigator should check the SAE form, make amendments as appropriate, sign and re-send to the MC CTU. The initial report shall be followed by detailed reports as appropriate.

iii. When submitting an SAE to the MC CTU research sites should also telephone the appropriate trial co-ordinator/data manager on telephone number **0151 282 4527** to advise that an SAE report has been submitted.

iv. Send the SAE form by fax (within 24 hours or next working day) to the CTU:

Fax Number: 0151 282 4721

v. For all SAEs, follow-up the patient as described in section 10.5.
The patient **must** be identified by trial number, date of birth and initials only. The patient's name **should not** be used on any correspondence

vi. For medical devices that have been involved in an adverse incident (related unexpected AE), whether classed as serious or not, ensure that they have been quarantined or as per local policy as described in section 10.6.

vii. The responsible investigator must **notify** their R&D department and medical device liaison officer of the event as per standard local governance procedures.

viii. Patient safety incidents that take place in the course of research should be reported to the National Patient Safety Agency (NPSA) by each participating NHS Trust in accordance with local reporting procedures.

10.7.1 Maintenance of Blinding

Systems for AE reporting should, as far as possible, maintain blinding of individual clinicians and of trials staff involved in the day-to-day running of the trial.

If simply removing the VPS is a viable option for the patient's care, it should not be necessary for unblinding to occur.

However, it may be unavoidable to unblind treating clinicians if the information is necessary for the medical management of particular patients. The safety of patients in the trial always takes priority.

In each report, seriousness, causality and expectedness should be evaluated for all of the trial interventions unless criteria have been fulfilled (section 7.4.2) and unblinding has taken place.

Cases that are considered serious, unexpected and possibly, probably or almost certainly related to one of the trial interventions would have to be unblinded at the MCRN clinical trials unit prior to reporting to the regulator.

10.8 Responsibilities – MC CTU

The MC CTU is undertaking duties delegated by the trial sponsor and is responsible for the reporting of AEs to the main REC and MHRA AIC as follows:

- Related unexpected SAEs must be reported to the main REC within 15 days of the MC CTU first becoming aware of the event;
- All investigators will be informed, in a timely manner, of all related unexpected SAEs occurring throughout the trial;
- All related unexpected SAEs will also be reported to the Sponsor.
- A list of all SAEs (expected and unexpected) will be reported annually to the main REC.
- All device-related unexpected SAEs and AEs (Adverse Incidents) will be reported to the MHRA AIC as part of user device vigilance reporting.
- Copies of the reports will be sent to the Principal Investigator at all institutions participating in the trial.

It is recommended that the following safety issues should also be reported to the main REC in an expedited fashion:

- New events related to the conduct of the trial or the development of the devices and likely to affect the safety of the subjects. For example, a SAE which could be associated with the trial procedures and which could modify the conduct of the trial.
- Recommendations of the Data Monitoring Committee, if any, where relevant for the safety of the subjects.

Staff at the CTU will liaise with the Chief Investigator (or designated other specified in the protocol) who will evaluate all SAEs received for seriousness, expectedness and causality. The causality assessment given by the Local Investigator at the hospital cannot be overruled and in the case of disagreement, both opinions will be provided with the report.

10.8.1 Safety reports

Safety reports will be generated during the course of the trial which allows for monitoring of AE reporting rates across centres. The CTU will send annual safety reports containing a list of all SAEs to the Main REC. Any concerns raised by the IDSMC or inconsistencies noted at a given centre may prompt additional training at centres, with the potential for the MC CTU to carry out centre visits if there is suspicion of unreported AEs in patient case notes. Additional training will also be provided if unacceptable delay in safety reporting timelines.

10.9 Reporting of Pregnancy

No pregnancy testing is planned as part of the trial procedures. Patients will be asked at each visit to disclose pregnancy, and all reported pregnancies should be followed up to delivery using a pregnancy form. Patients who are known to be pregnant will not be excluded from the trial.

11 ETHICAL CONSIDERATIONS

11.1 Ethical Considerations

The study will abide by the principles of the World Medical Association Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996). The relevant approvals will be obtained as described in section 11.2. The specific ethical issues are:

- **Informed consent in a paediatric population**

Admission to a neurosurgical unit is a time of enormous anxiety for children and their family. To minimise additional stress due to enrolment in the trial, recruiting investigators (such as consultant neurosurgeons and research nurses) will be experienced at imparting information to families with sick children. Parents or a legal representative of the child will be made aware that the VPSs under investigation are those that are routinely used. They will be informed of the potential risks and benefits associated with trial participation and their right to withdraw the child from the trial at any time without the child or family being subject to any resulting detriment. They will be provided with written information and contact details of the trial personnel, who will also be readily available, from whom further information about the trial may be obtained.

- **Assent from critically ill patients**

Due to the physical status of some the target population it may not always be possible to involve critically ill children in the consenting process. The ethics application will be supported by parent and child information sheets and parent and child consent/assent forms. Assent of trial participants, if appropriate, will be obtained as soon as their condition allows.

- **Consenting adults lacking mental capacity**

In adults lacking mental capacity, a consultee (typically next of kin or other family member) will be approached to discuss trial participation. The consultee will be will be made aware that the VPSs under investigation are those that are routinely used. They will be informed of the potential risks and benefits associated with trial participation and their right to withdraw from the trial at any time without being subject to any resulting detriment. They will be provided with written information and contact details of the trial personnel, who will also be readily available, from whom further information about the trial may be obtained. Consent will be sought to continue in the trial should they regain capacity.

11.2 Ethical Approval

The trial protocol, including the Parent/Patient Information Sheets and Consent/Assent forms and all other relevant trial documentation will be submitted for review by the Greater Manchester South Research Ethics Committee (REC). All participating centres must be granted NHS permission by their Local Research & Development (R&D) department prior to commencing recruitment. A copy of local R & D approval and the Parent/Patient Information and Consent/Assent form on local headed paper should be forwarded to MC CTU before the centre is initiated and patients recruited.

11.3 Informed Consent Process

Informed consent is a process initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. Informed consent is required for all patients participating in MRCN CTU coordinated trials. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.

Discussion of objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted are to be provided to patients by staff with experience in obtaining informed consent. Staff involved in the management of patients with hydrocephalus requiring VPS have experience of assessing mental capacity and obtaining advice from consultees in these situations. Where appropriate, age-and-stage-of-development appropriate Patient Information and Consent forms, describing in detail the trial interventions/products, trial procedures and risks will be approved by an independent ethical committee (IEC) and the patient (parent/legal representative in the case of minors) will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the patient (parent/legal representative in the case of minors). This information will emphasise that participation in the trial is voluntary and that the participant may withdraw from the trial at any time and for any reason. All participants will be given opportunity to ask any questions that may arise, should have the opportunity to discuss the study with their surrogates and time to consider the information prior to agreeing to participate. A contact point where further information about the trial may be obtained will be provided. The process of the provision of the patient information sheets should be documented in the participant's medical notes.

The patient (parent or legal representative in the case of minors) will then sign and date the informed consent document. Both the person taking consent and the participant must personally sign and date the form. A copy of the informed consent document will be given to the patient and their legally acceptable representative for their records. The original copy will be filed in the participant's medical notes and a further copy of the signed consent form will be given to the participant. One final copy of the consent form should be sent to the CTU.
The participant will be asked to sign the following consent forms as appropriate:

- Consent form for minors (as defined as participants under the age of 16)
- Consent from for adult (as defined as participants over the age of 16)
- Consent for participants aged 11-15 (**Scottish Sites Only)**

The patient may, without being subject to any resulting detriment, withdraw from the trial at any time by revoking the informed consent (Similarly, the parent or legal representative may withdraw a minor under the same conditions). The rights and welfare of the patients will be protected by emphasising to them that the quality of medical care will not be adversely affected if they decline to participate in this study.

If a patient's care is transferred to a participating hospital following their randomisation into the trial, they should be re-consented using the consent form for the hospital they are transferred to. In the event that a patient is transferred to a non-participating site, every effort should be made to collect relevant microbiology data.

11.3.1 Assent in minors

If capable, and under appropriate circumstances, minors should be approached to provide assent by a member of the research team with experience with minors. Age-and-state-of-development IEC-approved Patient information Sheet and Assent forms, describing (in simplified terms) the details of the trial intervention/product, trial procedures and risks should be used. The minor should personally write their name and date the assent form, which is then signed by the parent/legal representative and the researcher.

Assent forms do not substitute for the consent form signed by the patient's legally acceptable representative. Assent should be taken where appropriate and documented in the patient notes, however the absence of assent does not exclude the patient provided consent has been obtained from the parent/legal representative.

11.3.3 Re- Consent of 16 year olds.

A participant involved in the study who reaches the age of 16 (and is therefore deemed competent to provide consent) should be re-consented at their next scheduled visit after their 16th birthday.

11.3.4 Consent in adults who lack mental capacity

In adults who lack mental capacity trial participation will be discussed with a consultee (usually next of kin or other family member) by a suitably experienced member of the research team who is listed on the delegation log. The consultee will be provided with written information and asked to sign the Patient Representative Consultee Form. The patients should have their capacity re-assessed at each trial visit and this should be captured on log (**see section 6.2).** Should the patient regain capacity at any point during the trial they will be invited to continue with trial participation and an adult consent form will be completed. Patients will be given the option of withdrawing from trial follow up.
If the patient cannot attend participating site the responsible Research Nurse may make a judgement on discussion with the patient and the consultee whether capacity has been regained over the telephone, if capacity has been regained the Research Nurse should send out the adult consent via post.

11.3.5 Nominated Consent

As per the mental Health Act 2005 an Independent Healthcare Professional who has no involvement to the research taking place may consent for the patient until a relative/friend can re-consent on their behalf within seven working days..
Re-consent by a relative/friend should be obtained within seven days of nominated consent by signing the consent on behalf of the patient lacking capacity.

In exceptional cases where a family member or friend cannot re-consent on the patient's behalf, although the patient may continue in the study for the primary and some of the secondary outcomes (based on the original healthcare nominated professional consent) the Health Questionnaires and some of the health economic outputs would not need to be completed by the person who gave the nominated consent. In such circumstances, the research nurse will endeavour to complete as much follow up data as is possible from routine and emergency visits.

11.3.6 Scottish Sites

For Scottish sites children aged 11-15 deemed competent can consent for themselves, separate PIS&C's available for use in Scotland only**.**

Scottish Consent Forms will be scanned and emailed securely from site to lead Research Nurse within 24 hours using nhs.net.

11.4 Study Discontinuation

In the event that the study is discontinued, patients will revert to default care provided by each participating neurosurgical unit.

12 REGULATORY APPROVAL

The trial involves the use of CE-marked medical devices employed for their intended purpose, therefore this trial is not considered to be a clinical investigation under the Medical Devices Regulations 2002.

13 TRIAL MONITORING

Trial monitoring will be informed by the BASICS risk assessment and will be conducted as per the BASICS Trial Monitoring Plan to ensure that the rights and well-being of human participants are protected during the course of the clinical trial and that the data are credible and accurate.

Trial Oversight Committees related to the monitoring of the trial are detailed in section 16.

13.1 Source Documents

Each participating centre should maintain appropriate medical and research records for this trial, in compliance with International Conference on Harmonisation – E6- Good Clinical Practice guidelines Section 4.2 and regulatory and institutional requirements for the protection of confidentiality of participants.

Source data will be identified and documented in the BASICS Trial Monitoring Plan.

13.2 Data Capture Methods

13.2.1 Case Report Forms

The trial case report form (CRF) is the primary data collection instrument for the trial. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write “N/D”. If the item is not applicable to the individual case, write “N/A”. Or if the data item is un-known, write “NK”. If a data item has not been recorded on source data then write ‘NR’. All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialled and dated. Do not erase or white-out errors. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

CRF completion guidelines will be provided to all trial sites to assist in the completion of trial CRFs.

13.2.2 Data from electronic routine administrative databases

Data on Hospital Episode Statistics (HES) from the beginning of the financial year prior to baseline, to final follow up will be accessed centrally via the NHS Information Centre. Death data will be collected centrally from the Office of National Statistics (ONS) at final follow up. A database of patient identifiable data (e.g. participant name, NHS numbers, postcode and date of birth) will be generated. This will be used to request HES and ONS data within the specified date ranges from the NHS Information Centre and the ONS office.

Collection of these data will follow a standard procedure. Any transfer of data (requests for data and the return of the full dataset) will be transferred securely (encrypted) (see section

8.4.1for further details on using this data). Data will be stored at the MC CTU as described in section 13.4.1. Consent to data linkage will be sought.

13.3 Central Monitoring

Data stored at CTU will be checked for missing or unusual values (range checks) and checked for consistency within participants over time. Any suspect data will be returned to the site in the form of data queries. Data query forms will be produced at the CTU from the trial database and sent either electronically or through the post to a named individual (as listed on the site delegation log). Sites will respond the queries providing an explanation/resolution to the discrepancies and return the data query forms to CTU. The forms will then be filed along with the appropriate CRFs and the appropriate corrections made on the database. There are a number of monitoring features in place at the CTU to ensure reliability and validity of the trial data, to be detailed in the trial monitoring plan.

13.4 Clinical Site Monitoring

In order to perform their role effectively, the trial coordinator (or monitor) and persons involved in Quality Assurance and Inspection may need direct access to primary data, e.g. patient records, laboratory reports, appointment books, etc. Since this affects the patient's confidentiality, this fact is included on the Parent Information Sheet and Informed Consent Form.

13.4.1 Confidentiality

All individual participant information collected for the trial will be confidential, and will be handled, stored and destroyed in accordance with the Data Protection Act 1998. No names will be used in any publications or reports.

Case report forms containing clinical data will be labelled with patient initials, date of birth and a unique trial randomisation number. Medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

CSF and serum samples transferred for storage at the University of Liverpool (Institute of Infection and Global Health) will be identified by initials, trial randomisation number, date of birth and date/time.

Verification of appropriate informed consent will be enabled by the provision of copies of participants' signed informed consent/assent forms being supplied to the MC CTU by recruiting centres. This requires that name data will be transferred to the MC CTU, which is disclosed in the information sheet and consent form. Only the consent form will contain identifiable personal data of name, NHS number, postcode and date of birth. The assent forms will also contain name data.

Trial data collected on paper will be sent to the MC CTU and filed in locked filing cabinets. Paper copies of the consent/assent form will be kept separately to the clinical data. The MC CTU servers will be used to store electronic data related to the trial. These servers are located in an access controlled server room and are connected to the main university network, located behind a firewall. Physical access to these servers is limited to members of

the Universities computing services department; CTU IS staff have access to the server consoles. Trial data will be stored in a SQL server database with access limited to CTU staff with permission to access the trial data held on the MACRO (Infermed) system and CTU IS staff with database access privileges. CTU staff accounts on the MACRO system have different credentials to that required by the University computing systems (which must be accessed prior to logging into MACRO). Access to MACRO is limited to staff using the Universities network. The SQL Server database can only be accessed by computers with a University IP address.

In order to obtain resource use and death data from electronic routine administrative databases, the following personal identifying data will be collected: participant name, NHS number, postcode, date of birth, gender and trial randomisation number. This will be stored in a separate encrypted database with controlled access stored on the CTU server.

Members of the research team outside the MC CTU will have access to data generated by the trial, which is relevant to their role, but this will be anonymised.

The CTU will be undertaking activities requiring the transfer of identifiable data:
Verification that appropriate informed consent is obtained will be enabled by the provision of copies of participant's signed informed consent/assent forms being supplied to the CTU by recruiting centres, which requires that name data will be transferred to the CTU.

This transfer of identifiable data is disclosed in the PISC. The MC CTU will preserve the confidentiality of participants taking part in the trial and The University of Liverpool is registered as a Data Controller with the Information Commissioners Office.

13.4.2 Quality Assurance and Control

QA includes all the planned and systematic actions established to ensure the trial is performed and data generated, documented/recorded and reported in compliance with applicable regulatory requirements. QC includes the operational techniques and activities done within the QA system to verify that the requirements for quality of the trial-related activities are fulfilled. In accordance with the monitoring plan, centre visits will be conducted and source data verification performed if indicated to be required as a result of central monitoring processes. To this end:

- The Principal Investigator and Research Nurse from each centre will attend the trial launch meeting, coordinated by CTU in conjunction with the Chief investigator, which will incorporate elements of trial specific training necessary to fulfil the requirements of the protocol;

- The Trial Coordinator is to verify appropriate approvals are in place prior to initiation of a centre and the relevant personnel have attended trial specific training;

- The Trial Coordinator is to check safety reporting rates between centres;

- The Trial Coordinator is to monitor screening, recruitment and drop-out rates between centres;

- The Trial Coordinator is to conduct data entry consistency checks and follow-up data queries;

- Independent oversight of the trial will be provided by the Data and Safety Monitoring Committee and independent members of the Trial Steering Committee.

13.5 Records Retention

The investigator at each investigational site must make arrangements to store the essential trial documents, (as defined in Essential Documents for the Conduct of a Clinical Trial (ICH E6, Guideline for Good Clinical Practice)) including the Investigator Site File and Microbiology Site File, until the Clinical Trials Unit informs the investigator that the documents are no longer to be retained, or for a maximum period of 15 years (whichever is soonest).

In addition, the investigator is responsible for archiving of all relevant source documents so that the trial data can be compared against source data after completion of the trial (e.g. in case of inspection from authorities).

The investigator is required to ensure the continued storage of the documents, even if the investigator, for example, leaves the clinic/practice or retires before the end of required storage period. Delegation must be documented in writing.

The MC CTU undertakes to store originally completed CRFs for the same period, except for source documents pertaining to the individual investigational site, which are kept by the investigator only. The MC CTU will archive the documents in compliance with ICH GCP utilising the Records Management Service of the University of Liverpool. All electronic CRFs and trial data will be archived onto an appropriate media for long term accessible storage. Hard copies of data will be boxed and transferred to specially renovated, secure, premises where unique reference numbers are applied to enable confidentiality, tracking and retrieval.

14 INDEMNITY

BASICS is sponsored by Alder Hey Children's NHS Foundation Trust and co-ordinated by the CTRC in the University of Liverpool. As this is an investigator-initiated study, The Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation by the pharmaceutical industry do not apply.

Alder Hey Childrens NHS Foundation Trust shall provide an indemnity in respect of Clinical Negligence to the extent that such an indemnity is permitted by the NHS Litigation Authority's Clinical Negligence Scheme for Trusts.

Clinical negligence is defined as:
"A breach of duty of care by members of the health care professions employed by NHS bodies or by others consequent on decisions or judgments made by members of those professions acting in their professional capacity in the course of their employment, and which are admitted as negligent by the employer or are determined as such through the legal process" (NHS Indemnity: Arrangements for Clinical Negligence Claims in the NHS, October 1996).

15 FINANCIAL ARRANGEMENTS

This trial is funded by the Health Technology Assessment programme (HTA) of the Department of Health. Contractual agreements will be in place between sponsor and collaborating centres that will incorporate financial arrangements.

Trial participants will not be paid to participate in the trial. The schedule of the study will be in line with routine standard care, with the exception of the three monthly follow up phone calls / postal questionnaires.

As the study is funded by the NIHR HTA, it will automatically be adopted onto the NIHR portfolio, which will allow trusts to apply to their comprehensive local research network for service support costs if required.

15.1 Financial Support to Collaborating Centres

All VPS devices to be used for the trial will be purchased by each trial site using routine procurement procedures. No additional funding is allocated for supplies.

15.1.1 Staffing

0.5 FTE research nurses will be employed at selected participating trial sites to support the identification, recruitment and management of participants for the BASICS trial.

15.1.2 Cost per patient

For the remaining participating trial sites and all newly identified trial sites a cost per patient payment will be made to support the identification, recruitment and management of participants for the BASICS Trial

15.1.3 Other payments

Funding will be provided to sites on a per patient basis in order to facilitate the 3 monthly telephone calls and postal questionnaires. Funding to support archiving at end of trial will also be provided to each participating site.

16 TRIAL COMMITTEES

16.1 Trial Management Group (TMG)

A Trial Management Group (TMG) will be formed comprising the Chief Investigator, other lead investigators (clinical and non-clinical) and members of the MCRN Clinical Trials Unit.

The TMG will be responsible for the day-to-day running and management of the trial and will meet initially every two weeks during trial set up and subsequently every four weeks. Refer to the TMG terms of reference and trial oversight committee membership document for further details.

16.2 Trial Steering Committee (TSC)

The Trial Steering Committee will consist of an independent chairperson, an independent microbiologist, a lay representative from the SHINE Charity and an independent statistician...

The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chairman. The ultimate decision for the continuation of the trial lies with the TSC. Refer to the TSC terms of reference and trial oversight committee membership document for further details.

16.3 Independent Data and Safety Monitoring Committee (IDSMC)

The Independent Data and Safety Monitoring Committee (IDSMC) consists of an independent chairperson, plus 2 independent members: an expert in the field of microbiology and one who is an expert in medical statistics.

The IDSMC will be responsible for reviewing and assessing recruitment, interim monitoring of safety and effectiveness, trial conduct and external data. The IDSMC will first convene prior to trial initiation and will then define frequency of subsequent meetings (at least annually).

The IDSMC will provide a recommendation to the Trial Steering Committee concerning the continuation of the study. Refer to the IDSMC charter and trial oversight committee membership document for further details.

Details of the interim analysis and monitoring are provided in section 9.5.

17 PUBLICATION

The results from different centres will be analysed together and published as soon as possible. Individual Clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the Trial Management Group.

The Trial Management Group will form the basis of the Writing Committee and advise on the nature of publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected. All publications shall include a list of participants, and if there are named authors, these should include the trial's Chief Investigator(s), Statistician(s), Health economist(s) and Trial Manager(s) involved at least. If there are no named authors (i.e. group authorship) then a writing committee will be identified that would usually include these people, at least. The ISRCTN allocated to this trial should be attached to any publications resulting from this trial.

The members of the TSC and IDSMC should be listed with their affiliations in the acknowledgements / Appendix of the main publication.

18 PROTOCOL AMENDMENTS

18.1 Version 1.0 (22/10/12)

Original approved version, subject to receiving a complete response to the request for further information.

18.2 Version 2.0 (21/11/12)

Approved version with changes as requested for Version 1.0. Changes below:

- **Statistics**- Further clarification was given regarding the sample size calculation
- **Sites-** Clarified the number of sites as 15.
- **Protocol-** 'Allergy to antibiotics associated with the antibiotic shunt' added to the exclusion criteria.
- Copy of screening log was sent to the committee.
- **Information sheets**: ***For under 5 years*** the following sentence was added ''The scan shows you have too much fluid inside your brain and it is not draining away as it should. To make you feel better you need an operation to put a tube into your head to drain this fluid away'
- ***For ages 11 to 15:*** Patient Information was amended so that 'what is the purpose of the study' comes before 'why have I been chosen'.
- ***Consultee Sheet:*** Grammatical errors changed.
- The following sentence was reworded 'We don't know which shunt tubing is the most effective at reducing infection' to 'This study may help in finding out, which shunt tubing is the most effective at reducing infection'
- The following sentence was amended to make it clearer 'What will happen to my relative/friend if they join the study?' This was changed to 'The only thing that we will ask you to do (if your relative/ friend is still unable), is to fill in a short questionnaire every three months'
- **Consent and declaration form:** The following sentence has been added to the consent forms 'I understand that neither the blood or the CSF sample I have gifted will be used for genetic research'
- **Adult consent form:** Point 6 has been amended and now reads 'I agree for my data on NHS hospital admissions to be collected from electronic routine NHS health care records'
- Point five amended to ''I understand that my relative/friend is unable to give his/her own consent, based on the criteria set out in this form and the discussion with my relative/friend's health professional'
- Point 9 has been amended and now reads 'I agree for my data on NHS hospital admissions to be collected from electronic routine NHS health care records'
- A point relating to the relative's/friend's GP, has now been included as Point 11 and reads 'I understand that our relative/friends GP will be notified if requested.

- Minor typos and clarification throughout.

18.3 First substantial amendment Version 3.0 (22/03/13)

Section 1- Protocol Summary

- The number of sites has changed from 15 to 17
- The wording of primary objective has been changed throughout the protocol
- The wording of the Secondary Objective's has been changed and two new objectives have been added throughout the protocol
- Study flow chart amended to include CSF Samples for substudies

- Added the following 'NOTE: Where Bactiseal (Codman) is referenced throughout this protocol this also refers to any equivalent CE Marked Device which has identical specification'.
- A table has been added to allow the addition of future equivalent CE marked devices to be included.

Section 4- Trial Design

- Secondary endpoint added

Section 5- Study Population

- Study inclusion changed to now read 'Hydrocephalus of any aetiology (including IIH) requiring first VPS
- Points 2 & 3 removed
- 'Previous indwelling EVD allowed' now added
- 'Evidence of CSF infection at time of surgery for first VPS' added to exclusion criteria

Section 6- Enrolment and Randomisation

- 6.1 has now been changed to read Screening /Enrolment and a paragraph added from 6.2 (see protocol)
- 6.2 has been changed to 'Baseline'
- 6.2 The following paragraph has been added 'The Research Nurse should ensure that the log for patients lacking capacity is completed at every visit to record whether patient has regained capacity and re-consented.'

- Patient CRF's have been added to this section and sections 6.4. 6.5, 6.6, 6.7, 6.8, 6.9 and 6.10 created to explain what information is required on each CRF.

Section 7- Trial Interventions

- 7.2 clarification of labelling process
- 7.3 amended to reflect procedures for labelling
- 7.4.1 sentence added to explain labelling process for letter.
- 7.4.1.1 changed to 'Initial insertion of new randomised VPS'
- 7.4.1.2 changed to First Shunt Revision (includes first infection or mechanical revision)
- Removed 'an unblinding CRF should be completed at shunt revision for suspected mechanical failure'
- 7.4.1.3- 'Subsequent shunt surgery' paragraph added.

Section 8- Assessments and Procedures

- 8.1 Schedule for Follow- up amended.
- 8.4.1 note added to read ' A script will be provided for Researchers administering questionnaires via the telephone'
- 8.5 Substudies- site names removed and sentence to read 'Additional blood and CSF samples to be used for substudies will be taken from patients at trial sites that are able to contribute;

Section 9- Statistical Considerations

- 9.2 Method of Randomisation: The sentence 'Randomisation will be stratified by centre' has been removed.

Section 10- Safety Reporting

- Reporting procedures have been amended following MHRA guidance
- 10.4 amended expected adverse event list associated with VPS
- 10.4 added 'table 4' to include expected adverse events related to general anaesthetic

Section 11.3- Informed Consent

- '11.3.3 Re-consent of 16 year old' section added which reads: 'A participant involved in the study who reaches the age of 16 (and is therefore deemed competent to provide consent) should be re-consented at their next scheduled visit after their 16th birthday.

- Minor typos and clarification throughout.

18.4 Second substantial amendment Version 4.0 (25/07/13)

Section 4.2- Secondary Endpoint(s)

- Point d) has been changed to 'Time to VPS infection following first clean revision'

Section 4- Trial Design

- Secondary endpoint added

- Section 5- Study Population Section 5.1 Inclusion Criteria: note (b) has now been changed to read 'Indwelling ventricular access device (e.g. Ommaya or Rickham reservoir or –ventriculo-subgaleal shunt or similar) are allowed'
- 'Indwelling EVD allowed
- Section 5.2 Exclusion Criteria: Removed point 1: ' Evidence of CSF infection prior to surgery for first VPS'
- Added the note to exclusion point 3' previously infected cases allowed once clear of infection'

Section 6- Enrolment and Randomisation

- Section 6.3: Sentence changed to read' This is so that page 1 of the randomisation envelope containing information on the randomisation process and whether the VPS was inserted can be returned to the MC CTU in the pre-paid envelope'
- Note reading ' The randomised VPS or if this is not inserted, the first VPS within 12 hours from randomisation will be classed as the trial VPS and followed up accordingly' has now been removedSection 6.4: Health Economics Questionnaire removed from data list required at Early post op.
- The following sentence has been added ' At this point, the patient should also be given their first health service diary to complete over the next 3 months.
- Section 6.5: Sentenced changed to read ' We do not specify a timescale for this assessment to be completed'
- Section 6.7: The following paragraph has been added' During the first 12 weekly assessment the research nurse will complete the relevant quality of life questionnaires with the patient over the phone. Health service diaries are to be given/posted out to patients every 12 weeks. Patients will complete these and return to sites 12 weeks later. During the 12 weekly assessments the reasearch nurse should remind patients to return these diaries if they have not done so and prompt them to complete the new diaries that they should have received.'
- Section 6.9: CRF to be renamed 'Shunt revision/removal CRF'
- Clarification and changes made to the 'Shunt revision/removal CRF'
- Section 6.10: Health Economics removed from required data set at End of Study
- Section 6.10: The following sentence added ' At this point, the final health service diary should also be returned.

Section 7.4 – Allocation concealment and unblinding

- Section 7.4.13: has been renamed to 'Subsequent shunt surgery for clean shunt revisions'. This has been changed as we are only capturing information from removal after one clean revision.

Section 8.4.1- Quality of Life & Health Economics

- The following paragraph has been added- 'Once a child reaches the age of 16 they are normally classified as an adult, however Health Economic Questionnaires classifies adults as being age 18 and above. Participants who reach the age of 16 will continue to complete the EQ-5D-Y and the EQ-5D-3L-Proxy 1. The same applies for any participants who enter the trial between the ages of 16 – 18.'
-

Section 8.4.2- Special Assays or Procedures

- The following paragraph added 'Any positive isolates will be transferred to Great Ormond Street Hospital (as per Microbiology protocol) for future analysis. If the sample is clear of infection it will be disposed of'.

Section 8.5- Sub studies

- Volume of CSF and blood requested for substudies has been increased to a maximum of 4.5 mls of CSF and up to a maximum of 4.5 mls blood (less than a teaspoon) according to blood volume guidelines.
- This will be reflected on all PIS & C

Section 10.6- Quarantine, Labelling & Storage of Devices Involved in an Adverse Incident (i.e. Related Unexpected AE/SAE)

- The following wording has been added for clarification 'as per your local trust policy. Except for serious unexpected adverse incidents which should follow the MHRA guidelines below'. The flow chart on page 48 has been updated to reflect the clarification.

Patient Information Sheets

The following paragraph added: 'Any positive samples will be transferred to Great Ormond Street Hospital for future analysis. If the sample is clear of infection it will be disposed of'

- Minor typos and clarification throughout.

18.5 Third substantial amendment Version 5.0 (20/12/13)

Section 4- Trial Design

- Section 4.1 Primary Endpoint changed to read ' Time to failure of the first VPS due to infection '

Section 5- Study Population

- Section 5.2 Exclusion Criteria number 1 changed to 'Previous indwelling ventricular or lumbar peritoneal or atrial shunt. Added the note to exclusion point 3' previously infected cases allowed once clear of infection'
- Exclusion number 6 added as 'Allergy to silver'.

Section 6- Enrolment and Randomisation

- Section 6.3: Sentence changed to read 'Randomisation should be carried out in theatre by a designated staff member (as specified on the training log)'

Section 8.5- Sub studies

- The following paragraph added ' In view of the nature of out of hours shunt revisions, if the additional samples are not taken at this time then in cases where an EVD is inserted to treat the infection the additional CSF and blood samples can be taken at a later point'
- This will be reflected on all PIS & C with the following sentence added to part 3 of the PIS and also the consent form: ' If the shunt should need to be revised a second sample of CSF and blood may need to be taken at the time of, or after first shunt revision '

Section 10. Safety Reporting

- Table 3: Expected adverse events associated with VPS. 'Underdrainage' now added to table as well as 'valve change for symptomatic over/underdrainage.'
- Paragraph added to add clarification under heading 'Events listed in table 3 & 4.' The paragraph reads ' If the AE is admission with 'suspected infection' or 'mechanical shunt failure' as stated in table 3 and then graded as serious you are NOT required to complete an SAE form. This information is captured on other CRFs, so it is NOT a requirement to report to the MC CTU.'

Section 11.3 Informed Consent

- Section 11.3.4 Consent in adults who lack mental capacity: The following paragraph has been added re 'If the patient cannot attend participating site the responsible Research Nurse may make a judgement on discussion with the patient and the consultee whether capacity has been regained over the telephone, if capacity has been regained the Research Nurse should send out the adult consent via post'

- Minor typos and clarification throughout.

18.6 Fourth substantial amendment Version 6.0 (01/04/14)

• Change of PI at Royal Manchester Children's Hospital from Mr John Thorne to Mr Ian Kamaly

• Addition of Bristol Royal Hospital for Children as a site

Section 6.1 Screening/ Enrolment

•Sentence changed for clarity now reads 'All patients having a first VP shunt for hydrocephalus of any aetiology (including IIH) should be screened for eligibility and recorded on the screening log

Section 6.9 Shunt Revision/Removal

•The following paragraph has been added 'In instances were the shunt is removed for suspected infection concomitant medications but be reported up until 14 days after removal and the patient will be reviewed for 48 hours after removal for safety.'

Section 7.7 Concomitant Medications/Treatments

•The following paragraph added has been added 'Concomitant medications must be reported throughout the patients participation in the study. In instances where the shunt is removed for suspected infection concomitant medications but be reported up until 14 days after removal.'

Section 8.4.1 Quality of Life and Health Economics

•The following paragraph has been added for clarity:
` For consistency though throughout the patient's involvement with the trial, and so that we can best track the change in their health state over time using the same questionnaire (and therefore don't have to potentially allow for this in the final analysis), one option would be for the patient to complete the first questionnaire as appropriate for their age on the first occasion (as per the table in your email) and to then stick with this completing this same questionnaire throughout their involvement with the trial, even if they change age classes.'

The following section has now been added to the protocol:

Section 11.3.5 Nominated Consent

•As per the mental Health Act 2005 an Independent Healthcare Professional who has no involvement to the research taking place may consent for the patient until a relative/friend can re-consent on their behalf. Re-consent by a relative/friend should be obtained within five days of nominated consent.

PIS & C's

As separate Patient Information Sheets & Consent Forms have been added for Scottish sites only, the following sentence has been added for clarification:
'**For Scottish sites children deemed competent can consent for themselves, separate PIS&C's available for use in Scotland only.**'

Minor typos and clarification throughout.

18.7 Fifth substantial amendment Version 7.0 (13/10/14)

Protocol updated - References to MCRN have been changed throughout the protocol to read MC CTU

Section 8.4.2 Routine Data Collection

Following section added to protocol

- Subject to agreement with participating site Finance departments and in line with their usual financial data practices, data on trial patient hospital resource use will be collected annually from the PLICS datasets. These datasets include Health Resource Groups (HRG) which detail costs for patient stays and treatments. Responsibility for the data collection and anonymisation will rest with the site RN who will supply their site Finance departments with the necessary details to ensure only information on consented participating patients is provided. It is the responsibility of the site Finance departments to provide the site RNs with the data in a timely fashion and should the site RN so request, ensure all patient identifying data has been replaced with the patient BASICS trial number.

  A secure webpage will be set up for the two-way flow of information between the BASICS team and each site RN. It will be the responsibility of the site RN to keep safe their password and user name, ensure any data uploaded to this site is anonymised and ensure each line of resource use data is marked with the patient trial number. Anonymised PLICS Data will be stored on this secure web page until final analysis

Section 10.4 Reporting Procedures

- Table 3: Expected adverse events associated with VPS amended with the the following events added under the abdominal complication category:
  Abdominal Fistula
  Adominal Hernia
  Bowel perforation as a result of shunt surgery
  Adhesions
  Malabsortion
  Independent abdominal infections (such as appendicitis/cholecystitis/diverticulitis/other

- Intracranial haemorrhage related to shunt placement added to table 3.

- Table 4 and references removed from section 10.4

Section 11.3.5 Nominated Consent

- The following paragraph added has been added

'As per the mental Health Act 2005 an Independent Healthcare Professional who has no involvement to the research taking place may consent for the patient until a relative/friend can re-consent on their behalf within seven working days..

By signing the consent on behalf of the patient lacking capacity, the relative /friend is also agreeing to provide regular follow-up information for the 12 weekly follow calls and health economic questionnaires (part of the secondary outcome measures of the trial) in order for the relative/friend to complete the ongoing health questionnaires.

In exceptional cases where a family member or friend cannot re-consent on the patient's behalf, although the patient may continue in the study for the primary and some of the secondary outcomes (based on the original healthcare nominated professional consent) the Health Questionnaires and some of the health economic outputs would not need to be completed by the

person giving who gave the nominated consent. In such circumstances, the research nurse will endeavour to complete as much follow up data as is possible from routine and emergency visits.'

Section 11.3.6 Scottish Sites

- The following paragraph has been added for clarity: 'For Scottish sites children aged 11-15 deemed competent can consent for themselves, separate PIS&C's available for use in Scotland only.

Scottish Consent Forms will be scanned and emailed securely from site to lead Research Nurse within 24 hours using nhs.net.'

The following section has now been added to the protocol

Section 15.1.2 Cost per patient

- For the remaining participating trial sites and all newly identified trial sites a cost per patient payment will be made to support the identification, recruitment and management of participants for the BASICS Trial

Minor typos and clarification throughout

18.7 Sixth substantial amendment Version 7.0 (13/10/14)

- Early closure of site

18.9 Seventh substantial amendment Version 8.0 (10/08/15)

The following changes have been made:

- Protocol Approval: Lead Statistician Signatory added
- Protocol Summary Section, Study Duration: Maximum Follow up changed from 2.5 years to 2 years

18.10 Eight substantial amendment Version 9.0 (10/08/16)

- Change of study end date to 31st August 2018

- **Section 1 Protocol Summary:**
- **Population** : Trial population changed to up to 1650 patients
- **Study Centres and Distribution**: amended to 19 neurosurgical wards across the United Kingdom & Ireland
- **Study Duration-** amended the duration to 'utilising a recruitment period of 4 years, 2 months

- **Section 6.1 Screening/Enrolment**
- Paragraph moved to section 6.1 from 6.2: 'Once written consent has been [……]patient has regained capacity and reconsented.

- **Section 6.2 Baseline**
- Paragraph added: The research nurse will confirm to the operating team that written informed consent has been provided and that the patient has been confirmed as being fully eligible for trial participation by PI/CO-CI (Confirmation of eligibility should only be carried out by physicians) the Baseline Preoperative Assessment CRF should then be completed

- **Section 6.3 Randomisation**
- First paragraph amended to read Once the Research Nurse has confirmed that written consent has been provided and that patient has been deemed fully eligible for the trial by

the PI/ Co-PI, the designated staff member will randomise the patient in surgery and select the appropriate type of VPS to be inserted.

- ` Date of Eligibility confirmed (must be before randomisation date)' added to the data recorded list.

- **Section 6.9 Shunt Revision/Removal**
- Paragraph deleted 'This CRF should only be [.....] shunt Revision/Removal CRF pathway
- Shunt Revision/ Removal Pathway flowchart added

- **Section 6.9 End of Study Phone Call**
- Clarity given for end of study phone call: `RN's should endeavour to contact the participant a maximum of three times, at different times of the day and different days of the week. If patient is uncontactable this should be documented on the CRF and returned the CTU.'

- **Section 7.5.2 Randomisation Envelopes**
- Wording amended for clarity:

c. Upon receipt of the randomisation envelopes for the trial, the research nurse will be requested to check they are intact and that they are in sequence and send confirmation of this back to the MC CTU.

d. Any discrepancies will be immediately reported to the MC CTU

- **Section 10.4 Reporting Procedures**
- Events listed in table 3: The following paragraph changed to 'If the AE is a hospital admission with any expected events as stated in table 3 and then graded as **serious** you are **NOT** required to complete an SAE form. This information is captured on other CRFs, so **it is** a requirement to report to the MC CTU but the report will not be expedited.
- Safety flowchart updated

19. REFERENCES

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19 DOCUMENTS SUPPLEMENTARY TO THE PROTOCOL

- Patient information sheets and consent / assent forms
- Patient representative consultee form
- GP Letter
- Patient Contact Card
- Health Economics questionnaires (EQ-5D-3L, EQ-5D-Y and Hydrocephalus Outcome Questionnaire)
- Participating sites list
- Microbiology laboratory protocol
- Oversight committee membership
- Site inclusion criteria