The BASICS trial

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

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Statistical Analysis Plan
V4.0 08/11/2018

	ORIGINATED BY	QC PERFORMED BY	APPROVED BY
Name	Beth Conroy	Ashley Best	Carrol Gamble
Title	Trial Statistician	QC Statistician	Lead Statistician
Date	8th November 2018		
Protocol Version and Date	Version 12.0 (13/06/2018) Superceded versions: V11.0 (05/04/2018); V10.0 (11/08/2017); V9.0 (10/08/2016) V8.0 (10/08/2015); V7.0 (13/10/2014); V6.0 (01/04/2014); V5.0 (20/12/2013); V4.0 (25/07/2013); V3.0 (22/03/2013); V2.0 (21/11/2012); and V1.0 (22/10/2012).		

1. Change Control

Protocol version	Updated SAP version no.	Section number changed	Description of change	Date changed
12.0	2.0	17.4.2.4	Presentation of sensitivities of organisms added.	09/08/18
12.0	2.0	17.4.2.4.2	Removal of wording 'This will be further split by type of VPS infection (Definite – Culture positive, Probable – Culture uncertain, Probable – Culture negative and Possible – Culture uncertain).' as outcome only applicable for definite infections. Now consistent with 17.4.2.4.1	09/08/18
12.0	2.0	Throughout	Typos and formatting corrected	09/08/18
12.0	3.0	2	C Gamble replaces M Brown as sign off.	04/09/18
12.0	3.0	3	C Gamble added.	04/09/18
12.0	3.0	17.2.	Summary statstics changed to medians and IQR only (means and sd removed) due to skew of continuous data items (identified in blind review).	04/09/18
12.0	3.0	17.4.1.1	Change of source for VPS deep incisional infection. Wording changed from '(indicated on early post op, first routine post op, subsequent routine post op and unscheduled visit follow up CRFs)' to 'identified using the CRF data and confirmed by the committee.' Source changed in Figure 1 from 'CRFs' to 'Primary outcome tool'.	04/09/18
12.0	3.0	17.4.1.2.	Adults stratification factor corrected to consider adults over 65 and under 65 seperately.	04/09/18
12.0	3.0	17.4.2.4.	Outcome extended to include infection type 1B. Antibiotics added to line listings to aid interpretation of sensitivities. Summary of sensitivies through counts therefore removed due to complexity of data requiring presentation.	04/09/18
12.0	3.0	17.4.2.5.1	Source changed in Figure 5 from 'CRFs' to 'Primary outcome tool'.	04/09/18
12.0	3.0	19.	Exploratory analysis comparing committee assessment against operating surgeon assessment of infection for first revisions added.	04/09/18
12.0	4.0	17.4.2.6	EQ-5D questionnaire removed from Quality of Life outcome assessment at time of reporting. These questionnaires will be used to assess Health Economics outcomes only.	08/11/18

2. Approval and agreement

At a minimum two versions of the SAP should be approved and stored within the statistics trial file.

1. SAP version 1.0 should be created after it has been reviewed and signed-off to ensure all are in agreement with the planned analysis and no further changes are foreseen.

2. The final SAP version should be converted to PDF and signed following the blinded review for protocol deviations and immediately prior to database lock as evidence of the analysis planned prior to unblinding of the study.

SAP Version Number being approved: 4.0

Trial Statistician

Name Beth Conroy

Signed _____ Date 8/11/2018

Lead Statistician

Name Carrol Gamble

Signed _____ Date 08/11/2018

Chief Investigator/clinical lead

Name Conor Mallucci

Signed _____ Date 8/11/2018

OR Electronic approval attached ☐

3. Roles and responsibilities

B Conroy (Department of Biostatistics, University of Liverpool): Trial Statistician, L Sutton (Department of Biostatistics, University of Liverpool): QoL Statistician, M Brown (Department of Biostatistics, University of Liverpool): Senior Statistician (V1.0-V2.0 of SAP), C Gamble (Department of Biostatistics, University of Liverpool): CTU Director (V3.0 of SAP), C Mallucci (Alder Hey Children's NHS Foundation Trust): Chief Investigator.

Author's contributions

B Conroy, L Sutton and M Brown proposed the statistical analysis plan. B Conroy and L Sutton prepared the analysis plan. M Brown and C Mallucci read, amended and approved the statistical analysis plan (V1.0 and V2.0). C Gamble and C Mallucci read, amended and approved the statistical analysis plan (V3.0 and V4.0).

4. List of abreviations and definitions of terms

AE	Adverse Event
CONSORT	Consolidated Standards Of Reporting Trials
CRF	Case Report Form
CTRC	Clinical Trials Research Centre
HEAP	Health Economics Analysis Plan
HOQ	Hydrocephalus Outcome Questionnaire
IDSMC	Independent Data and Safety Monitoring Committee
IQR	Inter-quartile Range
ITT	Intention to Treat
QoL	Quality of Life
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOP	Standard Operating Procedure
TSC	Trial Steering Committee
VPS	Ventriculoperitoneal Shunt

Contents

5. Statement of Compliance

This Statistical Analysis Plan (SAP) provides a detailed and comprehensive description of the pre-planned **final** analyses for the study "The BASICS Trial: The British Antibiotic and Silver Impregnated Catheters for ventriculoperitoneal Shunts multi-centre randomised controlled trial". The planned statistical analyses described within this document are compliant with those specified in brief within the BASICS protocol version 12.0 dated 13th June 2018.

This study is 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, Clinical Trials Research Centre (CTRC) Clinical Trials Unit (CTU) Standard Operating Procedures (SOPs) and EU Directive 2001/20/EC, transposed into UK law as the UK Statutory Instrument 2004 No 1031: Medicines for Human Use (Clinical Trials) Regulations 2004.

These planned analyses will be performed by the trial statistician.

The results of the final analysis described within this statistical analysis plan will be contained within a statistical analysis report. This report will be used as the basis of the primary research publications according to the study publication plan.

All analyses are performed with standard statistical software (SAS version 9.3 or later). The finalised analysis datasets, programs and outputs will be archived following Good Clinical Practice guidelines and standard operating procedure (SOP) TM021 Archiving procedure in CTRC.

6. Background and Rationale

The rationale for the trial is outlined in the protocol. To be brief, shunt failure due to infection has plagued the neurosurgical advance ever since it was developed. The incidence of shunt infection varies markedly in the literature from 3-27% and is higher in certain groups, e.g. neonates, children under 1 year old, and 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.

7. The BASICS Trial Study Objectives

The primary objective of this trial is to determine whether antibiotic or silver impregnated VPS reduce infection compared to standard VPS in hydrocephalus following insertion of de novo VPS.

The null hypothesis is that there is no difference in time to infection following insertion of de novo VPS between the standard VPS arm and the antibiotic or silver impregnated VPS arms. The alternative hypothesis is that there is a difference between the three groups.

Secondary objectives are:

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

8. Investigational Plan and Study Design

8.1. Overall study design and plan- description

The BASICS trial is a national three-arm, double blind, multi-centre randomised controlled trial. Treatment allocation is a 1:1:1 ratio. Patients with Hydropcephalus of any aetiology (including IIH) requiring first VPS are randomised to receive Bactiseal (antibiotic-impregnated); Silverline (silver-impregnated) or standard (non-impregnated) VPS in patients undergoing insertion of their first permanent shunt.

8.2. Treatments studied

The three treatments used in the BASICS trial are:

- A standard non impregnated ventriculoperitoneal shunt (VPS);
- A Silverline* (Silver impregnated) VPS;
- A Bactiseal* (antibiotic impregnated) VPS.

* All VPS used for the trial are CE marked medical devices being used for their intended purposes. Only devices listed in Section 1.1 of the protocol are permitted for use within the BASICS trial.

8.3. Treatment compliance

All treatments are delivered as a single intervention once the patient has been randomised to BASICS. The trial intervention is described in further details in Section 7 of the BASICS Protocol. Briefly, the allocated trial VPS will be inserted by the operating surgeon. Data on treatment compliance will be collected on the “Eligibility and Randomisation CRF”. As the trial is blinded, the “Randomisation Envelope” will collect data on the type of VPS inserted.

8.4. Patient population studied

The trial population is up to 1606 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.

8.5. Inclusion criteria

The inclusion criteria can be found in section 5 of the protocol.

8.6. Exclusion criteria

The exclusion criteria can be found in section 5 in the protocol.

8.7. Removal of patients from therapy or assessment

Due to the nature of the outcomes, patients who do not have a VPS inserted will not be followed up for primary or secondary endpoints.

All participants who withdraw, through completion of the Participant Data Withdrawal CRF or Withdrawal from Study CRF, from any aspect of the BASICS trial will be assessed as follows:

CRF	Item	Action	Data analysed
Participant Data Withdrawal (PRTWDCRF)	Participant/parent/legal representative provided reason as to why they longer wish the data collected to date to be used in the final analysis (PWDRFWC=”Yes”)	Removed from all assessments.	Only randomisation number, date and information collected on Participant Data Withdrawal will be analysed.
Withdrawal from Study CRF (BWDCRF)	Level of withdrawal (BWDLWDC=” Withdrawal from completing additional study materials (phone calls, diaries, etc) but happy for data routinely collected at future visits to still be used”)	Patient removed from assessments that stem from non-routine data (phone calls, diaries, etc) from the date of withdrawal.	Data collected up to the point of withdrawal, and routine data collected from the point of withdrawal, will be analysed.
	Level of withdrawal (BWDLWDC=” Withdrawal from all further data collection”	Patient removed from all assessments from the date of withdrawal.	Data collected up to the point of withdrawal, and no data collected from the point of withdrawal, will be analysed.
	Level of withdrawal (BWDLWDC=” Withdrawal of consent for additional substudy samples to be taken”	Patient not removed from assessment.	All data collected as part of the main trial will be analysed.

8.8. Consent process

The consent process is described in section 11 of the protocol.

8.9. Blinding

Blinding will be maintained for all trial personnel as far as possible. Due to the nature of the intervention i.e. shunts are different colours it is not possible to blind all staff members present in theatre.

Additionally, the primary outcome is assessed blind as far as pragmatically possible. Specifically, the primary outcome, shunt infection, occurs when the patient experiences at least one of the following:

1. *VPS CSF or peritoneal infection*: classified by an assessor blind committee

and/or

2. *VPS deep incisional infection*: classified by an assessor blind clinician (unless the clinician making this assessment with in theatre at the time of the initial insertion).

Allocation concealment and unblinding is described in Section 7.4 of the BASICS protocol.

8.10. Method of assignment to treatment

Full details of the randomisation procedure can be found in Sections 6.3 and 9.1 of the protocol. The randomisation lists were generated by a statistician (who is not involved with the BASICS trial) at the CTRC. Participants are randomised to each of the three arms in a ratio 1:1:1. Randomisation is stratified by centre, envelope storage space (for sites with more than one storage unit e.g. two theatres) and age (adults vs. paediatric patients. Sequentially numbered randomisation envelopes are prepared for each storage area. Details of block sizes can be found in the Statistical Trial File under section 4.

8.11. Sequence and duration of all study periods

A schematic of the study design can be found in Section 1 and a table of trial assessments can be found in Seciton 8.1 of the study protocol.

8.12. Schedule of assessments

A full schedule of trial assessments and timeline of data collection can be found in section 8.1 of the protocol.

9. Listing of Outcomes

9.1. Primary outcome(s)

The primary outcome is time to failure of the first VPS due to infection. Infection will be classified as in Section 8.2 of the BASICS Protocol. Where there is insufficient information to classify in this way, the information captured on whether the VPS was removed for suspected infection or revised for mechanical failaure will be used to make this classification.

9.2. Secondary outcomes

The secondary outcomes are:

1. Time to removal of the first VPS due to suspected infection
2. Time to shunt failure of any cause
3. Reason for shunt failure (infection, mechanical, patient, other)
4. Types of bacterial VPS infection (organism, antibiotic resistance)
5. Time to VPS infection following first clean revision
6. Quality of Life
7. Incremental cost per VPS failure
8. Incremental cost per QALY gained

10. Determination of Sample Size

The sample size calculation can be found in Section 9.4 of the protocol.

11. Study Framework

The overall objectives for each of the study outcomes (primary and secondary) is to test the superiority of antibiotic and silver impregnated VPS to standard VPS.

12. Confidence Intervals, p-values and Multiplicity

All applicable statistical tests will be two-sided and will be performed using 2.5% significance level; confidence intervals presented will be 97.5% to allow for multiple testing of the three arms. No adjustment will be made for multiplicity for the secondary outcomes.

13. Timing and Objectives of Interim and Final Analyses

13.1. Interim monitoring and analyses

Details on interim analyses are compatible with those found in the protocol in Section 9.4. The Independent Data and Safety Monitoring Committee (IDSMC) should meet at least annually as stated within Section 4.1 of the Independent Data and Safety Montoring Committee Charter.

A formal interim analysis of the primary outcome half way through the trial after approximately 50% of the total events had been observed was planned using Peto-Haybittle rules. However, due to the low number of events experienced in the BASICS trial, this analysis was postponed and, following a recalculation of the sample size in light of the accruing event rate, a single final analyses was considered more suitable. This was agreed by both independent committees: the TSC and the IDSMC.

13.2. Final analysis

All outcomes will be analysed after the end of the trial, which is defined in Section 8.7 of the protocol as “the date of database lock”. This is the date on which data modification privaleges are withdrawn from the trial database.

14. Disposition of Participants

14.1. Screening, eligibility and recruitment

A CONSORT flow diagram [4] will be used to summarise the number of patients who were:

- assessed for eligibility
- not randomised, where all patients not randomised will be accounted for within the following mutually exclusive sub groups*
    - not eligible*
    - consent not sought*
    - consent not provided*
    - consent provided though not randomised*
- randomised
- shunt not inserted
- received the randomised allocation
- did not receive the randomised allocation
- withdrawn from trial*

Reasons for non randomisation will be summarised in a table with the following categories for reasons, within the subgroup as listed:

- Not eligible (NE):
    - No hydrocephalus
    - Previous/indwelling ventricular or lumbar peritoneal or atrial shunt
    - Active and ongoing CSF or peritoneal infection
    - Multi-loculated hydrocephalus requiring multiple VPS or neuroendoscopy
    - Ventriculo-atrial or ventriculo-pleural shunt planned
    - Allergic to antibiotics associated with antibiotic impregnated shunt
    - Previously participated in the BASICS trial
    - Allergic to silver
    - Other (classified free text)
- Consent not sought (CNS):
    - Missed by research nurse/doctor
    - Not approached because of patient's lack of understanding
    - Not approached because of consultant preference (provide further details details provided will be classified)
    - Not approached because of other reason (further details provided will be classified)
    - Other (classified free text)

- Consent not provided (CNP):
    - Doesn't want to take part in research
    - Doesn't want to be randomly assigned to treatment
    - Doesn't want to have a standard shunt
    - Doesn't want to have antibiotic impregnated shunt
    - Doesn't want to have silver impregnated shunt
    - Already enrolled in another trial
    - No reason provided
    - Other (classified free text)
- Consent provided but not randomised (CPNR):
    - Trial shunt not available
    - Trial trained staff not available
    - Unable to locate randomisation envelope
    - Other (classified free text)

Frequencies of each reason provided will be presented along with percentages using the number of patients within that category (total number of patients NE, CNS, CNP or CPNR respectively) as the denominator.

The following centre specific randomisation details will be reported. This data will also be summarised for all patients across all centres:

- Date site opened
- Date site closed
- Planned total recruitment
- Date of first randomisation
- Date of last randomisation
- Total number randomised.

The following centre specific screening details will be reported. This data will also be summarised for all patients across all centres. Frequencies and percentages will be reported:

- Number of patients screened (s)
- Number of patients deemed ineligible (s_i, denominator s)
- Number of eligible patients where consent not sought (s_{ii}, denominator s)
- Number of eligible patients where consent sought but not provided (s_{iii}, denominator s)
- Number of patients who consented but were not randomised (s_{iv}, denominator s)
- Number of patients who were randomised (s_v, denominator s)
- Consent rate (reported as percentage, calculated $\frac{s_{iv}+s_v}{s_{iii}+s_{iv}+s_v}$)

14.2. Post randomisation discontinuations

Reasons for patients not receiving the randomised allocation will be summarised in a table with categories dependent on the free text provided on the CRF. Frequencies will be presented along with percentages using the number of patients who were randomised as the denominator.

Withdrawals from the trial will be presented as line listings detailing:

- Randomisation number
- Who made the decision to withdraw participant from trial:
  - Clinician
  - Participant/Parent/Guardian
  - Clinician and participant
- Reason for withdrawal
  - Unexpected related adverse event of SAE
  - Burden of additional study data collection
  - Other
- Level of withdrawal
  - Withdrawal from completing additional study materials (phone calls, diaries, etc) but happy for data routinely collected at future visits to still be used
  - Withdrawal from all further data collection
  - Withdrawal of consent for additional substudy samples to be taken

15. Protocol Deviations

Protocol deviations that will be reported are defined in the monitoring plan for the trial. Protocol deviations are classified prior to unblinding of treatment to the statistical team. All protocol deviations will be defined and signed off using ST001TEM03 Protocol deviations and population exclusions template prior to unblinding. The number (and percentage) of patients with each separate protocol deviation will be presented in this analysis report along with the number (and percentage) of patients with (i) at least one major protocol deviation; (ii) at least one minor protocol deviation; and (iii) at least one protocol deviation of any classification (minor or major). No formal statistical testing will be undertaken.

Envelopes used out of sequence is defined as a protocol deviation in the monitoring plan of the trial. However, as the BASICS trial uses envelope to randomisation, additional checks on the randomisation process will be presented in the analysis report. A list of randomisation checks performed are:

- Used envelopes

    - Envelope used but not returned to CTU
    - Envelope used out of sequence
    - Envelope used in error
    - Envelope strata error
- Envelopes not used
    - Envelope lost and not found
    - Envelope opened in error
    - Envelope missed in error

These checks will be reported as counts (number of envelopes and number of sites).

Finally, a check that the randomisation was balanced will be performed by summarising the number of envelopes within each stratification factor, split by treatment. This check will be summarised as counts, with percentages within treatment group presented, where percentages are calculated using the denominator of the number of envelopes within that strata.

16. Unblinding

The number of patients who were unblinded will be reported for each treatment group. Based on the reasons provided, instances of unblinding will be categorised by intentional or accidental. These categories will be agreed by the CI prior to reporting. The number (and percentage, using the denominator number of patients recruited within group) of patients and sites with accidental or intentional unblinding will be presented together with line listings of the reasons provided.

17. Efficacy Evaluations

17.1. Data Sets Analysed

The efficacy analysis will use the intention to treat principle as far as practically possible. These analyses will be conducted on all randomised participants for whom consent was obtained and whom received a VPS shunt, within the group to which they were allocated. No imputations will be made. A per protocol analysis is not anticipated. The membership of the analysis set for each outcome will be determined and documented and reasons for participant exclusion will be given prior to the blind being broken and the randomisation lists being requested. Reasons for exclusion may include missing data or withdrawals (see Section 8.7).

The numbers within the intention to treat data set will be presented as count data and as a percentage using the total randomised as a denominator. This will be presented both overall and split by treatment group.

17.2. Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics are reported on the “Baseline Preoperative Assessment CRF. The following characteristics will be reported.

Patient details and physical examination data will be presented descriptively with respect to:

- Age (overall in years and split by categories of: <16 years = paediatric, 16<=x<65 years = adult, >65 years = elderly)
- Gender (male, female)
- Weight (kg)
- Heart rate (BPM)
- Neurological assessment (GCS) (both overall score and split by type: eyes, verbal and motor)

Patient risk of infection assessment data will be presented descriptively with respect to:

- Previous staphylococcus aureus infection (requiring treatment in the last six months) (yes, no)
- Active skin/wound infection (yes, no)
- MRSA infection in the last six months (yes, no)
- Pre-term at birth (yes, no)
- Abdominal surgery in the last month (yes, no)
- Tracheotomy (yes, no)
- Percutaneous endscopitc gastromy (yes, no)
- Previous CSF leak within the last month (yes, no)
- Previous EVD in last three months (yes, no)

These will be presented both overall and for each randomised group.

Categorical data will be summarised by numbers and percentages. Continuous data will be summarised by medians and inter-quartile ranges (IQR) if data are skewed. Minimum and maximum values will also be presented for continuous data. Tests of statistical significance will not be undertaken for baseline characteristics; rather the clinical importance of any imbalance will be noted.

17.3. Complance with treatment

For details on treatment adherence, see Section 8.3.

Treatment adherence will be summarised descriptively as frequency tables presenting the number of patients receiving the VPS as allocated, receiving an alternative VPS and receiving no VPS. Frequency tables will be presented overall and split by treatment and centre. expressed as a frequency and a percentage with the denominator being those who were randomised.

Reasons for non-adherence will be presented descriptively as frequency tables overall and split by treatment expressed as a frequency and a percentage with the denominator being those who were randomised and consented.

17.4. Analysis of outcomes

17.4.1. Primary Outcome

The primary outcome is the time to failure of the first VPS due to infection. Infection will be classified as in Section 8.2 of the BASICS Protocol. Where there is insufficient information to classify in this way, the information captured on whether the VPS was removed for suspected infection or revised for mechanical failure will be used to make the classification.

A sensitivity analysis will be undertaken where infection is defined only by the classification in Section 8.2, where patients who are unable to be classified will be assumed to not have had an infection.

17.4.1.1. Derivation

Figure 1 gives an overview of how the primary outcome for the main analysis is categorised as a revision for infection.

Time to failure of any cause will be calculated in months, therefore dates will be used to enter into the model.

Date of randomisation will be taken as the origin when calculating the primary endpoint. This will be taken from the Eligibility CRF and, if this is missing, the Randomisation Envelope.

Date of failure of first VPS due to infection will be taken as the date of knife to skin as reported on the **first** Shunt Revision/Removal CRF for the patient ([B] in Figure 1). If this data is missing,

the date anaesthetic was started will be used as an equivalent date. If the Shunt Revision/Removal CRF is not returned but a revision indicated on the Shunt Surgery Log, then the date on the log will be taken as the date of revision.

Infections are classified as defined in Section 8.2 of the BASICS Protocol. Briefly, shunt infections are classified as *I1: VPS CSF or peritoneal infection* and/or *I2:VPS deep incisional infection*.

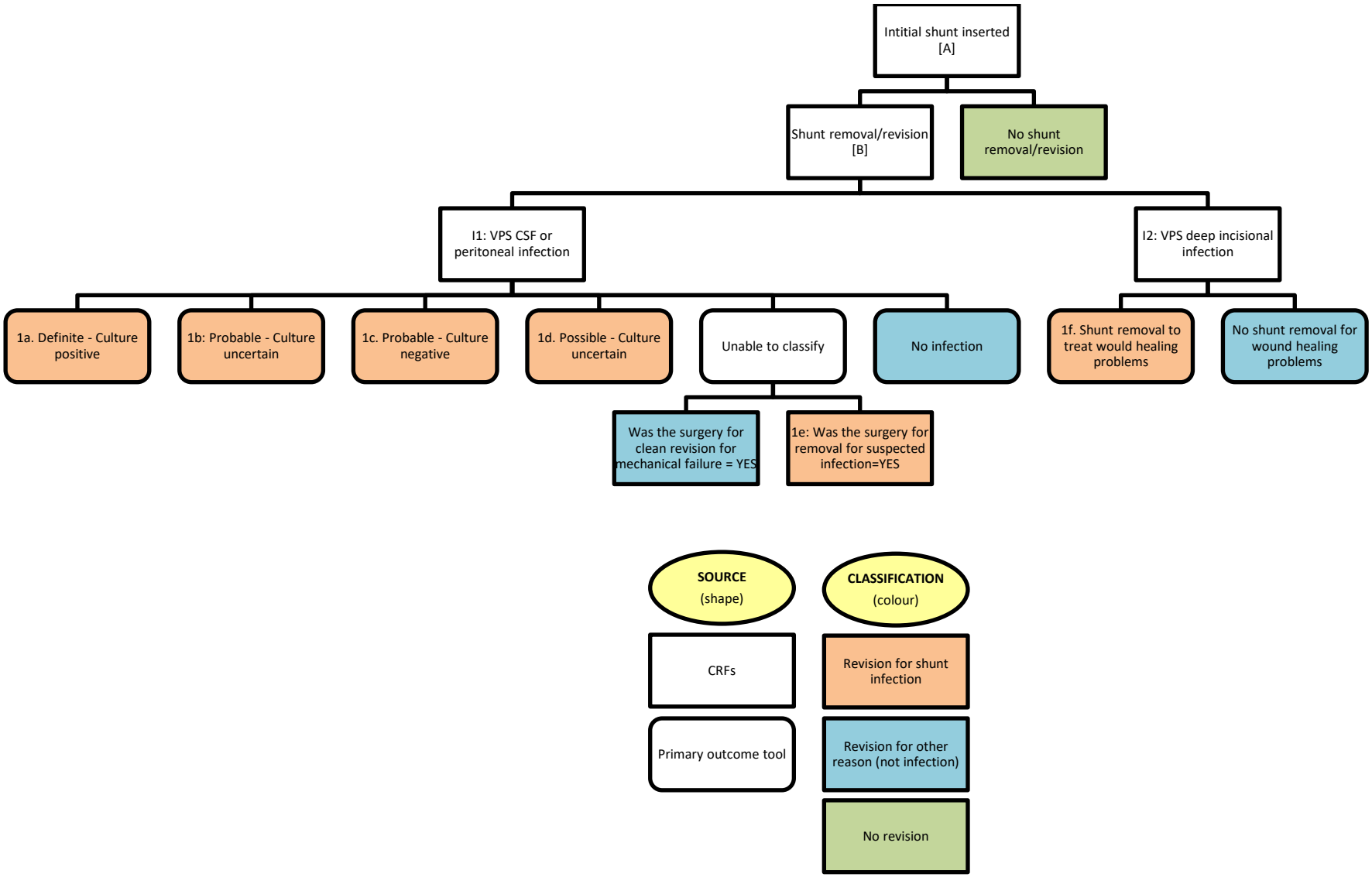
I1: VPS CSF or peritoneal infection will be classified by a committee within the BASICS Primary Outcome Tool. This committee will subclassify each VPS CSF or peritoneal infection as:

- 1a. Definite – Culture positive
- 1b. Probable – Culture uncertain
- 1c. Probable – Culture negative
- 1d. Possible – Culture uncertain
- 1e. Unable to classify
- No infection

In which, 1a to 1d will be considered a removal for shunt infection in the analysis. Infections that the committee categorise as “1e: Unable to classify” will be categorised as infection, or not, using the Shunt Revision/Removal CRF variable “Was the surgery for removal for suspected infection?” when checked. See Figure 1.

I2: VPS deel incisional infection will be detected when patients have shunt removal as a result of wound healing problems identified using the CRF data and confirmed by the committee.

FIGURE 1: DEFINING PRIMARY OUTCOME



17.4.1.2. Analysis

The following will be reported overall and split by treatment. Summaries will be reported as count data and percentages, defined as follows:

- *Summary of surgeries:*
    - Number randomised (i);
    - Number of patients with de novo shunt inserted (ii, denominator i);
    - Number of patients with de novo shunt removed/revised (iii, denominator ii);
    - Number of patients with de novo shunt not removed/ revised (iv, denominator ii).
    - Number of patients with infection (v, denominator i)
    - Number of patients with revision/removal for reasons other than infection (vi, denominator i)
- *Summary of infections*
    - Number of patients with infection (v)
    - VPS CSF or peritoneal infection
        - Number of patients, as assessed by the committee, with definite – culture positive, probable – culture uncertain, probable – culture negative, possible – culture uncertain, no infection, and unable to classify (denominator v);
    - VPS deep incisional infection
        - Number of patients with VPS deep incisional infection (denominator v);
        - Number of patients with noVPS deep incisional infection (denominator v).

Formal analysis of this time to event outcome will be conducted using a competing risks analysis. Revison for reason other than infection constitutes a competing event, if occurring before the revision for infection. The event of interest is time from de novo shunt insertion to revision for infection on treatment (Standard, Antibiotic impregnated and Silver impregnated). In addition, age group (stratification factor, paediatric vs. adult (<=65 years) vs. adults (>65 years)) will be included when modelling the cumulative incidence of revision for infection as age group is considered a clinically important prognostic factor [5].

The analysis conducted will follow available recommendations for analysing competing risk [6]. Patients who do not experience an event of interest, or competing risk event, will be censored at verying lengths of follow up, between six and 24 months depending on date of randomisation. The cause specific hazard (CSH) model will be analysed by a Cox model and will estimate the effect of treatment, adjusting for age group, on the rate at which events occur

in patients who are currently event free. Subdistribution hazard ratios (SH) obtained from the Fine-Gray model [7] will describe the relative effect of covariates on the subdistribution hazard function. Covariates will be considered via a univariate and a multivariate model. Estimated cause specific hazard and subdistribution hazard ratios for both univariate and multivariate models will be reported, with associated confidence intervals and p-values. Plots for all cumulative incidences for categorical variables, VPS type and age group, will be presented. Summary statistics of groups within the model will also be presented for completeness, giving count data for each variable within each fitted model.

17.4.1.3. Goodness of fit

To check for the appropriateness of the fitted model. In terms of the underlying statistical assumptions, the proportional hazards (PH) assumption of the CSH will be checked using Schoenfeld residuals. Checking PH of the Fine-Gray model will be investigated using Schoenfeld residuals tailored for the SHs. In the circumstance that these checks raise concern over the appropriateness of the fitted model, time varying coefficients will be fitted to the model to allow for conclusions to be made in the presence of non proportional hazards [7].

17.4.1.4. Sensivity analysis

A sensitivity analysis will be undertaken where infection is defined only by the classification in Section 8.2, where patients who are unable to be classified will be assumed to not have had an infection.

The formal analysis described in Section 17.4.1.2 will be conducted on the outcome time to first VPS revision/removal as defined in the protocol to check the robustness of the model to the assumption that for revisions deemed “Unable to classify” by the committee, the clinical definition is used. For this, all infections deemed “Unable to classify” by the committee will be treated as “No infection”.

17.4.1.5. Heterogeneity within site

As randomisation is also stratified by site, and this is not independent of age group added to the formal analysis model (described above), heterogeneity in treatment between sites will be explored graphically and by summary statistics. Infection rates (v/ii), revison rates (iii /ii) and confidence intervals for these will be reported, split by VPS, on a per site level. [1]

17.4.2. Secondary Outcomes

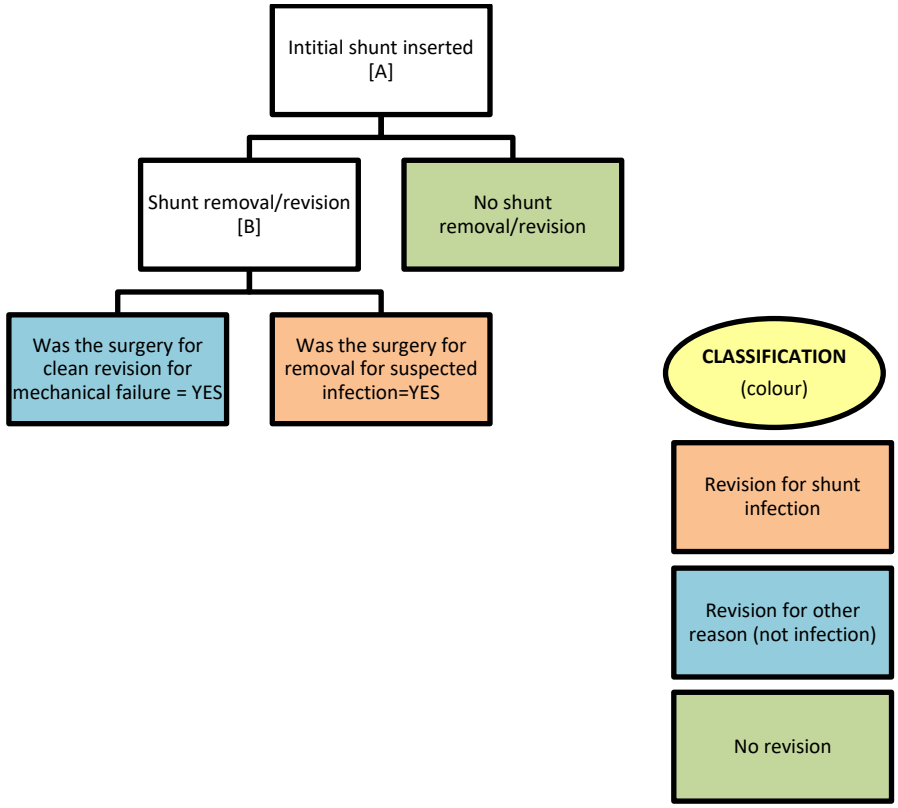
17.4.2.1. Time to removal of first VPS due to suspected infection (classified by operating surgeon)

17.4.2.1.1. Derivation

Figure 2 gives an overview of how the secondary outcome is categorised as a revision for infection (as assessed by the clinical team at site and reported on the patient CRFs). Time to event will be calculated in the same way as the primary outcome (see Section 17.4.1.1).

In this outcome, an infection is defined as clinically reported. Therefore the First Revision/Removal form will be the only data source for an event.

FIGURE 2: DEFINING TIME TO REMOVAL OF FIRST VPS DUE TO SUSPECTED INFECTION (OPERATING SURGEON REPORTED)



17.4.2.1.2. Analysis

As in Section 1.1.1.1, the following will be reported overall and split by treatment. Summaries will be reported as count data and percentages, defined as follows:

- *Summary of surgeries:*
    - Number randomised (i);
    - Number of patients with de novo shunt inserted (ii, denominator i);
    - Number of patients with de novo shunt removed/revised (iii, denominator ii);
    - Number of patients with de novo shunt not removed/ revised (iv, denominator ii).
- *Summary of revisions*
    - Number of patients with infection (v, denominator ii)
    - Number of patients with revision for other reason (vi, denominator ii)

This outcome will be analysed as specified in Section 1.1.1.1, treating an event of interest as v and the competing risk as vi.

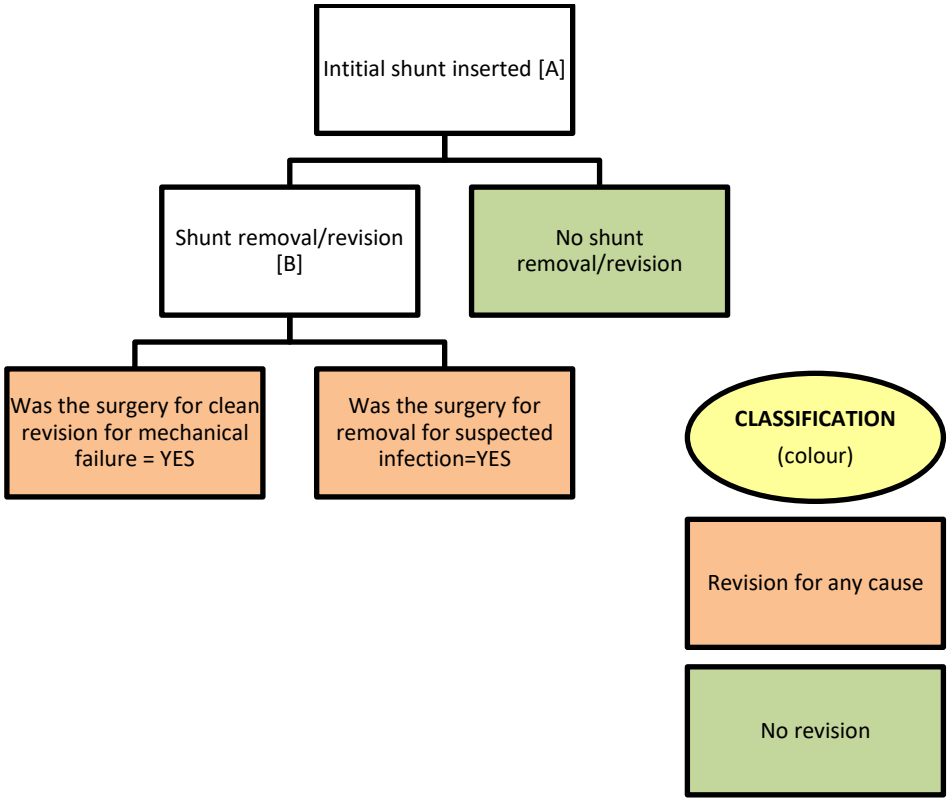
17.4.2.2. Time to shunt failure of any cause

17.4.2.2.1. Derivation

Figure 3 gives an overview of how the secondary outcome is categorised as a revision of any cause (as assessed by the operating surgeon). Time to event will be calculated in the same way as the primary outcome (see Section 17.4.1.1).

In this outcome, shunt failure of any cause is defined as clinically reported. Therefore the First Revision/Removal form will be the only data source for an event.

FIGURE 3: DEFINING TIME TO SHUNT FAILURE OF ANY CAUSE



17.4.2.2.2. Analysis

This outcome is a time to event and will be primarily analysed using the log-rank test and Kaplan-Meier curves presented with the numbers at risk at specified time points (e.g. every one month) for each treatment group.

Analysis, adjusted for stratification factor age group as a fixed effect, will be conducted using a Cox Proportional Hazards model. The hazard ratio and confidence intervals will be presented alongside the p-value.

Cox proportional hazards models rely on the proportional hazards assumption. This assumption will be checked by inspection of Kaplan-Meier plots, if the survival curves clearly cross this indicates non-proportional hazards, and time varying effects will be considered.

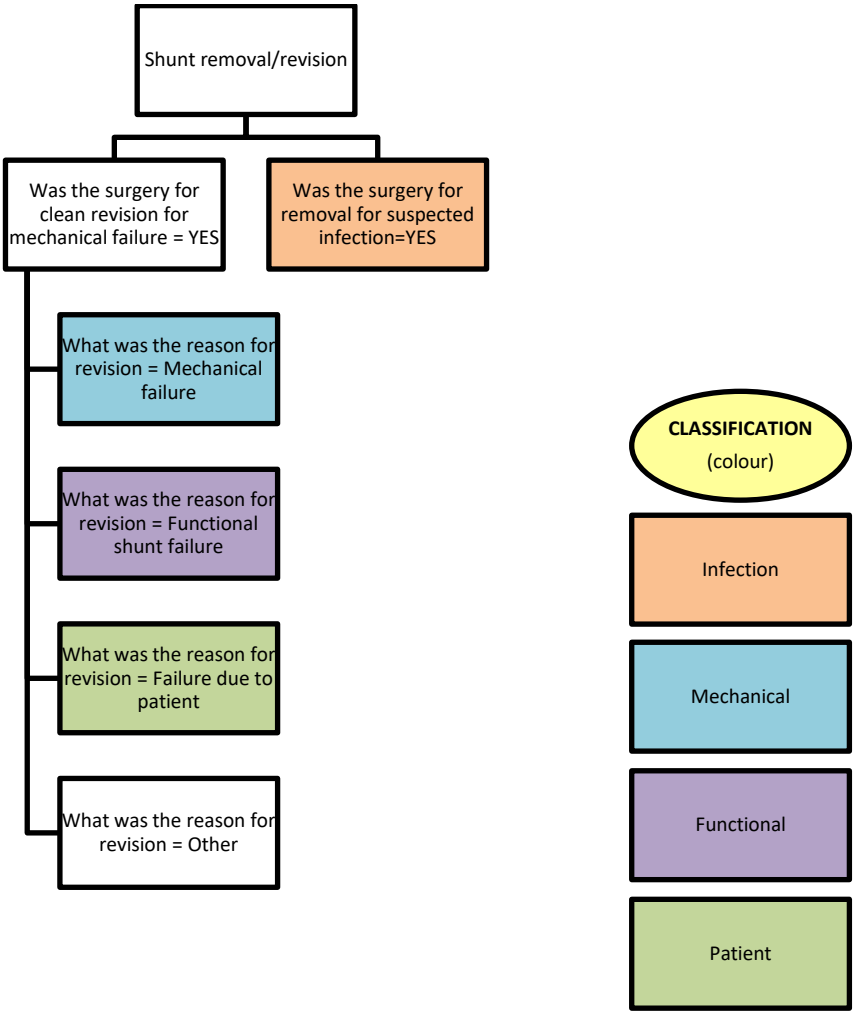
17.4.2.3. Reason for shunt failure (infection, mechanical, patient, other)

17.4.2.3.1. Derivation

Figure 4 gives an overview of how the reason for shunt failure is derived directly from the Shunt removal/revision CRF into four categories (Infection; Mechanical; Functional; Patient).

For CRF reported reason for revision = “Other”. These will be classified by the CI and, if necessary, reclassified into one of the four classifications listed for analysis.

FIGURE 4: DEFINING REASON FOR SHUNT FAILURE



17.4.2.3.2. Analysis

Causes of failure will be broken down by randomised VPS and comparisons between randomized groups will be made using Chi-squared tests. The critical level of significance for statistical testing will be set at 2.5% to account for multiple testing of standard vs. antibiotic impregnated and standard vs. silver impregnated VPS.

17.4.2.4. Type of bacterial VPS infection

17.4.2.4.1. Derivation

Type of bacterial infection is recorded on the Microbiology CRF under "Organism cultured" e.g. acinetobacter baumani. A cultured organism should be reported for all *1A: Definite – culture positive* and *1b. Probable – Culture uncertain* infections. Therefore, a patient can suffer a bacterial infection at any point in the trial and this is picked up on the CRF. Following the de novo shunt, the infection identified at the first revision is the time point of interest. This outcome will therefore be derived as follows:

1) All patients who are deemed to have *1A: Definite – culture positive* and *1b. Probable – Culture uncertain* VPS infection (see Figure 1) will be eligible for this outcome.
2) All organisms associated with each infection, as identified by the committee (see Section 17.4.1.1) will be listed alongside the antibiotics and sensitivities for each of these organisms (the source of all antibiotic and sensitivity data will the microbiology CRF).

17.4.2.4.2. Analysis

Types of organisms cultured will be presented descriptively with frequency tables. No formal statistical analysis will be undertaken. The number of patients who had any VPS infection (nVPS) and the types of organism associated with each of these infections (denominator nVPS) will be presented.

All antibiotic and sensitivity data for each organism within each infection will be listed.
Line listings will be presented for all patients with a *1A: Definite – culture positive* and *1b. Probable – Culture uncertain* VPS infection (see Figure 1). These line listings will present randomisation number, VPS inserted, type of VPS infection, organisms cultured, and antibiotic sensitivities.

17.4.2.5. Time to VPS infection following first clean revision

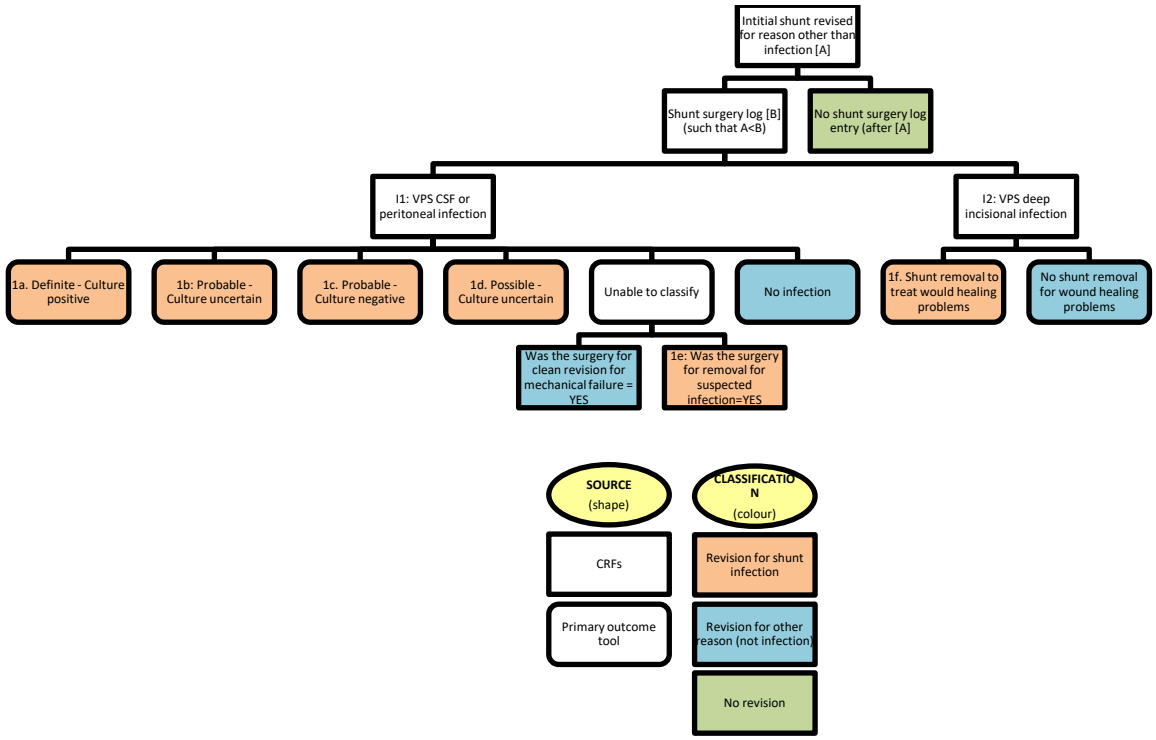
17.4.2.5.1. Derivation

Figure 5 gives an overview of how the secondary outcome is categorised.

DATE OF INSERTION AT FIRST CLEAN REVISION WILL BE TAKEN AS THE DATE OF KNIFE TO SKIN AS REPORTED ON THE FIRST SHUNT REVISION/REMOVAL CRF FOR THE PATIENT ([A] IN FIGURE 5. IF THIS DATA IS MISSING, THE DATE ANAESTETIC WAS STARTED WILL BE USED AS AN EQUIVALENT DATE.

Date of revision following first clean insertion will be taken as the date of surgery on the Shunt Surgery Log ([B] in Figure 5).

FIGURE 5: CLASSIFICATION OF TIME TO VPS INFECTION FOLLOWING FIRST CLEAN REVISION



17.4.2.5.2. Analysis

This outcome will be analysed as specified in Section 1.1.1.1 and Section 17.4.1.3.

17.4.2.6. Quality of Life

17.4.2.6.1. Derivation

Quality of Life (QoL) data is collected on the following Questionnaire in the BASICS trial:

- Hydrocephalus Outcome Questionnaire (HOQ) [8]
    - Child version (aged 8-18) {1}
    - Parent version {2}

Forms required for completion are age dependent, the forms required for each participant age are as indicated, with an X, in the following table:

		Participant age			
QoL Questionnaire		<5 years	5 to <8 years	8 to <18 years	>=18 years
{1}	HOQ (child)			X	
{2}	HOQ (parent)		X		

Each required questionnaire is completed at the following timepoints:

- Baseline
- Early post op
- 12 weekly follow up
- End of study

Hydrocephalus Outcome Questionnaire {1,2}:

Items are scored on a five-point scale from 0 to 4, where the worst health status is given a value of 0 and the best a value of 4. With the exception of questions 19-21 and 42, this requires the following coding:

"Not at all true" = 4

"A little true" = 3

"Somewhat true" = 2

"Quite a bit true" = 1

"Very true" = 0

(For questions 19-21 and 42, the scale is reversed.)

Scale scores will be calculated by summing the responses and dividing by the maximum possible summed score:

Physical health = (sum of items 1-15)/60

Socio-emotional health = (sum of items 16-39)/96

Cognitive health = (sum of items 40-51)/48

Total health = (sum of items 1-51)/204

Summing and dividing by the highest possible score provides a final score on a 0 to 1 metric where 0 indicates worse health status and 1 better health status.

If >50% items are missing for a given scale, the scale score will not be calculated. If <=50% items are missing, the sum of the completed items will be divided by the maximum possible score for the completed items, to retain the 0 to 1 metric.

17.4.2.6.2. Analysis

Hydrocephalus Outcome Questionnaire {1,2}:

Summary statistics will be presented for each subscale and the total scale at each of the four timepoints, for child and parent HOQs. Individual profile plots will be presented for both questionnaires. Data will be analysed using mixed models for repeated measures, with an unstructured covariance matrix, with the HOQ score as the dependent variable and fixed effects for treatment group, time and the corresponding interaction. Co-efficients from the model will be presented along with the mean differences between the treatment groups at each time point and associated p-values and confidence intervals.

17.4.2.7. Incremental cost per VPS failure

17.4.2.7.1. Derivation

This is a health economics question analysed by a separate unit. Details of the derivation of this outcome will therefore be covered in a separate Health Economincs Analysis Plan (HEAP).

17.4.2.7.2. Analysis

This is a health economics question analysed by a separate unit. Details of the analysis of this outcome will therefore be covered in a seperate HEAP.

17.4.2.8. Incremental cost per QALY gained

17.4.2.8.1. Derivation

This is a health economics question analysed by a separate unit. Details of the derivation of this outcome will therefore be covered in a seperate HEAP.

17.4.2.8.2. Analysis

This is a health economics question analysed by a separate unit. Details of the analysis of this outcome will therefore be covered in a seperate HEAP.

18. Missing data and withdrawals

As randomisation is performed in theatre, withdrawals from treatment are expected to be low and not without clinical reason.

For the primary outcome, there are many components that the committee will use to determine that the revision was due to infection. Where the committee is unable to make an assessment, the reason for revision (infection or not) will be taken from the CRF.

Patients with insufficient data for the committee to make their assessment will be expressed as a frequency and a % with the denominator being those who were randomised, treated, consented and subsequently revised.

Withdrawals over the course of the trial will be summarised by treatment arm. This will be presented in a CONSORT diagram alongside a table summarising reasons for withdrawal, level of withdrawal and details as to who made the decision for the withdrawal. Line listings will also be presented with this information.

19. Additional analyses

Sensitivity analysis will be performed as detailed in Section 17.4.1.4.

Exploratory analysis will be performed on all first revisions comparing infection classifications made by the committee (primary outcome, see Section 17.4.1) against infections classified by the operating surgeon (secondary outcome 1, Section 17.4.2.1). This data will be derived as for each outcome. Counts and percentages will be presented in a two by two table presenting revisions for infection and revisions for no infection by each classification method. Percentages will be calculated using the denominator number of first revisions.

20. Safety Evaluations

Adverse events will be categorised according to severity as “Mild”, “Moderate”, or “Severe”. They will also be classified in relation to the causality with the treatment as “Possibly”, “Probably”, and “Almost certainly”. AEs will be further classified within tables as “Expected” and “Unexpected” to the treatment. Full details on the definition and classification of these adverse events are presented in section 10 of the protocol.

Safety reporting requirements changed during the BASICS trial. Specifically:

- AEs related to the anaesthetic were only reportable up until Version 4.0 of the CRF.
- If an AE is admission with ‘suspected infection’ or ‘mechanical shunt failure’ and graded as serious an SAE form was no longer required.

The BASICS Protocol gives further information with regards to these changes. When reporting, safety data will presented in its entirety with the distinction between events historically considered reportable made clear.

20.1. Data sets analysed

For the safety analysis, patients will be analysed according to the initial shunt inserted in order to accurately represent the adverse effects of each treatment. Patients who experience an event after having a shunt revision, where the shunt was not replaced like for like, will be summarised as part of an *Other VPS* group. All patients who had a VPS shunt inserted at baseline will be included within the safety analysis population.

The numbers within the safety data set will be presented as count data and as a percentage using the total randomised as a denominator. This will be presented both overall and split by treatment group at baseline.

20.2. Presentation of the data

Adverse and serious adverse events will be presented using descriptive statistics.

The number of occurrences and patients (with percentage of patients) for each AE will also be presented for each treatment arm, and overall. AE events will be further summarised categorised by severity, and causality. For each patient, only the maximum severity, and causality respectively, experienced of each type of AE will be displayed.

Serious adverse events will be presented as line listings including the following information:

- Description
- Treatment (Standard VPS / Antibiotic impregnated VPS / Silver impregnated VPS)
- Serious criteria (Death / Immediate life threatening / Required hospitalisation / Prolonged existing hospitalisation / Persistent or significant disability or incapacity / Congenital anomaly or birth defect / Medically significant or important)
- Severity (PI assessment; Mild / Moderate / Severe)
- Expectedness (PI and CI assessment; Expected / Unexpected)
- Relationship to device (PI and CI assessment; Almost certainly / Probably / Possibly / Unlikely / Unrelated)
- Actions taken (Treated with concomitant medication / Hospital admission / Shunt removal or revision / Prolongation of hospitalisation / Attendance at GP / Attendance at A & E / GP home visit / Other / No action taken)
- Outcome (Resolved / Resolved with sequelae / Not resolved or ongoing / Ongoing at final follow up / Fatal / Unknown)
- Status (Continuing in trial / Completed trial / Withdrawn from trial)

No formal statistical tests will be undertaken.

21. Quality Control

To ensure quality control, an independent statistician will follow this SAP to independently program the primary outcome analysis and safety analysis from the raw data. Any discrepancies found will be discussed with the trial statistician to resolve. No programming will be shared or shown between the statisticians. The independent statistician will also check the report against their output obtained from the statistical software.

22. References

[1] International Conference on Harmonisation. Topic E3 Structure and content of clinical study reports.(CPMP/ICH/137/95). 1995.

[2] International Conference on Harmonisation. Topic E9 Statistical Principles for Clinical Trials (CPMP/ICH/363/96). 1998.

[3] Guidance for the Content of Statistical Analysis Plans in Clinical Trials. Gamble C, Krishan A, Stochen D, et al. JAMA. 2017 Dec 19;318(23):2337-2343. doi: 10.1001/jama.2017.18556.

[4] Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMJ 2010;340:c332..

[5] *Kahan BC:* Bias in randomised factorial trials. *Stat Med 2013, 32(26):4540–4549.*

[6] Latouche A, Allignol A, Beyersmann J, et al. A competing risks analysis should report results on all cause-specific hazards and cumulative incidence functions. Journal of Clinical Epidemiology. 66 (2013) 648-653.

[7] Fine JP and Gray RJ: A Proportional Hazards Model for the Subdistribution of a Competing Risk. Journal of the American Statistical Association. June 1999, Vol. 94, No. 446, Theory and Models.

[8] Kulkarni AV, Rabin D, Drake JM: An instrument to measure the health status of children with hydrocephalus: the Hydrocephalus Outcome Questionnaire. J Neurosurg Pediatr 101:134-140, 2004.