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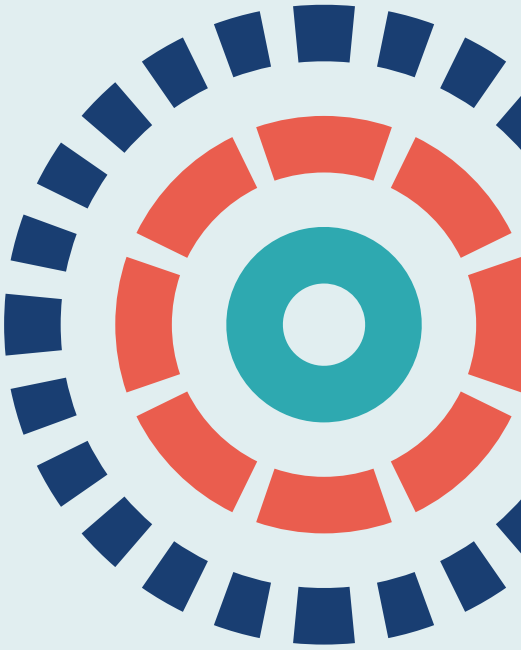

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Silver-impregnated, antibiotic-impregnated or non-impregnated ventriculoperitoneal shunts to prevent shunt infection: the BASICS three-arm RCT

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Declared competing interests of authors: Michael J Griffiths has a patent 068347A1 pending for a novel method of detection of bacterial infection. Tom Solomon reports grants from the National Institute for Health Research (NIHR) outside the submitted work and other support from the Data Safety and Monitoring Committee of the GlaxoSmithKline plc (London, UK) study to evaluate the safety and immunogenicity of a candidate ebola vaccine in children (GSK3390107A) (ChAd3 EBO-Z), outside the submitted work. He also chairs the Siemens Healthineers (Munich, Germany) Clinical Advisory Board. Dyfrig Hughes was member of the Health Technology Assessment (HTA) programme Pharmaceuticals Panel (2008–12) and the HTA programme Clinical Evaluation and Trials board (2010–16). Carrol Gamble reports grants from NIHR outside the submitted work and is a member of the NIHR Efficacy and Mechanism Evaluation programme committee (January 2015–present).

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Abstract

Silver-impregnated, antibiotic-impregnated or non-impregnated ventriculoperitoneal shunts to prevent shunt infection: the BASICS three-arm RCT

Conor L Mallucci,[1*] Michael D Jenkinson,[2,3] Elizabeth J Conroy,[4] John C Hartley,[5] Michaela Brown,[4] Tracy Moitt,[4] Joanne Dalton,[4] Tom Kearns,[4] Michael J Griffiths,[6,7] Giovanna Culeddu,[8] Tom Solomon,[6,9] Dyfrig Hughes,[8] Carrol Gamble[4] and the BASICS study collaborators†

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Background: Insertion of a ventriculoperitoneal shunt to treat hydrocephalus is one of the most common neurosurgical procedures worldwide. Shunt infection affects up to 15% of patients, resulting in long hospital stays, multiple surgeries and reduced cognition and quality of life.

Objectives: The aim of this trial was to determine whether or not antibiotic-impregnated ventriculoperitoneal shunts (hereafter referred to as antibiotic shunts) (e.g. impregnated with rifampicin and clindamycin) or silver-impregnated ventriculoperitoneal shunts (hereafter referred to as silver shunts) reduce infection compared with standard ventriculoperitoneal shunts (hereafter referred to as standard shunts).

Design: This was a three-arm, superiority, multicentre, parallel-group randomised controlled trial. Patients and a central primary outcome review panel, but not surgeons or operating staff, were blinded to the type of ventriculoperitoneal shunt inserted.

Setting: The trial was set in 21 neurosurgical wards across the UK and the Republic of Ireland.

Participants: Participants were patients with hydrocephalus of any aetiology who were undergoing insertion of their first ventriculoperitoneal shunt.

Interventions: Participants were allocated 1 : 1 : 1 by pressure-sealed envelope to receive a standard non-impregnated, silver-impregnated or antibiotic-impregnated ventriculoperitoneal shunt at the time of insertion. Ventriculoperitoneal shunts are medical devices, and were used in accordance with the manufacturer's instructions for their intended purpose.

Main outcome measures: The primary outcome was time to ventriculoperitoneal shunt failure due to infection. Secondary outcomes were time to failure for any cause, reason for failure (infection, mechanical), types of ventriculoperitoneal shunt infection, rate of infection after first clean (non-infected) revision and health economics. Outcomes were analysed by intention to treat.

Results: Between 26 June 2013 and 9 October 2017, 1605 patients from neonate to 91 years of age were randomised to the trial: $n = 36$ to the standard shunt, $n = 538$ to the antibiotic shunt and $n = 531$ to the silver shunt. Patients who did not receive a ventriculoperitoneal shunt ($n = 4$) or who had an infection at the time of insertion ($n = 7$) were not assessed for the primary outcome. Infection occurred in 6.0% ($n = 32/533$) of those who received the standard shunt, in 2.2% ($n = 12/535$) of those who received the antibiotic shunt and in 5.9% ($n = 31/526$) of those who received the silver shunt. Compared with the standard shunt, antibiotic shunts were associated with a lower rate of infection (cause-specific hazard ratio 0.38, 97.5% confidence interval 0.18 to 0.80) and a decreased probability of infection (subdistribution hazard ratio 0.38, 97.5% confidence interval 0.18 to 0.80). Silver shunts were not associated with a lower rate of infection than standard shunts (cause-specific hazard ratio 0.99, 97.5% confidence interval 0.56 to 1.74). The ventriculoperitoneal shunt failure rate attributable to any cause was 25.0% overall and did not differ between arms. Antibiotic shunts save £135,753 per infection avoided. There were no serious adverse events.

Limitations: It was not possible to blind treating neurosurgeons to the ventriculoperitoneal shunt type. The return rate for patient-reported outcomes was low. Limitations to the economic evaluation included failure to obtain Hospital Episode Statistics data from NHS Digital, as per protocol. Reliance on patient-level information and costing systems data mitigated these limitations.

Conclusions: Antibiotic shunts have a reduced infection rate compared with standard shunts, whereas silver shunts do not. Antibiotic shunts are cost-saving.

Future work: A sample collection has been established that will enable the study of surrogate markers of ventriculoperitoneal shunt infection in cerebrospinal fluid or blood using molecular techniques. A post hoc analysis to study factors related to shunt failure will be performed as part of a future study. An impact analysis to assess change in practice is planned.

Trial registration: Current Controlled Trials ISRCTN49474281.

Funding: This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 24, No. 17. See the NIHR Journals Library website for further project information.

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Report Supplementary Material 1 Statistical analysis plan

Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/hta24170).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

List of abbreviations

A&E	accident and emergency
AE	adverse event
AIC	Akaike information criterion
BASICS	British Antibiotic and Silver Impregnated Catheters for ventriculoperitoneal Shunts
BIC	Bayesian information criterion
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CSF	cerebrospinal fluid
csHR	cause-specific hazard ratio
CTU	Clinical Trials Unit
EQ-5D	EuroQol-5 Dimensions
EQ-5D-3L	EuroQol-5 Dimensions, three-level version
EQ-5D-Y	EuroQol-5 Dimensions Youth
EQ-VAS	EuroQol Visual Analogue Scale
EVD	external ventricular drain
FMI	fraction of missing information
GLM	generalised linear model
GP	general practitioner
HOQ	Hydrocephalus Outcome Questionnaire
HR	hazard ratio
HRG	Healthcare Resource Group
ICER	incremental cost-effectiveness ratio
IDSMC	Independent Data and Safety Monitoring Committee
IIH	idiopathic intracranial hypertension
LCTC	Liverpool Clinical Trials Centre
LQ	lower quartile
NICE	National Institute for Health and Care Excellence
PI	principal investigator
PLICS	Patient-Level Information and Costing Systems
QALY	quality-adjusted life-year
RCT	randomised controlled trial
RR	relative risk
SAE	serious adverse event
Shine	Spina bifida Hydrocephalus Information Networking Equality
sHR	subdistribution hazard ratio
TMG	Trial Management Group
TSC	Trial Steering Committee
UQ	upper quartile
VPS	ventriculoperitoneal shunt

Plain English summary

Hydrocephalus (commonly known as 'water on the brain') is a condition that can affect all age groups, from babies to the elderly. In hydrocephalus, there is an accumulation of the normal brain fluid in the fluid cavities (ventricles) of the brain. Untreated, hydrocephalus can be life-threatening. The most common treatment involves an operation to insert a tube into the swollen ventricles to drain off the excess fluid. This is called a ventriculoperitoneal shunt.

In the UK, 3000–3500 shunt operations are performed each year. The main risks of a shunt operation are infection (surgical meningitis) and blockage without infection. Infection results in the need for at least two further surgeries, antibiotic treatment and a prolonged hospital stay (minimum of 2 weeks). Shunt infections can affect mental abilities and can be life-threatening. People who have blockages without infection, on the other hand, usually need only a single operation to replace the blocked part and only a few days in hospital.

Two new types of shunt catheter have been introduced to try to reduce shunt infection: antibiotic-impregnated shunts and silver-impregnated shunts. This study was designed to assess whether or not either of these new shunts reduce infection compared with standard shunts. This study also included an analysis of the cost and health benefits of the different shunts used.

A total of 1605 children and adults, who were treated in neurosurgical units across the UK and the Republic of Ireland, participated in this study. Consent was provided by all participants in the trial. Each participant had an equal chance of receiving one of the three shunt types.

Shunt infection occurred in 6% of participants receiving standard shunts, 5.9% of participants receiving silver-impregnated shunts and 2.2% of participants receiving antibiotic-impregnated shunts.

This study has demonstrated a major reduction in shunt infections in new shunts when using antibiotic-impregnated shunts compared with standard or silver-impregnated shunts. A health economic analysis has indicated that antibiotic-impregnated shunts are cost-saving.

Scientific summary

Background

Hydrocephalus affects one in every 500 births; thus, it is 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.

Standard treatment for hydrocephalus remains the ventriculoperitoneal shunt. Insertion of a ventriculoperitoneal shunt to treat 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. Currently, three types of shunt catheter are available: standard silicone shunts (hereafter referred to as standard shunts), antibiotic-impregnated shunts (hereafter referred to as antibiotic shunts) and silver-impregnated shunts (hereafter referred to as silver shunts). There is no standard practice or guidance in the UK as to which shunt catheter is the most effective at reducing infection.

The incidence of shunt infection varies markedly in the literature from 3% to 27%, and is higher in certain groups, such as neonates and children aged < 1 year. 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, intravenous and intrathecal antibiotics, and further surgery to place a new shunt once the infection has been treated. This trial, therefore, addresses the primary question of which shunt catheter is the most effective in reducing shunt infection and has secondary questions addressing the consequences of infection in a clinical and financial context.

Objectives

The trial addressed the following objectives.

Primary outcome

The primary outcome was the time to failure of a first ventriculoperitoneal shunt due to infection, as assessed by a blinded central review panel. The central review panel comprised the chief investigator (or delegate, for participants treated by the chief investigator) and a microbiologist, both of whom were masked to participant allocations.

Secondary outcomes

The secondary outcomes were to compare the following outcomes in the standard shunt arm with the antibiotic and silver shunt arms, respectively:

- time to removal of a first ventriculoperitoneal shunt due to suspected infection, as assessed by the treating surgeon
- time to ventriculoperitoneal shunt failure for any cause
- reason for failure (infection, mechanical, patient, functional)
- types of bacterial ventriculoperitoneal shunt infection (organism, antibiotic resistance)
- time to ventriculoperitoneal shunt infection following first clean (non-infected) revision
- quality of life, assessed using the Hydrocephalus Outcome Questionnaire
- incremental cost per ventriculoperitoneal shunt failure (any cause) averted
- incremental cost per quality-adjusted life-year gained.

Methods

Participants

Participants were screened for eligibility in 21 neurosurgical units across the UK and the Republic of Ireland. All participating centres met the British Antibiotic and Silver Impregnated Catheters for ventriculoperitoneal Shunts (BASICS) centre inclusion criteria.

Patients were eligible to participate in the trial if they had hydrocephalus of any aetiology (including idiopathic intracranial hypertension) requiring a first ventriculoperitoneal shunt. Note that failed primary endoscopic third ventriculostomy, indwelling ventricular access device (e.g. Ommaya or Rickham reservoir or ventriculosubgaleal shunt or similar) and indwelling external ventricular drains were allowed.

Patients with the following characteristics were excluded from the trial:

- previous indwelling ventricular or lumbar peritoneal or atrial shunt
- active and ongoing cerebrospinal fluid or peritoneal infection (previous infected cases were allowed once cleared of infection)
- multiloculated hydrocephalus requiring multiple ventriculoperitoneal shunts or neuroendoscopy
- ventriculoatrial or ventriculopleural shunt planned
- allergy to antibiotics associated with the antibiotic shunt
- allergy to silver.

Trial procedures

Patients were eligible to be randomised to the trial if written consent was provided by the patient, parent, legal representative or consultee, as appropriate. Patients were randomised, by envelope, in a ratio of 1 : 1 : 1 in the operating theatre at the time when the ventriculoperitoneal shunt was required. The randomisation sequence was generated by an independent statistician and stratified by neurosurgical unit, age group (adult or paediatrics were defined according to unit practice) and envelope storage room within the neurosurgical unit. Patients and a central review panel, but not surgeons or operating staff, were blinded to the type of ventriculoperitoneal shunt inserted. All ventriculoperitoneal shunt types were medical devices used in accordance with the manufacturers' instructions for their intended purpose.

All patients having a first ventriculoperitoneal shunt for hydrocephalus of any aetiology (including idiopathic intracranial hypertension) were screened for eligibility and recorded on a centre-held screening log. Reasons for non-recruitment were documented (e.g. not eligible, declined consent) and the information was used for monitoring purposes.

Data were collected at baseline (pre-operative assessment), randomisation (first surgery), early post-operative assessment, first routine post-operative assessment, 12-weekly follow-up assessments, subsequent routine post-operative assessments and, when applicable, unscheduled visits/admissions and at shunt revision/removals. Patients were followed for a minimum of 6 months and a maximum of 2 years.

An economic evaluation was conducted to estimate the incremental cost-effectiveness of impregnated ventriculoperitoneal shunt catheters, expressed as all-cause ventriculoperitoneal shunt failures averted.

Sample size

The sample size for the primary outcome was calculated using the Pintilie method (Pintilie M. Dealing with competing risks: testing covariates and calculating sample size. *Stat Med* 2002;**21**:3317–24), and assumed the following: (1) failure due to infection was the event of interest, with all other reasons for failure a competing risk; (2) the rate of infection was 8% in the standard silicone arm and 4% in the impregnated shunt catheter arms; (3) the competing risk event rate was 30%; and (4) a 5% loss to

follow-up. An initial total sample size of 1200 with 119 events demonstrated good statistical power (88%), with leverage for a lower event rate if required.

Ongoing monitoring of the infection rate identified a deviation from the assumptions and, subsequently, a need to revise the original sample size. In January 2016, the target sample size was increased to 1606 participants with 101 events and 80% power. The Independent Data and Safety Monitoring Committee oversaw this revision and the Trial Steering Committee agreed and approved this change.

Statistical analysis

Efficacy outcomes were analysed according to the intention-to-treat principle, as far as practically possible, and safety analyses were analysed according to the type of ventriculoperitoneal shunt in situ. A Bonferroni adjustment was made to allow for multiple comparisons and a 2.5% statistical significance level, and 97.5% confidence intervals were used throughout. The statistical analysis plan was developed prior to analysis.

Outcomes with infection as the event of interest used Fine and Gray (Fine PF, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;**94**:496–509) survival regression models with cause-specific hazard ratios and subdistribution hazard ratios presented. Cox regression models were used to analyse time to ventriculoperitoneal shunt failure as a result of any cause. Reason for ventriculoperitoneal shunt failure is presented descriptively and with a chi-squared test. Types of organisms, and their resistances and sensitives, are presented descriptively. Quality-of-life outcomes were analysed using mixed models.

Economic evaluation

The health economic analysis adopted the perspective of the NHS and Personal Social Services. Costs (2016/17) were estimated from questionnaires, entries made in case report forms and from patient-level information and costing systems. The primary economic effectiveness outcome was ventriculoperitoneal shunt failure as a result of any cause, with failure due to infection and quality-adjusted-life years – based on responses to the EuroQol-5 Dimensions, three-level version – as important secondary outcomes. Costs and benefits occurring after the first year were discounted at 3.5% per annum. The joint uncertainty in costs and benefits were considered in regression analyses and in non-parametric bootstrapping. Stratified cost-effectiveness analyses considered important subgroups [paediatrics (aged up to 16 years), adults aged 16–65 years and adults aged > 65 years].

Results

Participants

A total of 3505 patients were screened for eligibility from 21 centres, 1605 of whom were subsequently randomised. The overall consent rate in patients who were approached for consent was 82% ($n = 1672/2041$). The three arms were similar in their baseline characteristics and their baseline risk assessments. Approximately 40% of all participants were admitted as paediatric patients ($n = 599/1605$) and one-quarter of all participants were aged < 1 year.

The randomised groups were approximately equal in size (standard shunt: $n = 536$; antibiotic shunt: $n = 538$; silver shunt: $n = 531$). Of those randomised, 1585 (98.8%, $n = 1605$) received the ventriculoperitoneal shunt as randomised; 16 (1.0%) received an alternative trial ventriculoperitoneal shunt; and four (0.2%) received no ventriculoperitoneal shunt.

Primary outcome: time to failure of first ventriculoperitoneal shunt due to infection, as assessed by a blinded central review panel

Seven patients had an infection at insertion and were not included in the primary outcome set. Of those remaining ($n = 1594$), 398 patients had revision operations (25.0%), with 75 being centrally classified as having ventriculoperitoneal shunt infections (4.7%). The rate of infection was approximately equal in the standard and silver shunt arms [6.0% ($n = 32/533$) and 5.9% ($n = 31/526$), respectively] and lower in the antibiotic shunt arm (2.2%, $n = 12/535$).

When compared with the standard shunt, antibiotic shunts decreased the risk of infection (cause-specific hazard ratio 0.38, 97.5% confidence interval 0.18 to 0.80). Silver shunts were comparable to standard shunts (cause-specific hazard ratio 0.99, 97.5% confidence interval 0.56 to 1.74). The majority of centrally assessed infections were classified as definite – culture positive ($n = 53/75$, 70.7%).

Secondary outcome 1: time to removal of first ventriculoperitoneal shunt due to suspected infection, as assessed by the treating surgeon

Of the 398 revisions, 78 (4.9%) were defined by the treating surgeon as being due to suspected infection. As with the primary outcome, when compared with the standard shunt, the antibiotic shunt, but not the silver shunt, was associated with a significant decrease of infection [antibiotic shunt: cause-specific hazard ratio 0.45 (97.5% confidence interval 0.23 to 0.91), silver shunt: cause-specific hazard ratio 0.93 (97.5% confidence interval 0.53 to 1.64)].

Secondary outcome 2: time to ventriculoperitoneal shunt failure due to any cause

The revision rate was approximately equal across the three arms, and varied from 24.4% in the standard shunt arm ($n = 103/533$) to 25.9% in the silver shunt arm ($n = 136/526$). No significant difference was observed for time to failure between the antibiotic and silver shunt arms when compared with the standard shunt [antibiotic shunt: hazard ratio 1.01 (97.5% confidence interval 0.77 to 1.33), silver shunt: hazard ratio 1.08 (97.5% confidence interval 0.82 to 1.42)].

Secondary outcome 3: reason for shunt failure

Although the number of ventriculoperitoneal shunt failures was similar between the three arms, the underlying reason, as classified by the treating surgeon, differed when comparing the standard shunt with the antibiotic shunt ($p = 0.02$); there were fewer infections with antibiotic shunts, but a higher frequency of failure due to other causes. The underlying reason did not differ significantly when comparing the standard shunt with the silver shunt ($p = 0.71$).

Secondary outcome 4: type of bacterial infection

The central review panel classified all shunt infections that were 'definite – culture positive' and 'probable – culture uncertain' ($n = 56/75$) by one organism that was cultured. *Staphylococcus aureus* accounted for 30% of cultured organisms in ventriculoperitoneal shunt infection ($n = 17/56$).

Secondary outcome 5: time to ventriculoperitoneal shunt infection following first clean revision

Among participants with a first clean (non-infected) revision ($n = 323$), the proportion with a subsequent revision for any reason was 39.6% ($n = 128/323$). This rate was 25% ($n = 398/1594$) in participants with de novo ventriculoperitoneal shunts. The infection rate was 6.2% ($n = 20/323$) for participants who had their de novo shunt revised for reasons other than infection ($n = 323$) and subsequently went on to have this replacement shunt revised due to infection ($n = 20$). This infection rate was higher than that for de novo ventriculoperitoneal shunts [4.7% ($n = 75/1594$)]. However, there was no significant between-group difference in time to infection following first clean revision when comparing either antibiotic or silver shunts with the standard shunt [antibiotic shunt: cause-specific hazard ratio 0.55 (97.5% confidence interval 0.17 to 1.75); silver shunt: cause-specific hazard ratio 0.48 (97.5% confidence interval 0.14 to 1.67)].

Secondary outcome 6: quality of life, assessed using Hydrocephalus Outcome Questionnaire

Insufficient data were returned to formally analyse the Hydrocephalus Outcome Questionnaire results.

Cost-effectiveness analysis

Secondary outcome 7: incremental cost per ventriculoperitoneal shunt failure averted

In the base-case analysis, both antibiotic and silver shunts were located in the south-west quadrant of the cost-effectiveness plane, in relation to the standard shunt. Incrementally, silver shunts save £62,358 for each additional failure compared with standard shunts, and antibiotic shunt catheters save £638,600 per additional failure compared with silver shunts.

Secondary outcome 8: incremental cost per quality-adjusted life-year gained

Based on the incremental cost per confirmed ventriculoperitoneal shunt infection averted, antibiotic shunt catheters were dominant, saving £4059 (97.5% confidence interval −£1422 to £12,567) per 0.030 (97.5% confidence interval 0.002 to 0.058) fewer infection-related ventriculoperitoneal shunt failures; compared with the standard shunt, antibiotic shunt catheters save £135,753 per ventriculoperitoneal shunt infection avoided. Silver shunt catheters were dominated by the standard shunt.

In the cost–utility analysis of trial participants aged ≥ 5 years, antibiotic shunt catheters were dominated by silver shunts. Compared with standard shunts, the incremental cost-effectiveness of silver shunts was £1904 per quality-adjusted life-year gained. The probabilities of cost-effectiveness at £20,000 per quality-adjusted life-year are 0.206 (standard shunt), 0.274 (antibiotic shunt) and 0.52 (silver shunt); at £30,000 per quality-adjusted life-year, the cost-effectiveness probabilities are 0.147 (standard shunt), 0.267 (antibiotic shunt) and 0.586 (silver shunt).

Adverse events

There were no serious adverse events. A total of 654 adverse events were reported in 413 patients (constituting 25.8% of $n = 1601$ participants who received a de novo shunt). The proportion of patients experiencing an event was similar across the arms (standard shunt: $n = 135/531$, 25.4%; antibiotic shunt: $n = 136/545$, 25.0%; silver shunt: $n = 140/525$, 26.7%). Common adverse events were ventricular shunt catheter obstruction (96 events in 79/1601 patients, 4.9%), shunt valve obstruction (65 events in 52/1601 patients, 3.2%) and valve change for symptomatic over-/underdrainage (54 events in 50/1601 patients, 3.1%).

Conclusions

Implications for health care

Antibiotic ventriculoperitoneal shunt reduces the infection rate compared with standard shunts, and, in doing so, is cost-saving. Silver ventriculoperitoneal shunts are not associated with a lower rate of infection. The significant effective benefit for the patient of the antibiotic shunt in reducing shunt infection, combined with the economic benefit in terms of costs saved per ventriculoperitoneal shunt infection averted, would support all patients receiving an antibiotic-impregnated ventriculoperitoneal shunt at first shunt insertion.

Implications for research

The BASICS trial is the largest prospective randomised trial on ventriculoperitoneal shunts for hydrocephalus ever performed, to our knowledge. The information collected will fuel many future studies on both the molecular biology of infection and the reasons behind both infective and mechanical shunt failure.

Trial registration

This trial is registered as ISRCTN49474281.

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This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 24, No. 17. See the NIHR Journals Library website for further project information.

Chapter 1 Introduction

Current practice

Hydrocephalus affects one in every 500 births,[3] 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 a treatment with cerebral shunts revolutionised the management of these patients.

Standard treatment for hydrocephalus remains the ventriculoperitoneal shunt (VPS) catheter. A VPS comprises silicone tubing with the addition of an in-line valve that is designed to control the rate of cerebrospinal fluid (CSF) flow. The tubing passes from the brain fluid cavities (ventricles) under the skin to the peritoneum (abdominal cavity). The shunt drains CSF from the ventricles to the peritoneal cavity.

Insertion of a VPS to treat 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.[4] Once inserted, a shunt is generally required for life; it will inevitably be susceptible to failure, in terms of both infection (as it remains an implanted foreign body) and mechanical failure, usually due to blockage of tubing or valve failure. Thus, patients with shunts will need lifelong follow up and usually require multiple surgeries. Therefore, VPS treatment for hydrocephalus is a major health burden to the NHS.

Industry produces a number of different VPS types, and costs associated with these can vary. The market comprises a wide variety of different valves and, more recently, different types of shunt catheter. The treating surgeon and hospital often chooses the type of valve and shunt tubing based on personal preference and/or associated costs.

There are three types of VPS catheter available (standard, antibiotic impregnated and silver impregnated). There is no standard practice or guidance in the UK as to which shunt catheter is the most effective at reducing infection. Practice is variable across the UK and the world. There are no current National Institute for Health and Care Excellence (NICE) guidelines, nor is there a position statement from the Society of British Neurological Surgeons regarding the use of any type of VPS.

As an infection in a newly implanted shunt can have such devastating consequences for the patient, with far-reaching health economic sequelae,[5] the industry has led the way in trying to develop types of shunt catheters that will reduce infection. It is incumbent on clinical researchers to assess the effectiveness of these developments; this study attempts to answer this question.

Rationale

Shunt failure due to infection has plagued this neurosurgical advance ever since it was developed. The reported incidence of shunt infection varies markedly in the literature from 3% to 27%[6–10] and is higher in certain groups, for example neonates and children aged < 1 year, and patients treated with a previous temporary external ventricular drain (EVD). Episodes of shunt infection have a major impact on both 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 intelligence quotient (IQ) and loculation, have often been reported[8] but never formally studied in the context of a prospective clinical trial. The number of shunt infections is an independent predictor of death in patients requiring CSF shunts [hazard ratio (HR) 1.66, 95% confidence interval (CI) 1.02 to 2.72].[11]

The most common pathogens detected were staphylococcus species, but, in a proportion of patients with suspected infection, the organism is never determined, especially if the patient has already received antimicrobial treatment or if there was a delay in culturing the organism, both of which hamper microbiological treatment.[5] However, newer molecular approaches are being developed,[12] including the substudy within this trial.

Data from the UK shunt registry (to which most neurosurgical units contribute) report that 15% of shunt revisions are for infection.[13] In the largest randomised controlled shunt trial worldwide, the infection rate was 8.4% for primary VPSs.[14]

Impregnated VPS catheters have been introduced as a means to reduce VPS infection, in addition to the usual surgical site infection prevention care bundles that are not standardised across neurosurgery clinical practice.

There are three types of VPS catheters available, and there are cost implications associated with impregnated shunt catheters that, typically, are more than double the cost of the standard non-impregnated VPS catheters:

1. standard VPSs are made of silicone and are available and supplied by a number of different companies
2. antibiotic-impregnated VPSs are made of silicone and are impregnated with antibiotics (0.15% clindamycin and 0.054% rifampicin) [available as Bactiseal® (Codman®; Integra LifeSciences Holdings Corporation, Plainsboro, NJ, USA) and Ares™ (Medtronic plc, Dublin, Ireland)]
3. silver-impregnated VPSs are made of silicone and impregnated with silver [available as Silverline® (Spiegelberg GmbH & Co. KG, Hamburg, Germany)].

Despite a large number of publications[15–22] prior to our study, there has been limited evidence to date indicating the clinical effectiveness of these impregnated shunt catheters. Prior to our study, a systematic review and meta-analysis[23] of the Bactiseal VPS identified one randomised controlled trial (RCT)[15] and 11 observational studies. The RCT,[15] conducted in a single centre in South Africa, demonstrated a trend favouring impregnated VPSs, but did not show a statistically significant difference between the two trial groups [relative risk (RR) 0.38, 95% CI 0.11 to 1.30; $p = 0.12$]; however, meta-analysis of the 11 observational studies showed a statistically significant difference favouring the Bactiseal VPS (RR 0.37, 95% CI 0.23 to 0.60; $p < 0.01$).[23] Research on the Bactiseal VPS conducted in Liverpool, UK, has shown that, over a 2-year period, the infection rate reduced among paediatric patients who were given the Bactiseal VPS compared with historical controls.[16] However, continued data collection over 3.5 years, published as part of a Liverpool-led multicentre observational study in collaboration with two other UK paediatric neurosurgical units, showed no significant reduction in infection.[17] Indeed, the reduction in infection achieved by the Bactiseal VPS in the multicentre observational study[17] was seen only in neonates and was heavily weighted by the results from one unit. This study[17] was not part of the published systematic review.[23]

Silver-impregnated shunts were launched in the UK in March 2011. There is little doubt that silver ions have antimicrobial effects and they elute from Silverline shunt catheters. However, the efficacy of Silverline shunt catheters at preventing VPS infections is not proven. In vitro models have shown varying results and clinical studies are limited.[18,19] There is one observational study of the Silverline VPS,[20] in which the Silverline VPS was used to successfully treat seven patients with active CSF infection. There are no observational studies comparing Silverline VPS infection rates with those of either standard or Bactiseal VPSs. However, in a RCT of EVDs (an EVD is 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) with standard shunt catheters to 12.3% (17/138) ($p = 0.043$) for silver shunt catheters.[22] Two further observational studies comparing standard with Silverline EVDs also show a reduction in infection rates.[21,24]

Risks and benefits

The potential beneficial effect on health status of these impregnated shunt catheters is reduced shunt infection and its negative sequelae. Prior to this study, approximately 70%[4,13] of shunt operations in the UK were with Bactiseal shunts (verified by feasibility screening logs) and it was felt that, just like Bactiseal, there was likely to be a significant uptake of Silverline shunts by neurosurgeons, despite the lack of evidence of clinical or cost benefit.

The potential adverse effects of impregnated shunt catheters has never been studied prospectively, to our knowledge. One of the potential concerns of antibiotic-impregnated shunt catheters is the potential for selecting out resistant organisms or missing potential infections owing to an inability to culture them.

Thus, before the wide adoption of these impregnated shunt catheters, an adequately powered RCT is needed to assess their effectiveness at reducing infection and to determine their safety (including the type of organisms cultured), antibiotic sensitivities and antibiotic resistances.

Aims and objectives

Primary objective

The primary objective was to determine whether or not antibiotic- or silver-impregnated VPSs reduce infection compared with standard VPSs in patients with hydrocephalus, following insertion of a de novo VPS.

Secondary objectives

- To determine the proportion of first VPS infections occurring > 6 months after insertion of a de novo VPS.
- To determine whether or not antibiotic- or silver-impregnated VPSs reduce shunt failure due to any cause compared with standard VPSs in patients with hydrocephalus following insertion of a de novo VPS.
- To assess whether or not the reason for shunt failure is different across the three different types of VPS.
- To determine which organisms and their resistances/sensitivities subsequently infect three alternative VPSs.
- To determine whether or not antibiotic- or silver-impregnated VPSs reduce infection following first (non-infected) clean VPS revision for mechanical failure, compared with standard VPSs in patients with hydrocephalus, following insertion of a de novo VPS.
- To assess the impact of VPS infection on patients in terms of quality of life.
- To assess the cost-effectiveness of antibiotic- and silver-impregnated VPSs compared with standard VPSs.

Chapter 2 Trial design and methods

Trial design

A schematic representation of the trial design is given in *Figure 1*.

Ethics approval and research governance

The protocol was approved by the Greater Manchester South Research Ethics Committee (reference number 12/NW/0790). The trial was funded by the National Institute for Health Research Health Technology Assessment programme (number 10/104/30) and included on the International Standard Randomised Controlled Trial Number registry (ISRCTN49474281). Centre-specific approval was obtained at all of the recruiting centres.

The protocol has been published previously.[1] The trial opened on protocol version 3.0, and the final approved version of the protocol was version 13.0, which contains a complete list of protocol changes [see www.fundingawards.nihr.ac.uk/award/10/104/30 (accessed 22 January 2020)]. A summary of substantial protocol amendments are provided in *Table 1*.

Selection of trial centres

Participants were recruited from 21 regional adult and paediatric neurosurgery centres in the UK and the Republic of Ireland. To be eligible to participate in the trial, centres had to meet the British Antibiotic and Silver Impregnated Catheters for ventriculoperitoneal Shunts (BASICS) trial centre suitability assessment criteria:

- minimum of three patients per month
- neurosurgical unit treating adults or paediatrics
- evidence of a team to undertake trial activities
- principal investigator (PI) had previous experience of RCTs or a significant role
- no local issues to prevent trial set-up
- completion of prospective screening log.

Participants

The trial was open to all patients (children and adults) who had hydrocephalus requiring treatment with a first permanent VPS who met the eligibility criteria.

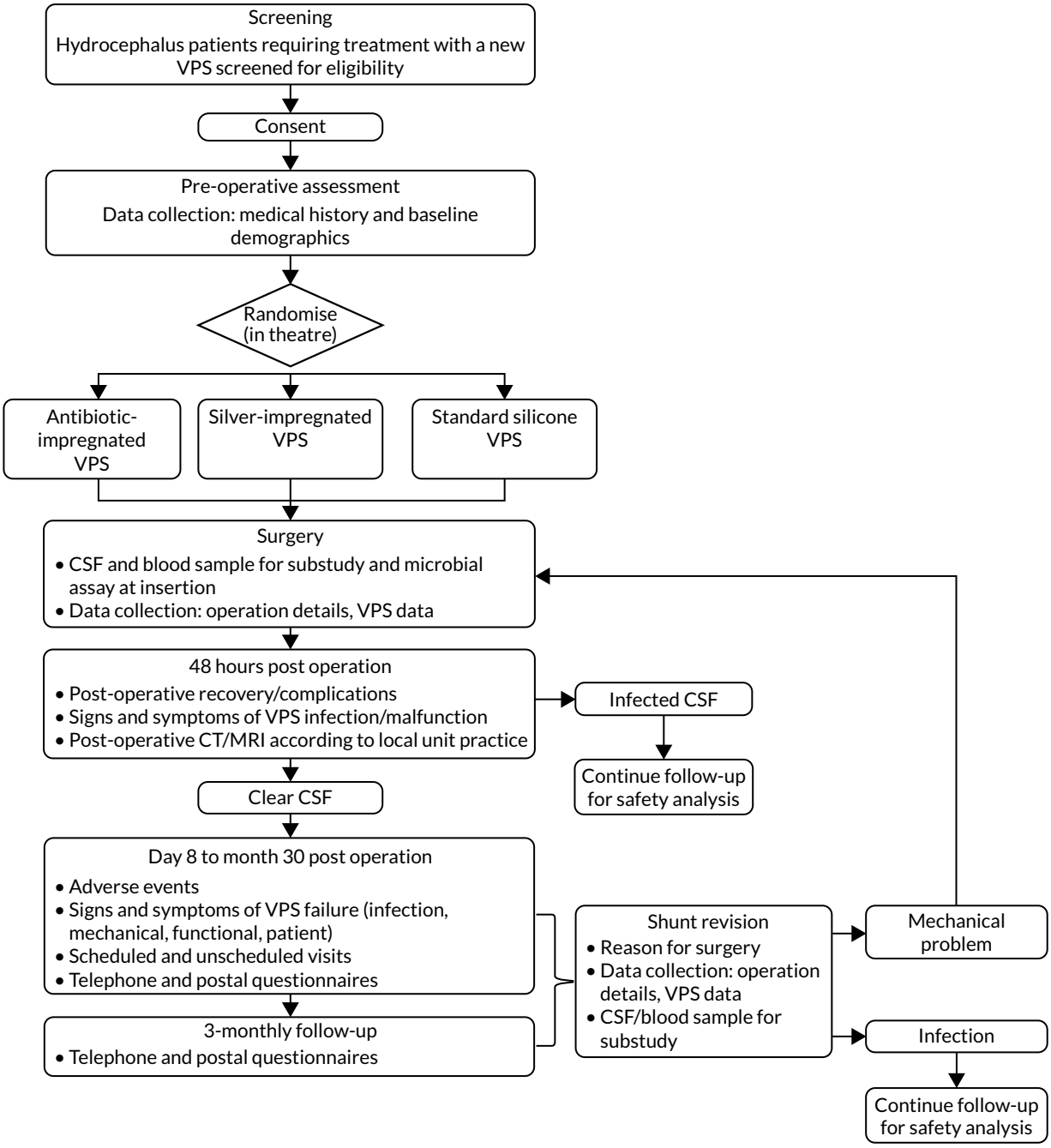

FIGURE 1 Trial design. CT, computerised tomography; MRI, magnetic resonance imaging. Reproduced from Jenkinson *et al.*[1] This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. The figure includes minor additions and formatting changes to the original.

Inclusion criterion

Patients were considered for inclusion in the trial if they met the following criterion:

- Hydrocephalus of any aetiology [including idiopathic intracranial hypertension (IIH)] requiring a first VPS.

Note that failed primary endoscopic third ventriculostomy was allowed, indwelling ventricular access devices (e.g. Ommaya or Rickham reservoir or ventriculosubgaleal shunt or similar) were allowed and indwelling EVDs were allowed.

TABLE 1 Key protocol amendments

Protocol version and date	Key amendments
2.0 (21 November 2012)	• Protocol: 'Allergy to antibiotics associated with the antibiotic shunt' added to the exclusion criteria

3.0 (22 March 2013)	• Section 1: protocol summary – primary objective wording changed to:
	
	To determine whether antibiotic or silver impregnated VPS reduce infection compared to standard VPS in hydrocephalus following insertion of de novo VPS
	
	• Section 4: trial design – secondary end point added: 'e. Quality of Life'
	
	• Section 5: inclusion criteria changed to 'Hydrocephalus of any aetiology (including IIH) requiring first VPS'
	• Section 7: trial interventions –
	  ○ 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)'

4.0 (25 July 2013)	• Section 5.1: inclusion criteria and exclusion criteria updated to –
	  ○ indwelling ventricular access devices (e.g. Ommaya or Rickham reservoir or ventriculosubgaleal shunt or similar) are allowed
	  ○ indwelling EVD allowed

5.0 (20 December 2013)	• Section 4: trial design
	• Primary end point changed to read 'Time to failure of the first VPS due to infection'
	
	• Section 5.2: exclusion criteria changed to –
	  ○ previous indwelling ventricular or lumbar peritoneal or atrial shunt
	  ○ allergy to silver

6.0 (1 April 2014)	• Section 11.3.5: nominated consent added
8.0 (10 August 2015)	• Protocol summary section, study duration: maximum follow-up changed from 2.5 years to 2 years

9.0 (10 August 2016)	• Change of trial end date to 31 August 2017
	• Section 1: protocol summary
	  ○ Population: trial population changed to up to 1650 patients
	  ○ Study Centres and Distribution: amended to 19 neurosurgical wards across the UK and the Republic of Ireland
	
	Trial duration: amended the duration to 'utilising a recruitment period of 4 years, 2 months'

10.0 (11 August 2017)	• Section 4.1 changed to: *Time to failure of the first VPS due to infection. Infection will be classified as in section 8.2. 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 removed from the analysis altogether* • Section 4.2: addition of 'Time to removal of the first VPS due to suspected infection'
11.0 (5 April 2018)	Section added to the protocol to access HES data for patients with a Welsh postcode
13.0 (25 September 2018)	• Trial end date changed to 31 January 2019

HES, Hospital Episode Statistics; IIH, idiopathic intracranial hypertension.

Exclusion criteria

Patients with the following characteristics were excluded from the trial:

- previous indwelling ventricular or lumbar peritoneal or atrial shunt
- active and ongoing CSF or peritoneal infection (previously infected cases were allowed once they were clear of infection)
- multiloculated hydrocephalus requiring multiple VPS or neuroendoscopy
- ventriculoatrial or ventriculopleural shunt planned
- allergy to antibiotics associated with the antibiotic shunt
- allergy to silver.

Recruitment procedure

Screening

Screening was performed daily by clinical staff or the designated research nurse (throughout this report, 'research nurse' means either the research nurse or someone who has been delegated that duty) to identify potentially eligible patients. This was carried out on the daily ward rounds or at an appropriate time point, depending on the clinical setting.

All patients having a first VPS for hydrocephalus of any aetiology (including IIH) were screened for eligibility and recorded on the screening log. Reasons for non-recruitment were documented (e.g. not eligible, declined consent) and the information was used for monitoring purposes.

Informed consent

Eligible patients were provided with patient information sheets. In the case of children or adults who lacked mental capacity to consent, the parents, consultee or legal representative were approached to discuss participation. When feasible, this was at a clinic visit prior to admission. The research nurse gave the family sufficient time to discuss the trial and to decide whether or not to consent to trial entry.

Patients were eligible to be randomised to the trial if written consent was provided by the patient, parent, legal representative or consultee.

Randomisation, concealment and blinding

Patients were randomised to standard silicone or antibiotic- or silver-impregnated VPS catheters in a ratio of 1 : 1 : 1 in random permuted blocks of three and six. The randomisation sequence was generated by an independent statistician and was stratified by neurosurgical unit, age group (adult or paediatrics was defined according to unit practice) and envelope storage room within the neurosurgical unit. Randomisation was undertaken in the operating theatre at the time when the VPS was required. Pressure-sealed envelopes were opaque and tamper-proof: they were opened by tearing perforated edges. Patients and a central review panel, but not surgeons or operating staff, were blinded to the type of VPS inserted. VPS type was not recorded in the operating record and was not disclosed outside the operating room. Training on non-disclosure of VPS type was provided to all investigators. All VPS types were medical devices used in accordance with the manufacturer's instructions for their intended purpose.

Trial assessments

Table 2 provides the schedule of trial assessments. Participants were followed up for a minimum of 6 months and a maximum of 2 years, dependent on their randomisation date.

Data collection

Data were collected on paper-based case report forms (CRFs) completed by centre staff who were authorised to do so and returned to the Liverpool Clinical Trials Centre (LCTC) Clinical Trials Unit (CTU).

TABLE 2 Trial assessments

	Time point									
	Screening	Baseline[a] (pre-operative assessment)	Randomisation (first surgery)	Early post-operative assessment	First routine post-operative assessment[b]	12-weekly follow up assessment	Subsequent routine post-operative assessment(s)	End-of-trial telephone call	Unscheduled visit/admission	Shunt revision/ removal
Informed consent[c]	✗									
Assessment of eligibility criteria	✗	✗	✗							
Review of relevant medical history	✗	✗								
Collect demographic data	✗	✗								
Review of concomitant medications		✗	✗	✗	✗	✗	✗	✗	✗	✗
Weight		✗								
Heart rate		✗		✗					(✗)	
Head circumference		(✗)		(✗)	(✗)		(✗)		(✗)	
Neurological assessment (Glasgow Coma Scale)		✗		✗					(✗)	
Temperature				✗					(✗)	
Randomisation			✗							
Trial intervention			✗							✗
Wound check				✗	(✗)		(✗)		(✗)	
CSF sample taken			✗[d]						(✗[e])	✗[d]

continued

TABLE 2 Trial assessments (*continued*)

	Time point									
	Screening	Baseline[a] (pre-operative assessment)	Randomisation (first surgery)	Early post-operative assessment	First routine post-operative assessment[b]	12-weekly follow up assessment	Subsequent routine post-operative assessment(s)	End-of-trial telephone call	Unscheduled visit/admission	Shunt revision/ removal
Additional CSF and blood taken for substudy			(✗)							(✗)
CSF results reviewed				✗[f]					(✗)	
Health economics questionnaire		✗		✗		✗[g]		✗		
Health service diary				✗		✗		✗		
Post-operative CT/MRI				(✗)	(✗)		(✗)		(✗)	
Assessment of AEs				✗	✗	✗	✗	✗	✗	✗

AE, adverse event; CT, computerised tomography; MRI, magnetic resonance imaging.

a At baseline, all procedures were carried out before the trial intervention.

b The schedule of post-operative follow-up visits was dependent on the trust's post-operative follow-up procedure, and the participant's clinical condition.

c Informed consent should have always been sought prior to trial intervention. The exception to this rule is adults lacking capacity to consent. If an adult lacking capacity regained capacity at any point during the trial, informed consent should have been sought.

d The CSF sample was taken during surgery.

e The CSF sample was taken using a CSF tap or lumbar puncture.

f The results were reviewed (and the microbiology form updated) within 72 hours of surgery, even if the patient had been discharged before the results were available. If the results indicated a CSF infection, patients were only followed up for safety (until 48 hours after VPS removal).

g The health economics questionnaires were completed during the first 3-monthly follow-up telephone call only.

Note

(✗), as appropriate: data measurements not taken for all participants.

Participants were issued with diaries to record their health-care utilisation every 12 weeks and administered questionnaires to measure quality of life. A planned analysis of data from NHS Digital could not be achieved as the sponsor was unable to meet NHS Digital requirements for obtaining Hospital Episode Statistics data within the project timeline. Electronic health-care data were therefore obtained from Patient-Level Information and Costing Systems (PLICS).

Data were collected at baseline, randomisation, the peri-operative assessment, the early post-operative assessment, the first routine post-operative assessment and the subsequent post-operative assessment, and at the time points described in the remainder of this section.

The 12-weekly follow-up assessment

The 12-weekly follow-up was conducted face to face if there was a routine appointment scheduled at the same time point; if not, the follow-up was conducted by telephone. The following data were recorded:

- related adverse events (AEs)
- concomitant medications
- pregnancy.

At the first 12-week assessment, the research nurse completed the relevant quality-of-life questionnaire (*Table 3*) with the participant over the telephone.

Unscheduled visit/admission assessment

The 'unscheduled visit/admission' CRF was completed for any non-routine attendance at the treating neurosurgical centre and the following data were recorded:

- source of unscheduled visit
- reason for return
- physical examination
- microbiology
- blood samples
- imaging
- wound check
- CSF leak
- related AEs
- concomitant medications
- pregnancy
- outcome of visit.

Shunt revision/removal

If a patient was admitted for a clean VPS revision (for mechanical shunt failure, functional shunt failure or failure due to the patient) or removal (for suspected infection), the following data were recorded:

- surgery details (separate sections for revision/removal)
- surgeon details
- CSF sample details (including samples for substudies, if patient is taking part)
- related AEs
- concomitant medications.

In addition, the shunt surgery log was completed for all surgeries that took place after the initial surgery when the randomised shunt was inserted.

For instances in which the shunt was removed for suspected infection, concomitant medications were reported up until 14 days after removal and the patient was reviewed for 48 hours for AEs and serious adverse events (SAEs).

TABLE 3 Health economics questionnaires

	Completed by	
Age (years)	Participant	Parent/carer
< 5	None administered	None administered
5 to < 8	None administered	HOQ (parent version)
		EQ-5D-3L (proxy 1)[a]
8 to < 18	HOQ (child version)	EQ-5D-3L (proxy 1)[a] (including EQ-VAS)
	EQ-5D-Y (including EQ-VAS)	
≥ 18 years	EQ-5D-3L (including EQ-VAS)	EQ-5D-3L (proxy 1)[b] (including EQ-VAS)

EQ-5D-3L, EuroQol-5 Dimensions, three-level version; EQ-5D-Y, EuroQol-5 Dimensions Youth; EQ-VAS, EuroQol Visual Analogue Scale; HOQ, Hydrocephalus Outcome Questionnaire.
a If 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 at subsequent time points.
b 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.

Quality of life and health service diaries

Questionnaires

The EuroQol-5 Dimensions, three-level version (EQ-5D-3L), the EQ-5D-3L Proxy, the EuroQol-5 Dimensions Youth (EQ-5D-Y) (youth version), the EuroQol Visual Analogue Scale (EQ-VAS) or the Hydrocephalus Outcome Questionnaire (HOQ)[25] were administered to participants, or their parent or carer, according to age (see *Table 3*) to measure participants' health outcome and quality of life.

Resource use questionnaires were given/posted out to participants every 12 weeks for participants to complete and return to the centres 12 weeks later. Participants were reminded by the research nurse to return diaries during the 12-weekly assessments if they had not done so.

Measures

Primary outcome

The primary outcome was time to VPS infection as assessed by the central review panel, which comprised the chief investigator (or delegate for participants treated at the centre of the chief investigator) and a microbiologist, who were masked to participant allocation. Each VPS revision was classified as infection or no infection. Infections were further classified as definite (culture positive), probable (culture uncertain), probable (culture negative), possible (culture uncertain) or VPS deep incisional infection according to the microbiological samples sent and the criteria in the trial protocol.

Secondary outcomes

Secondary outcomes were as follows:

- time to removal of the first VPS due to suspected infection, as defined by the treating surgeon at the time of revision
- time to VPS failure of any cause (infection, mechanical, patient or functional)
- reason for failure (infection, mechanical, patient, functional) as classified by the treating surgeon
- types of bacterial VPS infection (organism, antibiotic resistances)
- time to VPS infection following first clean (non-infected) revision, as classified by the central review panel
- quality of life measured using the HOQ[25]
- health economics outcomes – incremental cost per VPS failure averted and quality-adjusted life-year (QALY) gained, measured using the EQ-5D-3L, EQ-5D-3L Proxy and EQ-5D-Y questionnaires.

Data on complications and SAEs were also collected.

Sample size

The sample size for the primary outcome was calculated using the Pintilie[26] method with the following assumptions: (1) failure for infection was the event of interest, with all other reasons for failure a competing risk, (2) the rate of infection was 8% in the standard silicone arm[14] and 4% in the impregnated shunt catheter arms, (3) the competing risk event rate was 30% and (4) there was a 5% loss to follow-up. A total sample size of 1200 participants with 119 events demonstrated good statistical power (88%), with leverage for a lower event rate if required (*Table 4*). A feasibility study conducted in trial centres for 1 month indicated an annual eligible participant figure of 1200; a conservative estimate of consent of 50% suggested that the sample size would be achievable within a 2-year recruitment period, with participants followed up for a minimum of 6 months.

An interim analysis was planned after 50% of the total events had been observed, using the Haybittle–Peto method.[27]

Monitoring of the infection rate during the trial demonstrated that the majority of events occur within 1 month of VPS insertion (i.e. they are not exponentially distributed), and that the rates of infection, competing risk and loss to follow-up were lower than expected. In January 2016, the Independent Data and Safety Monitoring Committee (IDSMC) reviewed the sample size calculations and recommended increasing recruitment to a target of 1606 participants with 101 events, to provide 80% power; the Trial Steering Committee (TSC) agreed and approved this change. The early occurrence of events and assumption of exponential risk were managed in the Pintilie[26] method assumptions by reducing the accrual and follow-up rates to 1 month.

Statistical methods

The main features of the analysis plan were specified in the protocol; the final analyses were undertaken according to a more detailed and prespecified statistical analysis plan (see *Report Supplementary Material 1*), consistent with the protocol.

Efficacy outcomes were analysed according to the intention-to-treat principle as far as practically possible; AEs and SAEs were reported according to the type of VPS in situ. A Bonferroni adjustment[28] was made to allow for multiple comparisons (antibiotic-impregnated vs. standard VPS, and silver-impregnated vs. standard VPS) and a 2.5% level of statistical significance and 97.5% CIs were used throughout.

Outcomes with infection as the event of interest used Fine and Gray[29] survival regression models with cause-specific hazard ratios (csHRs) and subdistribution hazard ratios (sHRs) presented.[30,31] Cox regression models were used to analyse time to VPS failure due to any cause. Reason for VPS failure is presented

TABLE 4 Sample size parameters allowing for variation in observed event rate

Infection rate				
Control arm	Treated arms	HR	Power (%)	Total sample size (across the three trial arms) (*n*)
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

descriptively (see *Chapter 3*, *Secondary outcome 3: reason for shunt failure*) and with a chi-squared test. Types of organisms and their resistances and sensitivities are presented descriptively in *Chapter 3*, *Secondary outcome 4: types of bacterial infection*. Quality-of-life outcomes were analysed using mixed models. All survival models were adjusted for the age category of the recruiting centre (paediatric or adult), with adult centres further categorised by age > 65 years. A post hoc analysis was conducted that explored revision rates, and reason for revision, by aetiology of the hydrocephalus, type of valve and operative approach. Results of the post hoc analysis are presented descriptively in *Chapter 3*, *Post hoc analyses*.

Primary outcome and safety analyses were validated by independent programming from the point of raw data extraction. All analyses were carried out with SAS® software version 9.4 with SAS/STAT package 14.3 (SAS Institute Inc, Cary, NC, USA).

Patient and public involvement

The trial team collaborated with young people and parent contributors throughout the trial:

- Advice was sought from the Medicines for Children Research Network Young Person's Group on the content and presentation of patient information leaflets and consent forms. The Medicine for Children's Research Network is a division of the LCTC, part of the Liverpool Clinical Trials Collaborative.
- Three lay members were invited at the trial outset to join the Trial Management Group (TMG) and TSC; one was recruited to be a member of the TMG.
- Members of the TMG, including the lay member, met via teleconference with the patient and public involvement co-ordinator for the LCTC early in the trial to establish the timings for return of the patient-completed diaries and to identify ways to maximise the return rate of these diaries. They decided that it would be appropriate for the centre team to contact the participant or representative via telephone every 3 months as a reminder to complete and return the diaries.
- The charity Shine (Spina bifida Hydrocephalus Information Networking Equality) was continually supportive of the trial. A Shine representative was a member of the TSC.

Trial oversight and role of funders

The TMG, comprising the chief investigator, other lead investigators (clinical and non-clinical) and members of the LCTC CTU, was responsible for the day-to-day running and management of the trial. The membership of the oversight committees was suggested by members of the TMG to the trial funders and appointed by the funders with their constitution following funder requirements.

The TSC consisted of an independent chairperson, an independent microbiologist, a lay representative from the Shine charity and an independent statistician. The chief investigator was a non-independent member of the TSC. The role of the TSC was as the executive decision-making committee, considering the recommendations of the IDSMC. Monitoring reports viewed by the TSC were not split by treatment group.

The IDSMC consisted of an independent chairperson, plus two independent members: an expert in the field of microbiology and an expert in medical statistics. The IDSMC was responsible for reviewing and assessing recruitment, interim monitoring of safety and effectiveness, trial conduct and external data. The IDSMC provided recommendations to the TSC concerning the continuation of the trial and viewed accumulating data split by treatment group.

All protocol amendments were approved by the funder prior to ethics submission.

Chapter 3 Results

Recruitment and screening

The trial opened to recruitment on 26 June 2013 and closed on 9 October 2017.

During this period, 3505 patients were screened for eligibility, of whom 1605 patients were randomised from 21 centres. One patient was randomised twice and their data contributed from the first randomisation only. See *Appendix 2*, *Figure 8* and *Tables 32* and *33*, for screening and recruitment data.

Screened patients who were not randomised fell into four categories: the patient did not meet eligibility criteria ($n = 1020$); the patient was eligible but consent was not sought ($n = 435$); consent was sought but the patient declined ($n = 369$); and the patient was not randomised for another reason ($n = 67$). The overall consent rate in patients who were approached for participation was 82%.

A Consolidated Standards of Reporting Trials (CONSORT) flow diagram illustrating the pathway of patients from screening to consent and randomisation is provided in *Figure 2*.

Baseline comparability

The three groups were similar in their baseline characteristics (*Table 5*) and baseline risk assessment (*Table 6*). Approximately 40% of all participants were paediatric patients, with one-quarter of all participants being aged < 1 year at the time of randomisation. The factors recorded on the baseline risk assessment were those regarded within the literature as being associated with a high risk of infection.

Retention and adherence

Table 7 summarises compliance with the randomly allocated shunt. Of the 1605 participants randomised, four (0.2%) had no VPS inserted and 16 (1%) received a different VPS to the one that was randomly allocated. Reasons for participants having an alternative trial VPS inserted or no VPS are provided in *Appendix 2*, *Tables 35* and *36*, respectively. Participants receiving no VPS were excluded from the intention-to-treat population; for the safety analysis, participants were analysed according to the VPS received. The analysis sets are summarised in *Table 8*.

In total, 53 (3.3%) randomised participants withdrew from the trial. No participants withdrew consent to use collected data. *Table 9* summarises the level of and reasons for withdrawal.

Unblinding

A total of 32 participants from 10 centres were unblinded during the course of the trial.

Unblinding could be accidental or intentional. Accidental unblinding was defined as an unplanned occurrence; for example, the allocation was incorrectly recorded in the participant notes. Intentional unblinding occurred

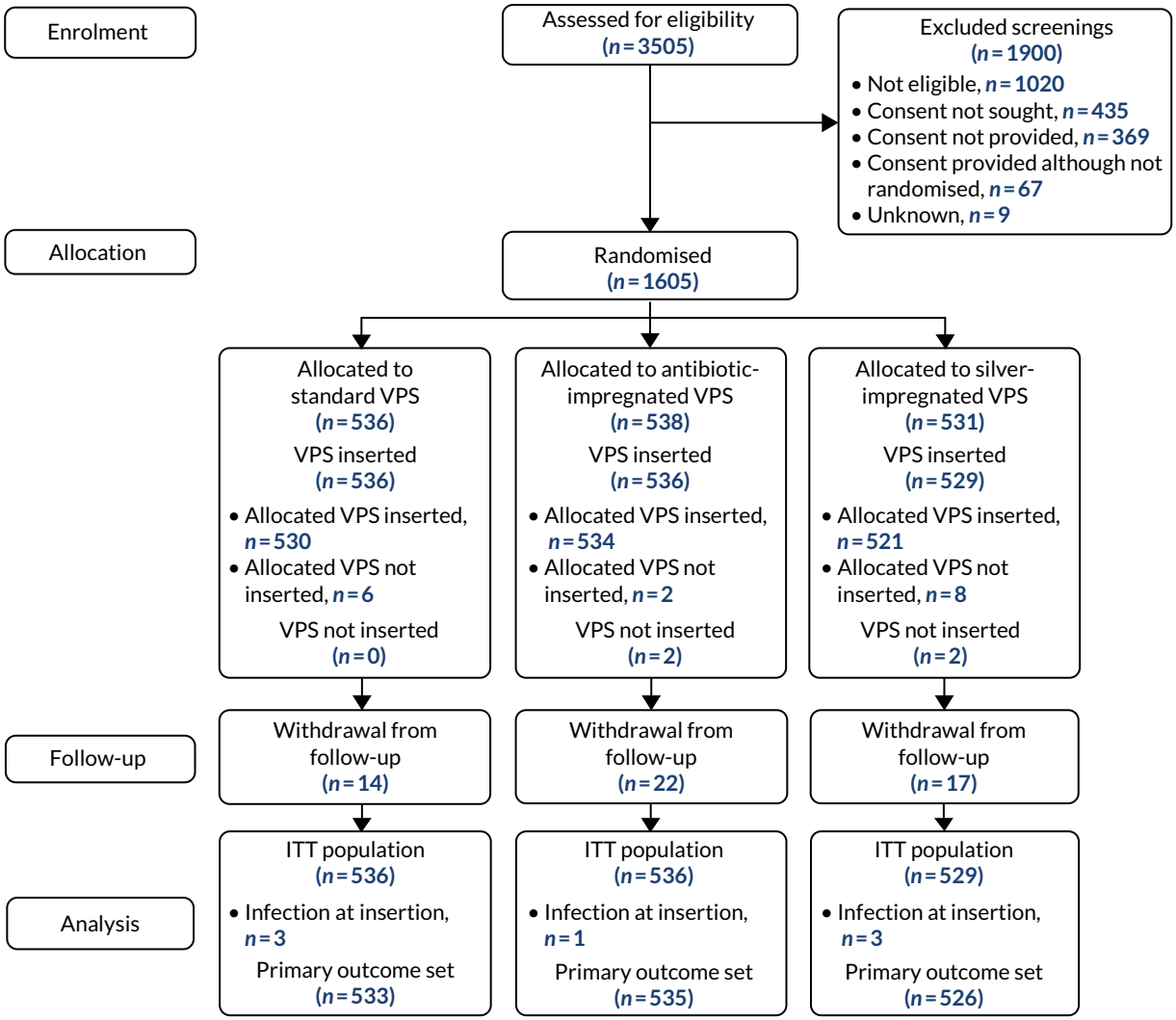

FIGURE 2 The CONSORT flow chart. ITT, intention to treat.

TABLE 5 Participant characteristics and physical examination

Characteristic	Trial group			Total
	Standard VPS	Antibiotic-impregnated VPS	Silver-impregnated VPS	
Number randomised	536	538	531	1605
Age (years)				
n (*n* missing)	536 (0)	538 (0)	531 (0)	1605 (0)
Median (IQR)	42.5 (0.8–69.7)	43.9 (1.1–70.8)	41.1 (0.5–68.8)	42.5 (0.8–69.6)
Minimum, maximum	0.0, 90.3	0.0, 88.9	0.0, 91.1	0.0, 91.1
Age category				
n (*n* missing)	536 (0)	538 (0)	531 (0)	1605 (0)
Paediatric, *n* (%)	200 (37.3)	201 (37.4)	198 (37.3)	599 (37.3)
Adult (≤ 65 years), *n* (%)	174 (32.5)	156 (29.0)	172 (32.4)	502 (31.3)
Adult (> 65 years), *n* (%)	162 (30.2)	181 (33.6)	161 (30.3)	504 (31.4)

TABLE 5 Participant characteristics and physical examination (*continued*)

Characteristic	Trial group			Total
	Standard VPS	Antibiotic-impregnated VPS	Silver-impregnated VPS	
Sex				
n (*n* missing)	535 (1)	538 (0)	531 (0)	1605 (0)
Female, *n* (%)	246 (46.0)	260 (48.3)	282 (53.1)	788 (49.1)
Male, *n* (%)	289 (54.0)	278 (51.7)	249 (46.9)	816 (50.9)
Weight (kg)				
n (*n* missing)	523 (13)	523 (15)	515 (16)	1561 (44)
Median (IQR)	64.0 (8.8–82.7)	63.0 (9.6–82.0)	63.0 (7.3–80.0)	63.1 (8.7–81.5)
Minimum, maximum	1.1, 161.0	0.8, 163.0	1.3, 145.0	0.8, 163.0
Heart rate (BPM)				
n (*n* missing)	530 (6)	532 (6)	521 (10)	1583 (22)
Median (IQR)	84 (72–120)	85 (70–116.5)	84 (70–124)	84 (70–121)
Minimum, maximum	48, 190	44, 185	43, 185	43, 190

BPM, beats per minute; IQR, interquartile range.

TABLE 6 Baseline risk indicators

Risk indicator	Trial group			Total
	Standard VPS (*N* = 536)	Antibiotic-impregnated VPS (*N* = 538)	Silver-impregnated VPS (*N* = 531)	
Previous *Staphylococcus aureus* infection (requiring treatment in the previous 6 months)				
n (*n* missing)	534 (2)	538 (0)	531 (0)	1603 (2)
Yes, *n* (%)	18 (3.4)	15 (2.8)	16 (3.0)	49 (3.1)
No, *n* (%)	516 (96.6)	523 (97.2)	515 (97.0)	1554 (96.9)
Active skin/wound infection				
n (*n* missing)	534 (2)	538 (0)	530 (1)	1602 (3)
Yes, *n* (%)	7 (1.3)	8 (1.5)	5 (0.9)	20 (1.2)
No, *n* (%)	527 (98.7)	530 (98.5)	525 (99.1)	1582 (98.8)
MRSA infection in the previous 6 months				
n (*n* missing)	535 (1)	537 (1)	529 (2)	1601 (4)
Yes, *n* (%)	6 (1.1)	4 (0.7)	5 (0.9)	15 (0.9)
No, *n* (%)	529 (98.9)	533 (99.3)	524 (99.1)	1586 (99.1)
Pre-term at birth				
n (*n* missing)	513 (23)	522 (16)	505 (26)	1540 (65)
Yes, *n* (%)	78 (15.2)	82 (15.7)	76 (15.0)	236 (15.3)
No, *n* (%)	435 (84.8)	440 (84.3)	429 (85.0)	1304 (84.7)

continued

TABLE 6 Baseline risk indicators (*continued*)

Risk indicator	Trial group			Total
	Standard VPS (*N* = 536)	Antibiotic-impregnated VPS (*N* = 538)	Silver-impregnated VPS (*N* = 531)	
Abdominal surgery in the previous month				
n (*n* missing)	533 (3)	538 (0)	531 (0)	1602 (3)
Yes, *n* (%)	3 (0.6)	3 (0.6)	8 (1.5)	14 (0.9)
No, *n* (%)	530 (99.4)	535 (99.4)	523 (98.5)	1588 (99.1)
Tracheotomy				
n (*n* missing)	534 (2)	538 (0)	531 (0)	1603 (2)
Yes, *n* (%)	32 (6.0)	13 (2.4)	21 (4.0)	66 (4.1)
No, *n* (%)	502 (94.0)	525 (97.6)	510 (96.0)	1537 (95.9)
Percutaneous endoscopic gastrostomy				
n (*n* missing)	534 (2)	538 (0)	531 (0)	1603 (2)
Yes, *n* (%)	14 (2.6)	7 (1.3)	15 (2.8)	36 (2.2)
No, *n* (%)	520 (97.4)	531 (98.7)	516 (97.2)	1567 (97.8)
CSF leak in the previous month				
n (*n* missing)	534 (2)	538 (0)	531 (0)	1603 (2)
Yes, *n* (%)	57 (10.7)	51 (9.5)	35 (6.6)	143 (8.9)
No, *n* (%)	477 (89.3)	487 (90.5)	496 (93.4)	1460 (91.1)
EVD in previous 3 months				
n (*n* missing)	532 (4)	538 (0)	531 (0)	1601 (4)
Yes, *n* (%)	105 (19.7)	95 (17.7)	90 (16.9)	290 (18.1)
No, *n* (%)	427 (80.3)	443 (82.3)	441 (83.1)	1311 (81.9)

MRSA, methicillin-resistant *Staphylococcus aureus*.

TABLE 7 Compliance with treatment

Randomised VPS	Number randomised	Allocated VPS inserted, *n* (%)	Other VPS inserted, *n* (%)	No VPS inserted, *n* (%)
Standard	536	530 (98.9)	6 (1.1)	0 (0.0)
Antibiotic impregnated	538	534 (99.3)	2 (0.4)	2 (0.4)
Silver impregnated	531	521 (98.1)	8 (1.5)	2 (0.4)
Total	1605	1585 (98.8)	16 (1.0)	4 (0.2)

TABLE 8 Data sets analysed

Population	Trial group, *n* (%)			Total, *n* (%)
	Standard VPS	Antibiotic-impregnated VPS	Silver impregnated-VPS	
Randomised	536 (33.4)	538 (33.5)	531 (33.1)	1605 (100)
Intention to treat	536 (33.5)	536 (33.5)	529 (33.0)	1601 (99.8)
Safety	531 (33.2)	545 (34.0)	525 (32.8)	1601 (99.8)

TABLE 9 Withdrawal summary

Withdrawal summary	Trial group, *n* (%)			Total, *n* (%)
	Standard VPS	Antibiotic-impregnated VPS	Silver-impregnated VPS	
Randomised	536 (33.4)	538 (33.5)	531 (33.1)	1605 (100)
Withdrawals	14 (2.6)	22 (4.1)	17 (3.2)	53 (3.3)
Level of withdrawal				
Withdrawal of data[a]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Consent revoked to use data collected	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawal from follow-up[b]	14 (2.6)	22 (4.1)	17 (3.2)	53 (3.3)
Consent revoked for trial-specific data to be collected	6 (1.1)	9 (1.7)	9 (1.7)	24 (1.5)
Consent revoked for any trial data to be collected	8 (1.5)	13 (2.4)	8 (1.5)	29 (1.8)
Consent revoked for additional substudy samples to be taken	3 (0.6)	1 (0.2)	1 (0.2)	5 (0.3)
Reasons for withdrawal				
Unexpected related AE or SAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Burden of additional trial data collection	4 (0.7)	9 (1.7)	5 (0.9)	18 (1.1)
Other	10 (1.9)	16 (3)	13 (2.4)	39 (2.4)
Decision for withdrawal made by				
Participant (aged ≥ 16 years)	1 (0.2)	5 (0.9)	5 (0.9)	11 (0.7)
Parent/guardian/consultee	8 (1.5)	12 (2.2)	7 (1.3)	27 (1.7)
Clinical	4 (0.7)	5 (0.9)	5 (0.9)	14 (0.9)
None listed	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)

a Withdrawal of consent: revoke consent to use data collected.
b Withdrawal from follow-up: data up to the time of withdrawal will be included in the analysis.

when the unblinding envelope was opened; for example, if a patient was transferred to another hospital and staff needed to be aware of their allocation. Twenty-five participants from eight centres were accidentally unblinded and seven participants from four centres were intentionally unblinded. *Table 10* summarises unblinding events, both overall and by randomised VPS.

TABLE 10 Summary of unblinding events

Type of unblinding	Level	Trial group (*n*)			Total (*n*)
		Standard VPS	Antibiotic-impregnated VPS	Silver-impregnated VPS	
Accidental	Patient	10	5	10	25
	Centre	6	3	7	8
Intentional	Patient	1	1	5	7
	Centre	1	1	4	4
Total	Patient	11	6	15	32
	Centre	7	4	4	10

Protocol deviations

Prespecified protocol deviations are summarised in *Appendix 2*, *Table 37*. The most common major protocol deviation was that shunt components were not taken for culture at shunt revision/removal ($n = 320$, 19.9%). This was not routine practice in many units, and the impact of this deviation on the identification of infections for the primary outcome was mitigated by the low numbers of missing CSF at revision ($n = 14$), as CSF analysis and culture was the primary factor used for defining shunt infection (not culture of the shunt tubing or components).

Antibiotic sensitivity data were not returned on many isolates.

Primary outcome: time to ventriculoperitoneal infection as assessed by the central review panel

The primary outcome was time to VPS infection, as assessed by the central review panel.

Four participants received no shunt and seven participants had an infection at insertion; these participants were excluded from the primary analysis set (see *Figure 2*).

A summary of the first VPS revisions and infections among participants in the primary intention-to-treat analysis set is provided in *Table 11*. The overall revision rate of first VPS was 25% (398/1594), and was approximately equal between each of the three VPS groups.

TABLE 11 Summary of first VPS revisions and infections as classified by the central committee

Primary VPS revisions	Trial group, *n* (%)			
	Standard VPS ($N = 536$)	Antibiotic-impregnated VPS ($N = 538$)	Silver-impregnated VPS ($N = 531$)	Total, *n* (%)
Summary of surgeries				
Eligible for primary outcome[a]	533 (99.4)	535 (99.8)	526 (99.4)	1594 (99.6)
No VPS removal/revision	403 (75.6)	403 (75.3)	390 (74.1)	1196 (75.0)
VPS removal/revision (for any cause)	130 (24.4)	132 (24.7)	136 (25.9)	398 (25.0)
Reason for revision as classified by central review				
Reason for revision				
Revision for infection	32 (6.0)	12 (2.2)	31 (5.9)	75 (4.7)
Revision for other reason (no infection)	98 (18.4)	120 (22.4)	105 (20.0)	323 (20.3)
Type of infection				
VPS CSF or peritoneal infection				
Definite: culture positive	22 (68.8)	6 (50.0)	25 (80.6)	53 (70.7)
Probable: culture uncertain	1 (3.1)	0 (0.0)	2 (6.5)	3 (4.0)
Probable: culture negative	3 (9.4)	3 (25.0)	1 (3.2)	7 (9.3)
Possible: culture uncertain	1 (3.1)	0 (0.0)	1 (3.2)	2 (2.7)
Clinically classified infection[b]	1 (3.1)	0 (0.0)	0 (0.0)	1 (1.3)
VPS deep incisional infection	4 (12.5)	3 (25.0)	2 (6.5)	9 (12.0)

a Randomised participants who did not receive a VPS ($n = 4$) and had infection at time of insertion ($n = 7$) were excluded from the primary outcome set (see *Figure 2*).
b If the central review panel was unable to classify, an infection was classified by the operating surgeon on the CRFs. In one case, the committee could not classify and this was clinically classified as an infection.

All first revisions were classified as to whether or not the revision was for suspected infection by the central review panel. If there was insufficient information for the central review panel to classify an infection ($n = 1/398$; see *Table 11*), the clinical classification, as recorded on the CRFs by the treating surgeon, was used.

Of the total number of first revisions, 75 were classified infections (4.7%). The infection rate was approximately equal in the standard and silver-impregnated VPS arms (6.0% and 5.9%, respectively) and lowest in the antibiotic-impregnated VPS arm (2.2%). The time to infection was similar across all treatment arms {standard VPS arm: median 1 month [lower quartile (LQ)–upper quartile (UQ) 0–1.5 months]; antibiotic-impregnated VPS arm: median 1 month [LQ–UQ 0–2 months]; silver-impregnated VPS arm: median 1 months [LQ–UQ 0–1 months]}.

When compared with the standard VPS, antibiotic-impregnated VPSs decreased the risk of infection (csHR 0.38, 97.5% CI 0.18 to 0.80; $p < 0.01$) (*Table 12*). Silver-impregnated VPSs were comparable to standard VPSs (csHR 0.99, 97.5% CI 0.56 to 1.74; $p = 0.96$) (see *Table 12*). *Figure 3* displays the

TABLE 12 Estimates of csHRs and sHRs for first VPS revision for infection, as classified by the central review panel

Covariate	Infection, HR (97.5% CI); *p*-value	Competing risk, HR (97.5% CI); *p*-value
Cox: csHR		
VPS		
Standard	–	–
Antibiotic-impregnated	0.38[a] (0.18 to 0.80); < 0.01	1.22[b] (0.90 to 1.65); 0.15
Silver-impregnated	0.99[a] (0.56 to 1.74); 0.96	1.11[b] (0.81 to 1.51); 0.47
Age group		
Paediatric	–	–
Adult (≤ 65 years)	0.55[a] (0.31 to 0.97); 0.02	0.58[b] (0.44 to 0.77); < 0.01
Adult (> 65 years)	0.12[a] (0.04 to 0.34); < 0.01	0.28[b] (0.20 to 0.40); < 0.01
Fine–Gray: sHR		
VPS		
Standard	–	–
Antibiotic-impregnated	0.38[c] (0.18 to 0.80); < 0.01	1.26[d] (0.93 to 1.70); 0.08
Silver-impregnated	0.99[c] (0.56 to 1.72); 0.95	1.10[d] (0.81 to 1.50); 0.50
Age group		
Paediatric	–	–
Adult (≤ 65 years)	0.56[c] (0.32 to 0.99); 0.02	0.60[d] (0.45 to 0.80); < 0.01
Adult (> 65 years)	0.12[c] (0.04 to 0.35); < 0.01	0.30[d] (0.21 to 0.43); < 0.01

a Cause-specific HRs from multivariate Cox model with infection as event of interest and both VPS and age group as covariates.
b Cause-specific HRs from multivariate Cox model with competing risk (revision not for infection) as event of interest and both VPS and age group as covariates.
c Subdistribution HRs from multivariate Fine–Gray model with infection as event of interest, revision not for infection as a competing risk, and both VPS and age group as covariates.
d Subdistribution HRs from multivariate Fine–Gray model with competing risk (revision not for infection) as event of interest, infection as a competing risk, and both VPS and age group as covariates.

Notes
Follow-up time from first VPS summary statistics: $n = 1594$; median 22 months; LQ–UQ 10–24 months; minimum 0 months, maximum 24 months.
Time to infection from first VPS summary statistics: $n = 75$; median 1 month; LQ–UQ 0–1 months; minimum 0 months, maximum 21 months.

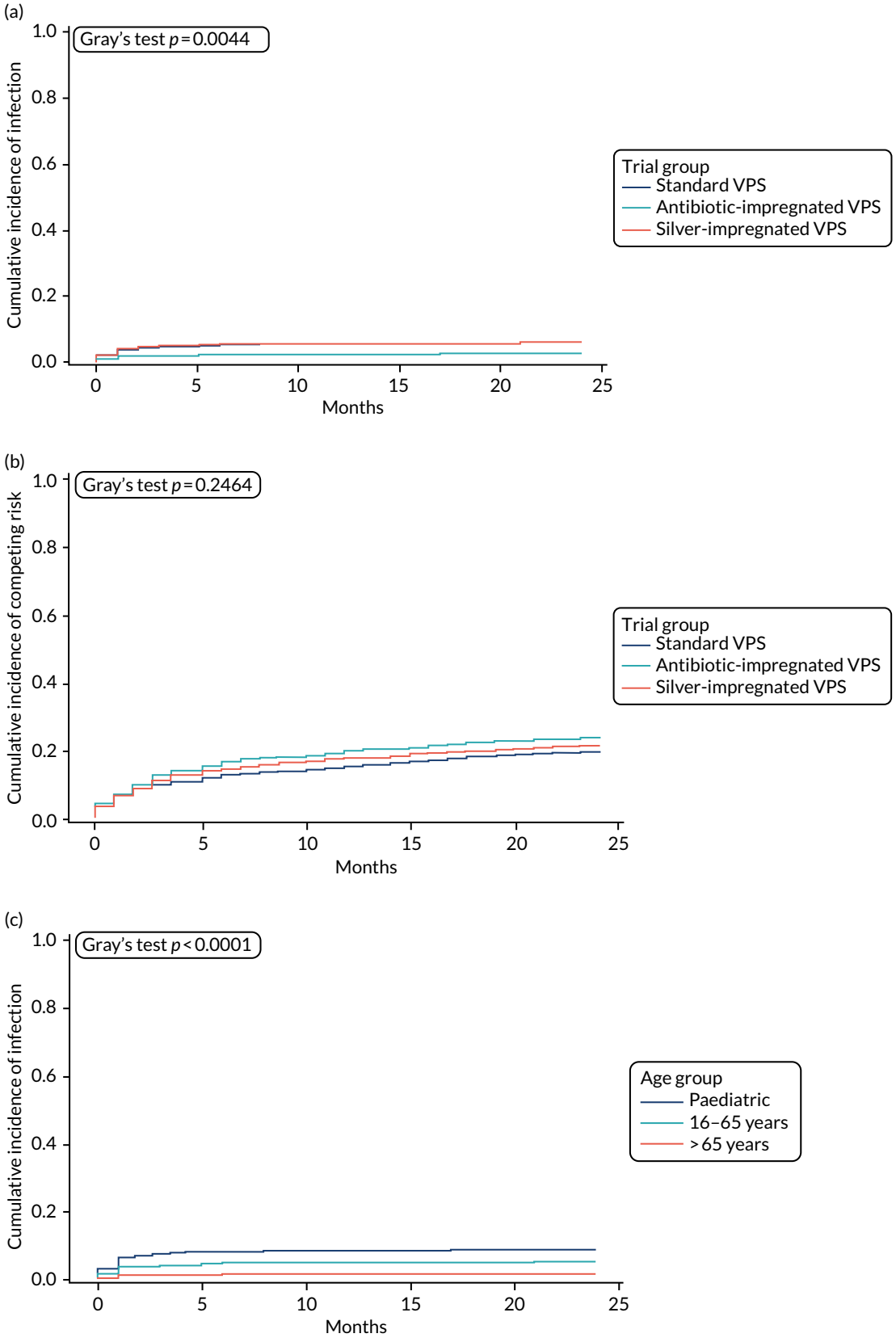

FIGURE 3 Cumulative incidence plots of revisions for infection and competing risk by VPS group and age group. (a) Infection by VPS group; (b) competing risk by VPS group; (c) infection by age group; and (d) competing risk by age group. (*continued*)

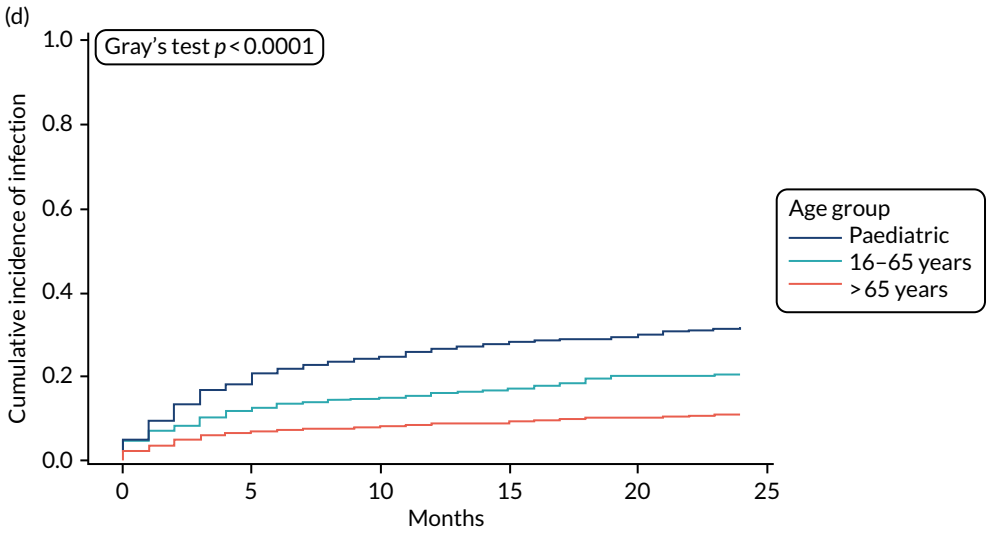

FIGURE 3 Cumulative incidence plots of revisions for infection and competing risk by VPS group and age group. (a) Infection by VPS group; (b) competing risk by VPS group; (c) infection by age group; and (d) competing risk by age group.

cumulative incidences of infection and no infection by VPS and age group. *Figure 4* displays the cumulative incidence plots of infection or no infection by VPS group, stratified by age group.

All revisions for infection were further classified by type, with the majority being classified as 'definite: culture positive' across all arms (standard VPS arm: 22/32, 68.8%; antibiotic-impregnated VPS arm: 6/12, 50%; silver-impregnated VPS arm: 25/31, 80.6%).

Secondary outcomes

Secondary outcome 1: time to removal of first ventriculoperitoneal shunt due to suspected infection as assessed by treating surgeon

This secondary outcome, time to removal of first VPS due to suspected infection, complemented the primary outcome of revision for infection classified by central review by defining revision for infection according to the treating surgeon, as reported on the CRFs.

Of the total number of revisions, 78 (4.9%) were classified as infections by the treating surgeon. As with the primary outcome, when revisions were centrally classified, the infection rate was approximately equal in the standard and silver-impregnated VPS arms (6.2% and 5.7%, respectively), and was lowest in the antibiotic-impregnated arm (2.8%) (*Table 13*).

When compared with the standard VPS, antibiotic-impregnated VPSs decreased the risk of infection (csHR 0.45, 97.5% CI 0.23 to 0.91; $p = 0.01$) (*Table 14*). Silver-impregnated VPSs were comparable to standard VPSs (csHR 0.93, 97.5% CI 0.53 to 1.64; $p = 0.77$) (see *Table 14*). *Appendix 2*, *Figure 9*, displays the cumulative incidences of infection and no infection by VPS and age group.

Secondary outcome 2: time to ventriculoperitoneal shunt failure due to any cause

The overall revision rate was 25.0% (398/1594), which was approximately equal between each of the three VPS groups (standard VPS arm: 130/533, 24.4%; antibiotic-impregnated VPS arm: 132/535, 24.7%; silver-impregnated VPS arm: 136/526, 25.9%) (see *Table 11*).

There was no significant difference for time to failure between the antibiotic-impregnated or silver-impregnated VPS arms when compared with the standard VPS arm (*Table 15*). *Figure 5* shows the Kaplan-Meier curve for time to VPS failure for any cause, split by VPS and age group.

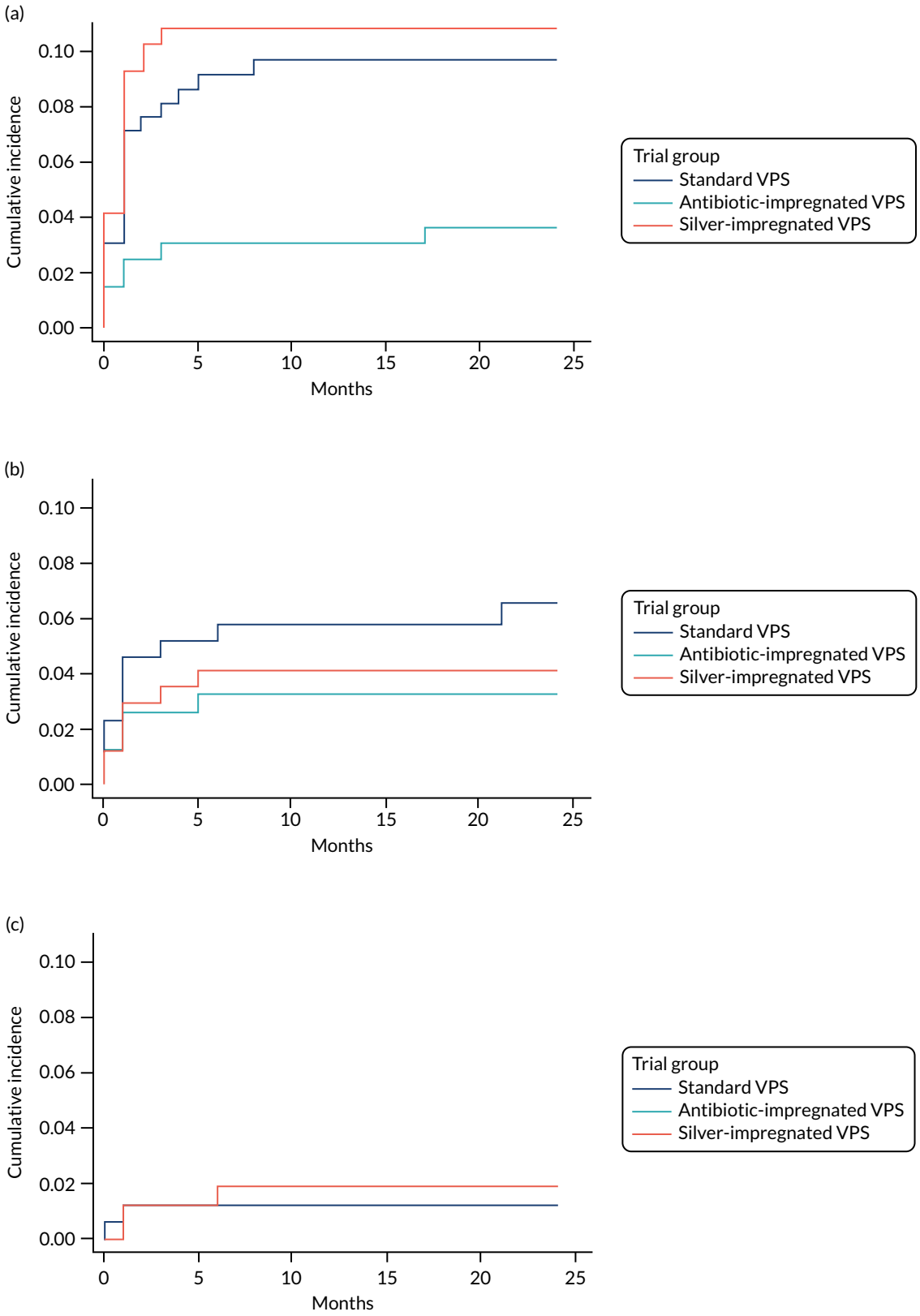

FIGURE 4 Cumulative incidence plots of revisions for infection and competing risk by VPS group, stratified by age group. (a) Infection in the paediatric group; (b) infection in those aged ≤ 65 years; (c) infection in those aged > 65 years; (d) competing risk in the paediatric group; (e) competing risk in those aged ≤ 65 years; and (f) competing risk in those aged > 65 years. (*continued*)

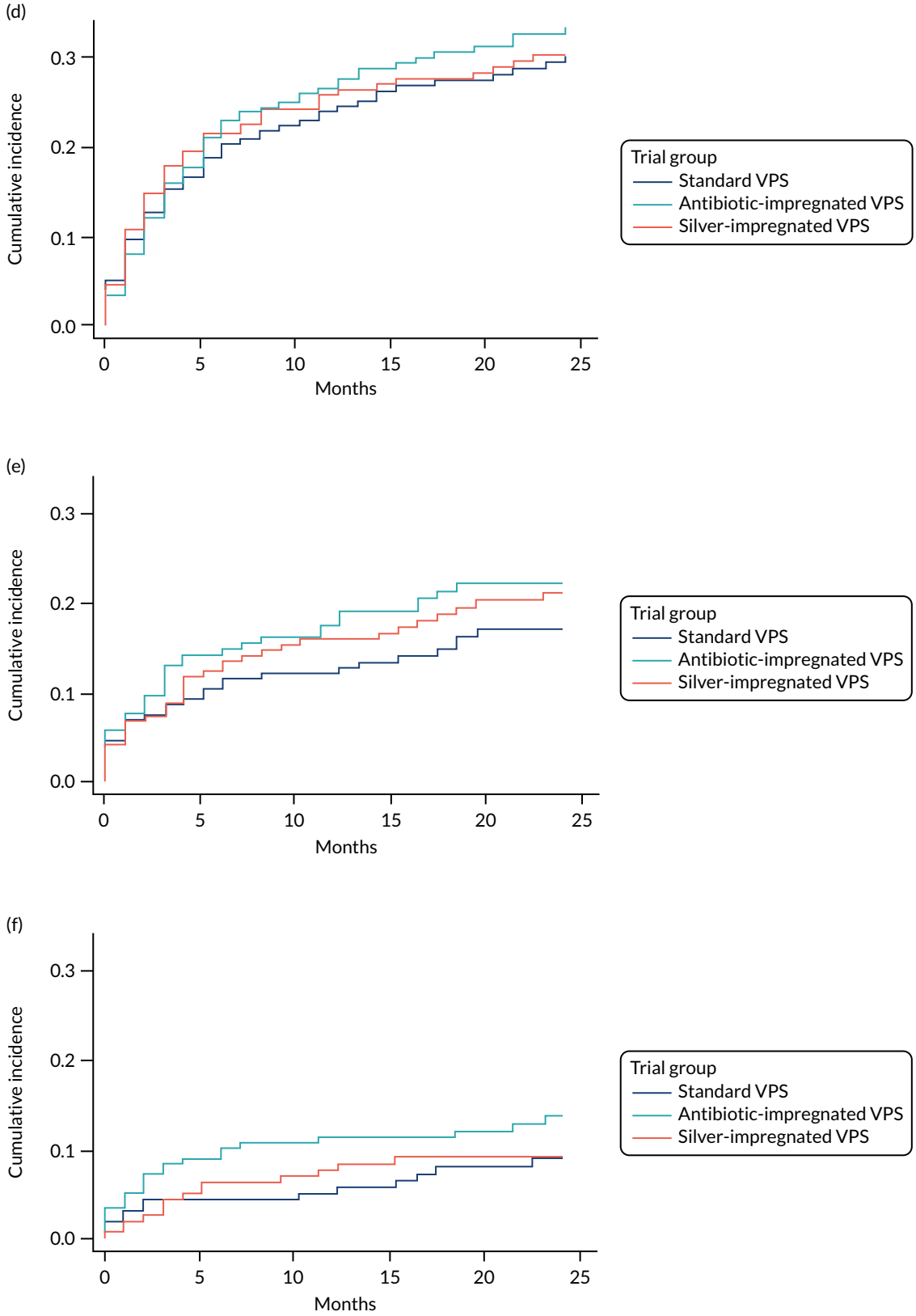

FIGURE 4 Cumulative incidence plots of revisions for infection and competing risk by VPS group, stratified by age group. (a) Infection in the paediatric group; (b) infection in those aged ≤ 65 years; (c) infection in those aged > 65 years; (d) competing risk in the paediatric group; (e) competing risk in those aged ≤ 65 years; and (f) competing risk in those aged > 65 years.

TABLE 13 Summary of VPS revisions for infection, as classified by the treating surgeon

Reason for revision	Trial group, *n* (%)			Total, *n* (%)
	Standard VPS	Antibiotic-impregnated VPS	Silver-impregnated VPS	
VPS removal/revision (for any cause)	130 (100)	132 (100)	136 (100)	398 (100)
Suspected infection	33 (6.2)	15 (2.8)	30 (5.7)	78 (4.9)
Revision for other reason (no infection)	97 (18.2)	117 (21.9)	106 (20.2)	320 (20.1)

TABLE 14 Estimates for csHRs and sHRs for VPS revisions for infection, as classified by the treating surgeon

Covariate	Infection, HR (97.5% CI); *p*-value	Competing risk, HR (97.5% CI); *p*-value
Cox: csHR		
VPS		
Standard	–	–
Antibiotic impregnated	0.45[a] (0.23 to 0.91); 0.01	1.20[b] (0.88 to 1.63); 0.19
Silver impregnated	0.93[a] (0.53 to 1.64); 0.77	1.13[b] (0.82 to 1.54); 0.39
Age group		
Paediatric	–	–
Adult (≤ 65 years)	0.51[a] (0.29 to 0.91); < 0.01	0.59[b] (0.44 to 0.79); < 0.01
Adult (> 65 years)	0.11[a] (0.04 to 0.31); < 0.01	0.29[b] (0.20 to 0.41); < 0.01
Fine–Gray: sHR		
VPS		
Standard	–	–
Antibiotic-impregnated	0.45[c] (0.23 to 0.91); 0.01	1.24[d] (0.92 to 1.68); 0.11
Silver-impregnated	0.92[c] (0.53 to 1.61); 0.74	1.13[d] (0.83 to 1.54); 0.38
Age group		
Paediatric	–	–
Adult (≤ 65 years)	0.53[c] (0.30 to 0.93); 0.01	0.61[d] (0.46 to 0.81); < 0.01
Adult (> 65 years)	0.12[c] (0.04 to 0.33); < 0.01	0.31[d] (0.21 to 0.44); < 0.01

a Cause-specific HRs from multivariate Cox model with infection as event of interest and both VPS and age group as covariates.
b Cause-specific HRs from multivariate Cox model with competing risk (revision not for infection) as event of interest and both VPS and age group as covariates.
c Subdistribution HRs from multivariate Fine–Gray model with infection as event of interest, revision not for infection as a competing risk, and both VPS and age group as covariates.
d Subdistribution HRs from multivariate Fine–Gray model with competing risk (revision not for infection) as event of interest, infection as a competing risk, and both VPS and age group as covariates.

Note
Follow-up time from first VPS summary statistics: median 22 months; LQ–UQ 10–24 months; minimum 0 months, maximum 24 months.

TABLE 15 Estimates for Cox proportional HRs

Covariate	Revision, HR (97.5% CI); *p*-value
VPS	
Standard	–
Antibiotic impregnated	1.01 (0.77 to 1.33); 0.94
Silver impregnated	1.08 (0.82 to 1.42); 0.54
Age group	
Paediatric	–
Adult (≤ 65 years)	0.57 (0.44 to 0.74); < 0.01
Adult (> 65 years)	0.25 (0.18 to 0.35); < 0.01

Follow-up time from first VPS summary statistics: median 22 months; LQ–UQ 10–24 months; minimum 0 months, maximum 24 months.

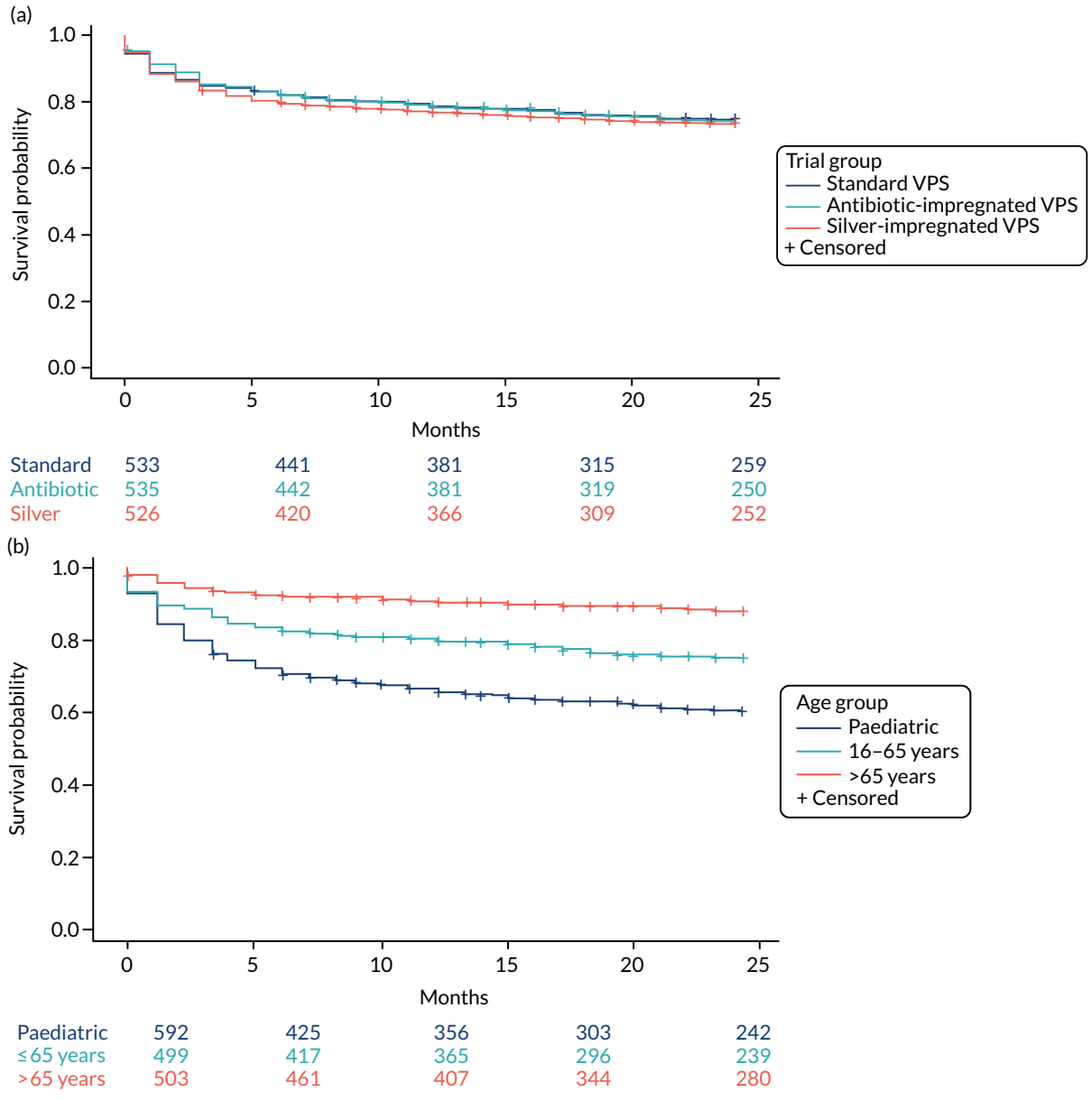

FIGURE 5 Kaplan–Meier curves for time to VPS failure for any cause, split by (a) VPS group and (b) age group.

Secondary outcome 3: reason for shunt failure

At the time of revision, the treating surgeon recorded the reason for shunt failure on the CRFs. The reason for shunt failure could fall into one of four categories: suspected shunt infection, mechanical shunt failure, functional shunt failure and failure due to the patient. The outcome explored the reasons for shunt failure in the antibiotic-impregnated and silver-impregnated VPS arms, compared with the standard VPS arm.

The reasons for shunt failure, according to VPS type, are summarised in *Table 16*. Although the number of revisions across the VPS groups is similar, comparing the reasons within group indicates:

- Failures due to suspected shunt infections are lower in the antibiotic-impregnated group ($n = 15/132$, 11.4%) than in the standard ($n = 33/130$, 25.4%) or the silver-impregnated VPS groups ($n = 30/136$, 22.1%).
- Mechanical shunt failures are higher in the antibiotic-impregnated VPS group ($n = 69/132$, 52.3%) than in the standard ($n = 52/130$, 43.0%) or the silver-impregnated VPS groups ($n = 64/136$, 47.1%).

These results indicate that, although the number of VPS failures is similar between the three groups, the underlying reason for failure differs when comparing standard with antibiotic-impregnated VPSs ($p = 0.02$), with fewer infections with antibiotic-impregnated VPSs, but a higher frequency of failure for other causes.

Secondary outcome 4: types of bacterial infection

The proportion of 'definite – culture positive' infections was 68.8% in the standard VPS group, 50.0% in the antibiotic-impregnated VPS group and 80.6% in the silver-impregnated VPS group. The central review panel classified all shunt infections that were 'definite – culture positive' and 'probable – culture uncertain' ($n = 56/75$; see *Table 11*) by the organism that was cultured.

The organisms cultured are summarised by species in *Tables 17* and *18*. Coagulase-negative staphylococci (37.5%) and *Staphylococcus aureus* (30%) accounted for the majority of cultured organisms in 'all VPS infection' but not in the antibiotic-impregnated VPS group. Culture results show a reduction in

TABLE 16 Reasons for VPS failure

	Reason for VPS failure, *n* observed failures (row %,[a] column %[b])					Chi-squared test results	
Comparator	Suspected infection	Mechanical shunt failure	Functional shunt failure	Failure due to patient	Total (*n*)	Test	Result
Antibiotic-impregnated vs. standard VPS							
Standard	33 (25.4, 68.8)	52 (40.0, 43.0)	40 (30.8, 47.6)	5 (3.8, 55.6)	130	Value	9.4
Antibiotic-impregnated	15 (11.4, 31.3)	69 (52.3, 57.0)	44 (33.3, 52.4)	4 (3.1, 44.4)	132	Degrees of freedom	3
Total (*n*)	48	121	84	9	262	*p*-value	0.02
Silver-impregnated vs. standard VPS							
Standard	33 (25.4, 52.4)	52 (40.0, 44.8)	40 (30.8, 51.9)	5 (3.8, 50.0)	130	Value	1.4
Silver-impregnated	30 (22.1, 47.6)	64 (47.1, 55.2)	37 (27.2, 48.1)	5 (3.7, 50.0)	136	Degrees of freedom	3
Total (*n*)	63	116	77	10	266	*p*-value	0.71

a Row percentages are calculated using a denominator as the total for that row. The total *n* for the row used as a denominator in computing the percentages is shown in the Total (*n*) column.
b Column percentages are calculated using a denominator as the total for that column. The total *n* for the column used as a denominator in computing the percentages is shown in the Total (*n*) row.
The numerator for each calculation is the number of observed failures in that cell.

TABLE 17 Summary of Gram-positive organisms cultured, split by VPS type

Summary of Gram-positive organisms cultured	Standard VPS	Antibiotic-impregnated VPS	Silver-impregnated VPS	Total
Total number of infections[a]	23[b]	6	27[c]	56
Gram-positive organisms isolated (*n*)	20	2	23	45
***Gram-positive organism cultured*, n *(%)*[d]**				
Staphylococcus aureus	6 (26.1)	0 (0.0)	11 (40.7)	17 (30.4)
Coagulase-negative staphylococci				
Coagulase-negative staphylococci, species not given	5 (21.7)	1 (16.7)	3 (11.1)	9 (16.1)
Staphylococcus epidermidis	4 (17.4)	0 (0.0)	3 (11.1)	7 (12.5)
Staphylococcus capitas	3 (13.0)	0 (0.0)	1 (3.7)	4 (7.1)
Staphylococcus hominis	1 (4.3)	0 (0.0)	0 (0.0)	1 (1.8)
Other Gram-positive organisms				
Enterococcus faecalis	0 (0.0)	0 (0.0)	2 (7.4)	2 (3.6)
Propionibacterium acnes	0 (0.0)	0 (0.0)	2 (7.4)	2 (3.6)
Propionibacterium species	0 (0.0)	1 (16.7)	0 (0.0)	1 (1.8)
Streptococcus mitis	0 (0.0)	0 (0.0)	1 (3.7)	1 (1.8)
Streptococcus salivaris	1 (4.3)	0 (0.0)	0 (0.0)	1 (1.8)

a Organisms cultured for infections centrally classified as 'definite – culture positive' and 'probable – culture uncertain' only; see *Table 11*.
b There were 22 'definite – culture positive' and one 'probable – culture uncertain' infections.
c There were 25 'definite – culture positive' and two 'probable – culture uncertain' infections.
d If more than one organism was grown from one infection episode, except for mixed coagulase-negative staphylococci, each organism has been listed.

TABLE 18 Summary of Gram-negative organisms cultured, split by VPS type

Summary of Gram-negative organisms cultured	Standard VPS	Antibiotic-impregnated VPS	Silver-impregnated VPS	Total
Total number of infections[a]	23[b]	6	27[c]	56
Gram-negative organisms isolated (*n*)	6	4	5	15
***Gram-negative organisms cultured*, n *(%)*[d]**				
Enterobacteriaceae				
Enterobacter cloacae	0 (0.0)	1 (16.7)	2 (7.4)	3 (5.4)
Escherichia coli	0 (0.0)	1 (16.7)	2 (7.4)	3 (5.4)
Klebsiella pneumoniae	3 (13.0)	0 (0.0)	0 (0.0)	3 (5.4)
Citrobacter species	0 (0.0)	0 (0.0)	1 (3.7)	1 (1.8)
Serratia marcescens	1 (4.3)	0 (0.0)	0 (0.0)	1 (1.8)
Serratia species	1 (4.3)	0 (0.0)	0 (0.0)	1 (1.8)
Proteus mirabilis	0 (0.0)	1 (16.7)	0 (0.0)	1 (1.8)
Pseudomonas aeruginosa	1 (4.3)	1 (16.7)	0 (0.0)	2 (3.6)

a Organisms cultured for infections centrally classified as 'definite – culture positive' and 'probable – culture uncertain' only; see *Table 11*.
b There were 22 'definite – culture positive' and one 'probable – culture uncertain' infections.
c There were 25 'definite – culture positive' and two 'probable – culture uncertain' infections.
d If more than one organism was grown from one infection episode, except for mixed coagulase-negative staphylococci, each organism has been listed.

staphylococcal/Gram-positive infections for the antibiotic-impregnated VPS group, compared with the standard and the silver-impregnated VPS groups. All three VPS types have a similar number of Gram-negative infections.

Line listings of details of each infection against their organism cultured and antibiotic sensitivities are provided in *Appendix 2*, *Table 38*. Antibiotic sensitivity data were not consistently returned, so displayed data are limited.

Secondary outcome 5: time to removal of ventriculoperitoneal shunt because of suspected infection

Following first clean revision

This outcome explored revisions for infections in patients who had their first VPS revised for a reason other than infection (clean revision), that is those with a competing risk in the primary outcome set ($n = 323$; see *Table 11*). Participants in this group, who subsequently had a second revision, had their data centrally assessed by the panel and had the reason for revision classified as infection, or no infection, based on the data available. As with the primary outcome, for which there was insufficient information for the central panel to classify, the clinical classification was used ($n = 4/128$; *Table 19*).

There were 128 secondary revisions following a first clean revision, of which 20 were classified as an infection (6.2%; see *Table 19*). The infection rate was approximately equal in the antibiotic-impregnated and silver-impregnated VPS groups (5.0% and 4.8%, respectively), and was higher in the standard VPS group (9.2%). However, these differences were not statistically significant when survival models were applied to the data (*Table 20*).

TABLE 19 Summary of second VPS revisions, following first clean revision, and infections classified by the central committee

Second VPS revisions	Standard VPS, *n* (%)	Antibiotic-impregnated VPS, *n* (%)	Silver-impregnated VPS, *n* (%)	Total, *n* (%)
Summary of revisions				
Eligible for primary outcome[a]	98 (100)	120 (100)	105 (100)	323 (100)
No VPS removal/revision	61 (62.2)	69 (57.5)	65 (61.9)	195 (60.4)
VPS removal/revision (for any cause)	37 (37.8)	51 (42.5)	40 (38.1)	128 (39.6)
Reason for revisions as classified by central review				
Revision for infection	9 (9.2)	6 (5.0)	5 (4.8)	20 (6.2)
Revision for other reason (no infection)	28 (28.6)	45 (37.5)	35 (33.3)	108 (33.4)
VPS CSF or peritoneal infection				
Definite – culture positive	7 (18.9)	3 (5.9)	5 (12.5)	15 (11.7)
Probable – culture uncertain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Probable – culture negative	1 (2.7)	0 (0.0)	0 (0.0)	1 (0.8)
Possible – culture uncertain	1 (2.7)	2 (3.9)	0 (0.0)	3 (2.3)
Clinically classified infection[b]	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.8)
VPS deep incisional infection				
VPS deep incisional infection	0 (0.0)	0 (0.0)	1 (2.5)	1 (0.8)

a Randomised participants who had their de novo VPSs removed for reasons other than infection, as assessed by central review, were eligible for the outcome set ($n = 323$); see *Table 11*.
b When the central review panel was unable to classify, an infection was classified by the operating surgeon on the CRFs. There was four cases for which the committee was unable to classify; one of these was clinically classified as an infection.

TABLE 20 Estimates of csHRs and sHRs for second VPS revision for infection, as classified by the central review panel

Covariate	Infection, HR (97.5% CI); *p*-value	Competing risk, HR (97.5% CI); *p*-value
Cox: csHR		
VPS		
Standard	–	–
Antibiotic-impregnated	0.55[a] (0.17 to 1.81); 0.26	1.38[b] (0.80 to 2.36); 0.19
Silver-impregnated	0.47[a] (0.13 to 1.63); 0.17	1.11[b] (0.63 to 1.97); 0.67
Age group		
Paediatric	–	–
Adult (≤ 65 years)	1.64[a] (0.58 to 4.61); 0.28	0.80[b] (0.49 to 1.30); 0.30
Adult (> 65 years)	0.34[a] (0.03 to 3.64); 0.14	0.43[b] (0.19 to 0.95); 0.10
Fine-Gray: sHR		
VPS		
Standard	–	–
Antibiotic-impregnated	0.55[c] (0.17 to 1.75); 0.25	1.40[d] (0.83 to 2.37); 0.16
Silver-impregnated	0.48[c] (0.14 to 1.67); 0.19	1.14[d] (0.65 to 1.99); 0.61
Age group		
Paediatric	–	–
Adult (≤ 65 years)	1.72[c] (0.62 to 4.81); 0.24	0.80[d] (0.50 to 1.28); 0.29
Adult (> 65 years)	0.38[c] (0.04 to 3.91); 0.14	0.44[d] (0.20 to 0.97); 0.11

a Cause-specific HRs from multivariate Cox model with infection as event of interest and both VPS and age group as covariates.
b Cause-specific HRs from multivariate Cox model with competing risk (revision not for infection) as event of interest and both VPS and age group as covariates.
c Subdistribution HRs from multivariate Fine–Gray model with infection as event of interest, revision not for infection as a competing risk, and both VPS and age group as covariates.
d Subdistribution HRs from multivariate Fine–Gray model with competing risk (revision not for infection) as event of interest, infection as a competing risk, and both VPS and age group as covariates.

Note
Follow-up time (months) from second VPS summary statistics: median 9 months; LQ–UQ 2–19 months; minimum 0 months, maximum 24 months.

Seventy-five per cent of the secondary revisions for infection were classified by the committee as 'definite – culture positive' ($n = 15/20$).

Additional analysis

Comparing the identification of infections between assessors

The reason for revision (infection or no infection), as classified by the central panel, was the primary outcome (see *Primary outcome: time to ventriculoperitoneal infection as assessed by the central review panel*), and the reason for revision, as classified by the treating surgeon, was a complementary secondary outcome (see *Secondary outcome 1: time to removal of first ventriculoperitoneal shunt due to suspected infection, as assessed by the treating surgeon*). The classification made by these two independent assessors was the same in 95.7% (381/398) of revisions. *Appendix 2*, *Table 39*, provides further detail.

Revision and infection rates by age group

The proportion of revisions of first VPS for any cause ranged from 38.0% ($n = 225/592$) for paediatrics to 10.9% ($n = 55/503$) for those aged > 65 years. The proportion of infections, as classified by the central review panel, was also higher for paediatrics than for older participants. *Table 21* provides more detail.

All survival models were adjusted for age category of the recruiting centre (paediatric or adult), with adult centre being further categorised by age > 65 years. The risk of infection was significantly lower for participants aged 16–65 years (csHR 0.56, 97.5% CI 0.32 to 0.99; $p = 0.02$) and for those aged > 65 years (csHR 0.12, 97.5% CI 0.04 to 0.35; $p < 0.01$) than for paediatric participants (see *Table 12*). See *Figure 3* for the cumulative incidence of infection by age category; see *Figure 4* for the cumulative incidence of infection by VPS type, stratified by age group.

Revision and infection rates by centre

Heterogeneity between centres in revision rates and infection rates was explored by summary statistics.

Revision rates varied from a minimum of 4.8% (97.5% CI 0.0% to 15.2%, adult-only centre) to a maximum of 75.0% (97.5% CI 40.7% to 100.0%, paediatric-only centre), as presented in *Appendix 2*, *Table 41*. Infection rates, presented in *Appendix 2*, *Table 41*, varied from 0.0% (97.5% CI 0.0% to 0.0%, adult-only centre) to 25.0% (97.5% CI 0.0% to 59.3%, paediatric-only centre). Paediatric-only centres generally had higher rates of revisions and infections than adult-only centres and centres that treated both adults and paediatrics.

Post hoc analyses

A post hoc analysis explored revision rates, and reason for revision, by aetiology of the hydrocephalus, type of valve, operative approach and component replaced at first revision.

Revision and infection rates by aetiology

Table 22 and *Appendix 2*, *Table 42*, summarise aetiologies of the hydrocephalus, overall and split by treatment group, respectively. The rates of revision for infection and mechanical failure varied within certain aetiologies. For example, the revision and infection rates for participants with congenital malformations was 38.4% and 9.2%, respectively, both higher than the equivalent overall rates of 25.0% and 4.7% (see *Table 11*). Similarly, participants with idiopathic normal pressure hydrocephalus had much lower revision and infection rates of 10.0% and 1.1%, respectively, than the rates for patients with other aetiologies of hydrocephalus.

Rates between VPS groups also differed according to aetiology. For example, the infection rate in participants with spina bifida in the antibiotic-impregnated VPS group was 2.9%, compared with 14.3% each for the standard and silver-impregnated VPS groups. The infection rate in participants with idiopathic normal pressure hydrocephalus was 13.6% in the standard VPS group and 2.9% in the antibiotic-impregnated VPS group.

TABLE 21 Summary of revisions, and reason for revisions, of first VPS according to age group

	Age group			
Summary of revisions	Paediatric	≤ 65 years	> 65 years	Total
Eligible for primary outcome	592 (100)	499 (100)	503 (100)	1594 (100)
No VPS removal/revision	367 (62.0)	381 (76.4)	448 (89.1)	1196 (74.5)
Revision for other reason (no infection)	178 (30.1)	95 (19.0)	50 (9.9)	323 (20.3)
Revision for infection	47 (7.9)	23 (4.6)	5 (1.0)	75 (4.7)

TABLE 22 Summary of aetiologies, and types of aetiologies, of the hydrocephalus

Summary of aetiology	Clean insertion,[a] *n* (%)	Revision required		Reason for revision				
		No revision, *n* (%)	Revision,[b] *n* (%)	Failure due to patient, *n* (%)	Functional shunt failure, *n* (%)	Mechanical shunt failure, *n* (%)	Failure due to infection, *n* (%)	Failure – no infection,[c] *n* (%)
Total number of patients	1594	1196	398	14	121	185	78	320
Congenital malformations								
Patients with congenital malformations	294 (18.4)	181 (61.6)	113 (38.4)	2 (0.7)	36 (12.2)	48 (16.3)	27 (9.2)	86 (29.3)
Type of congenital malformation								
Aqueduct stenosis	68 (23.1)	46 (67.6)	22 (32.4)	0 (0.0)	8 (11.8)	7 (10.3)	7 (10.3)	15 (22.1)
Dandy–Walker	7 (2.4)	6 (85.7)	1 (14.3)	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)	1 (14.3)
Chiari	62 (21.1)	43 (69.4)	19 (30.6)	0 (0.0)	7 (11.3)	7 (11.3)	5 (8.1)	14 (22.6)
Spina bifida	111 (37.8)	62 (55.9)	49 (44.1)	1 (0.9)	11 (9.9)	25 (22.5)	12 (10.8)	37 (33.3)
Other	72 (24.5)	38 (52.8)	34 (47.2)	1 (1.4)	12 (16.7)	13 (18.1)	8 (11.1)	26 (36.1)
Not known	1 (0.3)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Acquired hydrocephalus								
Patients with acquired hydrocephalus	819 (51.4)	615 (75.1)	204 (24.9)	9 (1.1)	54 (6.6)	102 (12.5)	39 (4.8)	165 (20.1)
Type(s) of acquired hydrocephalus								
Cysts (colloid or arachoid)	32 (3.9)	24 (75.0)	8 (25.0)	0 (0.0)	4 (12.5)	3 (9.4)	1 (3.1)	7 (21.9)
Trauma	30 (3.7)	25 (83.3)	5 (16.7)	1 (3.3)	1 (3.3)	3 (10.0)	0 (0.0)	5 (16.7)
Tumour: benign	124 (15.1)	96 (77.4)	28 (22.6)	2 (1.6)	9 (7.3)	14 (11.3)	3 (2.4)	25 (20.2)
Tumour: malignant	133 (16.2)	105 (78.9)	28 (21.1)	2 (1.5)	6 (4.5)	14 (10.5)	6 (4.5)	22 (16.5)
Post haemorrhagic/intracranial haemorrhage	337 (41.1)	244 (72.4)	93 (27.6)	2 (0.6)	21 (6.2)	45 (13.4)	25 (7.4)	68 (20.2)
Infection: meningitis	32 (3.9)	23 (71.9)	9 (28.1)	0 (0.0)	2 (6.3)	5 (15.6)	2 (6.3)	7 (21.9)

continued

TABLE 22 Summary of aetiologies, and types of aetiologies, of the hydrocephalus (*continued*)

Summary of aetiology	Clean insertion,[a] *n* (%)	Revision required		Reason for revision				
		No revision, *n* (%)	Revision,[b] *n* (%)	Failure due to patient, *n* (%)	Functional shunt failure, *n* (%)	Mechanical shunt failure, *n* (%)	Failure due to infection, *n* (%)	Failure – no infection,[c] *n* (%)
Infection: cerebral abscess	8 (1.0)	7 (87.5)	1 (12.5)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	1 (12.5)
Infection: other	21 (2.6)	17 (81.0)	4 (19.0)	0 (0.0)	0 (0.0)	4 (19.0)	0 (0.0)	4 (19.0)
Other factors	140 (17.1)	99 (70.7)	41 (29.3)	3 (2.1)	16 (11.4)	17 (12.1)	5 (3.6)	36 (25.7)
Idiopathic condition								
Patients with idiopathic condition	496 (31.1)	408 (82.3)	88 (17.7)	4 (0.8)	32 (6.5)	38 (7.7)	14 (2.8)	74 (14.9)
Type(s) of idiopathic condition								
Idiopathic normal pressure hydrocephalus of the elderly	361 (72.8)	325 (90.0)	36 (10.0)	1 (0.3)	15 (4.2)	16 (4.4)	4 (1.1)	32 (8.9)
IIH	98 (19.8)	63 (64.3)	35 (35.7)	2 (2.0)	10 (10.2)	16 (16.3)	7 (7.1)	28 (28.6)
Other	38 (7.7)	20 (52.6)	18 (47.4)	1 (2.6)	7 (18.4)	7 (18.4)	3 (7.9)	15 (39.5)

a Clean insertion = no revision + revision.
b Revision = failure due to patient + functional shunt failure + mechanical shunt failure + failure due to infection.
c Failure – no infection = failure due to patient + functional shunt failure + mechanical shunt failure.

Revision and infection rates by operative approach

Table 23 and *Appendix 2*, *Table 43*, summarise valve type and operative approach at insertion, both overall and split by treatment group.

The rate of revisions when there was no evidence of infection (the competing risk in the primary outcome analysis) was > 10% lower among participants with a programmable valve ($n = 82/627$, 13.1%) than among those with a fixed valve ($n = 227/935$, 24.3%). On the other hand, revision rates for no infection were equivalent when comparing frontal placement of proximal shunt catheter with parietal and/or occipital placement: 20.9% and 19.8%, respectively.

Revision and infection rates by component replaced at first revision

Table 24 and *Appendix 2*, *Table 44*, summarise the component replaced in participants who had their VPS revised for reason other than infection, as classified by the treating surgeon.

Most commonly, when a shunt is revised for a reason other than infection, the component replaced is the ventricular shunt catheter ($n = 72/268$, 26.9%) or the valve ($n = 76/268$, 28.4%). The component replaced was similar between VPS groups, although valve changes were more common in the antibiotic-impregnated VPS group than in the standard or silver-impregnated VPS groups.

Safety analysis

Efficacy outcomes were analysed by the intention-to-treat analysis population as much as possible. For AEs and SAEs, participants are reported according to the type of VPS in situ at the time of the event. The shunt in situ was known for all patients up to the first revision. However, events occurring following a revision whereby the shunt was not replaced like for like are reported in under 'other VPS' group.

The total number of AEs experienced and the number of participants experiencing at least one AE are provided, both overall and split according to the VPS in situ at the time of the event. Of the 1601 participants who received a trial shunt, 413 (25.8%) experienced 654 events. Summarising these events, split by VPS in situ at the time of event, indicates the following:

- Standard VPS – 135 out of 531 participants (25.4%) experienced 201 events.
- Antibiotic-impregnated VPS – 136 out of 545 participants (25.0%) experienced 210 events.
- Silver-impregnated VPS – 140 out of 525 participants (26.7%) experienced 191 events.
- Other VPS – when the initial trial shunt was removed and not replaced like for like, 35 out of 136 participants (25.7%) experienced 52 events.

Common events were ventricular shunt catheter obstruction (96 events in 79 participants), shunt valve obstruction (65 events in 52 participants) and valve change for symptomatic overdrainage (54 events in 50 participants).

Appendix 2, *Table 45*, provides the summary of related AEs.

No participant experienced a SAE.

TABLE 23 Summary of valve type and operative approach

Summary of operative approach/ valve type	Clean insertion,[a] *n* (%)	Revision required		Reason for revision				
		No revision, *n* (%)	Revision,[b] *n* (%)	Failure due to patient, *n* (%)	Functional shunt failure, *n* (%)	Mechanical shunt failure, *n* (%)	Failure for infection, *n* (%)	Failure – no infection,[c] *n* (%)
Total number of patients	1594	1196	398	14	121	185	78	320
Use of guidance system								
Patients for whom guidance system was used for VPS placement	653 (41.0)	489 (74.9)	164 (25.1)	7 (1.1)	45 (6.9)	78 (11.9)	34 (5.2)	130 (19.9)
Type of guidance system								
Electromagnetic	413 (63.2)	309 (74.8)	104 (25.2)	4 (1.0)	26 (6.3)	50 (12.1)	24 (5.8)	80 (19.4)
Ultrasonography	128 (19.6)	88 (68.8)	40 (31.3)	3 (2.3)	16 (12.5)	14 (10.9)	7 (5.5)	33 (25.8)
Optical	46 (7.0)	37 (80.4)	9 (19.6)	0 (0.0)	2 (4.3)	6 (13.0)	1 (2.2)	8 (17.4)
Stereotactic frame	63 (9.6)	52 (82.5)	11 (17.5)	0 (0.0)	1 (1.6)	8 (12.7)	2 (3.2)	9 (14.3)
Not known	3 (0.5)	3 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Placement of proximal shunt catheter								
Frontal	134 (8.4)	93 (69.4)	41 (30.6)	0 (0.0)	13 (9.7)	15 (11.2)	13 (9.7)	28 (20.9)
Parietal, occipital or parietal/occipital	1453 (91.2)	1100 (75.7)	353 (24.3)	14 (1.0)	107 (7.4)	167 (11.5)	65 (4.5)	288 (19.8)
Combination	3 (0.2)	2 (66.7)	1 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	1 (33.3)
Not known	4 (0.3)	1 (25.0)	3 (75.0)	0 (0.0)	0 (0.0)	3 (75.0)	0 (0.0)	3 (75.0)
Type of valve								
Fixed	935 (58.7)	652 (69.7)	283 (30.3)	10 (1.1)	91 (9.7)	126 (13.5)	56 (6.0)	227 (24.3)
Programmable	627 (39.3)	525 (83.7)	102 (16.3)	4 (0.6)	26 (4.1)	52 (8.3)	20 (3.2)	82 (13.1)
Not known	32 (2.0)	19 (59.4)	13 (40.6)	0 (0.0)	4 (12.5)	7 (21.9)	2 (6.3)	11 (34.4)

a Clean insertion = no revision + revision.
b Revision = failure due to patient + functional shunt failure + mechanical shunt failure + failure due to infection.
c Failure – no infection = failure due to patient + functional shunt failure + mechanical shunt failure.

TABLE 24 Summary of components replaced at revision

Summary of shunt components replaced	Failure – no infection,[a] *n* (%)	Reason for revision for no infection		
		Failure due to patient, *n* (%)	Functional shunt failure, *n* (%)	Mechanical shunt failure, *n* (%)
Total number of patients	320	14	121	185
Was a complete new shunt inserted?				
No	268 (83.8)	12 (4.5)	99 (36.9)	157 (58.6)
If no, which component was replaced?				
Ventricular shunt catheter only	72 (26.9)	0 (0.0)	22 (30.6)	50 (69.4)
Peritoneal shunt catheter only	31 (11.6)	3 (9.7)	5 (16.1)	23 (74.2)
Valve only	76 (28.4)	3 (3.9)	35 (46.1)	38 (50.0)
Combination	38 (14.2)	1 (2.6)	19 (50.0)	18 (47.4)
Not known	51 (19.0)	5 (9.8)	18 (35.3)	28 (54.9)

a Failure – no infection = failure due to patient + functional shunt failure + mechanical shunt failure.

Chapter 4 Economic evaluation

Introduction

A number of studies[32–36] (although none from the UK) have estimated the costs of managing patients with VPS infections. These often combine cost estimates with observed differences in infection rates, between antibiotic-impregnated and standard VPS catheters, in rudimentary cost-effectiveness analyses, to calculate the incremental cost (saving) per VPS infection avoided. This is relevant to inform the best use of health-care resources, given that impregnated VPS catheters are about twice as expensive as standard shunt catheters, but are limited in not assessing all-cause VPS failure or impacts on patients' health-related quality of life.

Adopting the perspective of the German health-care setting, Eymann *et al.*[32] estimated the costs of VPS infections by considering the lengths, and per diem costs, of adult and paediatric intensive care and ward stays. Based on 48 cases of VPS infections among a cohort of 197 hydrocephalus patients with antibiotic-impregnated VPS catheters and 98 patients with standard VPS catheters, the estimated mean cost per infection was US$16,933 in children and US$14,886 in adults. Considering the benefits and additional costs of antibiotic-impregnated shunt catheters, the authors estimated a net saving of US$51,651 for the 197 patients.

Farber *et al.*[33] conducted a retrospective cohort study of 500 shunt surgeries performed in adult patients with hydrocephalus in a US hospital: 250 received antibiotic-impregnated VPS catheters and 250 received standard VPS catheters. The hospital billing records of all patients who were treated were analysed to estimate the costs associated with hospital stays for infections. The overall mean cost per VPS infection was US$40,371 and, based on an absolute reduction in the risk of shunt infections of 2.8% with antibiotic-impregnated shunt catheters, savings of US$47,193 in infection-related direct costs were estimated per 100 shunt surgeries performed.

Attenello *et al.*[34] analysed the hospital billing records of 406 paediatric patients who underwent 608 shunt placement procedures (400 antibiotic-impregnated and 208 standard shunt catheters) in a single US hospital. The majority of procedures (93%) were for VPSs. The hospital resources used to treat the 38 patients in whom a shunt infection developed were estimated to cost an average of US$48,454. Based on an observed decreased incidence of shunt infection in the antibiotic-impregnated shunt catheter cohort, the estimated infection-related cost savings per 100 patients was $442,133 per 100 patients with shunts.

Parker *et al.*[35,36] analysed patient discharge and billing records from 287 US hospitals to estimate the shunt infection rates and costs of antibiotic-impregnated shunt catheters compared with standard shunt catheters. The unadjusted difference in the incidence of shunt infection was 1.4% and 4.5% in adult and paediatric populations, respectively, and the costs of managing infections was US$45,714 and US$56,104, respectively. The authors estimated that the use of antibiotic-impregnated shunt catheters in adults was associated with infection-related cost savings of US$42,125 per 100 de novo shunts placed (US$230,390 per 100 in paediatrics), which corresponds to US$30,854 and US$51,181 per shunt infection avoided, respectively (calculated from data presented in the paper).

Each of the above studies relied on retrospective cohorts of patients, mainly from single centres, but result in estimates for the costs of managing VPS infections in the order of US$50,000 in the US health-care setting. A key limitation, however, is that, in each of these analyses, infection rates were determined from observational data, and were therefore potentially subject to bias, reducing the reliability of the cost-effectiveness estimates. Analyses that considered the RR of VPS infection associated with antibiotic-impregnated shunt catheters, determined from clinical trial data, are limited to three studies.[37–39]

Root *et al.*[37] conducted a meta-analysis of clinical trials and observational studies, and estimated that the number needed to treat with antibiotic-impregnated (compared with standard) EVDs to prevent a shunt catheter-associated infection was 19 (95% CI 15 to 36). Based on assumed costs of US$100 per antibiotic-impregnated shunt catheter and US$30,000 per episode of infection, they estimated that antibiotic-impregnated shunt catheters could result in overall savings, from the perspective of a US neurosurgical unit, of US$28,100 (95% CI US$26,400 to US$28,500) for each shunt catheter-associated infection prevented.

Klimo *et al.*[38] similarly reviewed the literature for clinical trials and observational studies of antibiotic-impregnated shunts, and conducted a meta-analysis and a simple cost calculation. Assuming a cost of US$50,000 to treat a shunt infection, the cost savings per shunt infection prevented ranged from just under US$90,000 to > US$1.3M per 200 shunts performed. No data were presented on the incremental cost (saving) of avoiding a shunt infection.

Edwards *et al.*[39] developed a decision-analytic model of the clinical and economic consequences of using antibiotic-impregnated shunts from the perspective of a US hospital. Using trial and observational data, they estimated that, for every 100 patients requiring shunts, antibiotic-impregnated shunt catheters may be associated with 0.5 fewer deaths, 71 fewer hospital days, 11 fewer surgeries and a net saving of US$128,228 owing to decreased infection. The cost of a shunt infection was US$46,394, derived from earlier estimates of Attenello *et al.*[34] and Farber *et al.*[33]

All analyses have many limitations, not least the assumption that potential avoidance of the cost of managing VPS infections can be equated to a cost saving. Moreover, the analyses lacked any consideration of health outcomes associated with shunt catheter-associated infections or other potential causes of VPS failure.

Aim

The aim of the economic evaluation was to assess the cost-effectiveness of antibiotic-impregnated, silver-impregnated and standard VPS catheters in children and adults with hydrocephalus who were recruited in the BASICS trial.

Methods

The economic analysis adopted the perspective of the NHS and Personal Social Services providers in the UK. The analytical approach for the primary analysis was a cost-effectiveness analysis, based on the incremental cost per first shunt failure (due to any cause) averted for impregnated and standard VPSs. A cost–utility analysis was conducted to estimate the incremental cost per QALY gained in a restricted sample of trial participants.

Resource use and costs

Within-trial costs were estimated by measuring the health-care resource use associated with each of the trial interventions during the trial period. These included (1) hospital inpatient procedures; (2) hospital outpatient and accident and emergency (A&E) visits; (3) concomitant medications; and (4) contact with other health-care professionals, including general practitioners (GPs) and school nurses.

Estimation of resource use was based on complementary approaches using data collected as part of the trial and as part of routine care. These were as follows:

- Patient-Level Information and Costing System (PLICS). PLICS data contain details of admission and discharges, Healthcare Resource Group (HRG) codes relating to the type of care patients received, and the point of delivery (A&E, inpatient, outpatient). PLICS data were requested for all participants from 3 months prior to randomisation to the final follow-up of the last participant (April 2018).
- Resource use questionnaires completed by trial participants, their guardian or their parents. These were designed to collect information on participants' use of primary care services, Personal Social Services and non-scheduled clinic attendances.[40,41] Resource use questionnaires were administered early post operatively, and then posted to participants by research nurses every 12 weeks until the end of the trial. Participants completed these and returned them to the trial centre.
- Dedicated sections in the CRF. These were used to record trial participants' use of concomitant medications at each clinic visit and for the duration of their participation in the trial, or up until 14 days following shunt removal in cases of confirmed infection.
- Interventions. The type of initial VPS catheter was according to a participant's treatment allocation. Costs associated with any subsequent revisions were included in participants' PLICS data.

Unit costs

All resource use was valued in monetary terms using appropriate UK unit costs for the 2016–17 cost year. When necessary, for any costs from an earlier period, adjustments were made for inflation using the pay cost index and the health service cost index.[42]

The unit costs of shunt catheters were sourced from the manufacturers. A silver antimicrobial shunt catheter set (Silverline), consisting of ventricular and peritoneal shunt catheters, costs £361.62. A Bactiseal shunt catheter kit (ventricular and peritoneal) costs £384.00; and standard, plain Codman® Hakim® (Integra LifeSciences Holdings Corporation) ventricular or peritoneal shunt catheters each cost £172.00.

Health resource groups were used as the main currency of the economic analysis[43] for inpatient stays (see *Appendix 3*, *Table 46*) and outpatient contacts (see *Appendix 3*, *Table 47*), with cost codes allocated based on the latest available national schedule of reference costs[44] or, when not available, based on the national tariff.[45] Reference costs are the average unit costs of providing services to NHS patients in England, and are collected each financial year. National tariff costs relate to bundled care packages reimbursed at a national level, based on the NHS payment-by-results scheme. National average unit costs were based on the hospital spell, and incorporated excess ward days and whether the case was elective or emergency. National tariff codes were obtained primarily from PLICS data, but, if unavailable, appropriate HRG codes were assigned based on the reason for admission and a patient's condition, extracted from the patient resource use questionnaires, which asked about participants' contacts with health-care professionals during their time in the trial.

The compendium of *Unit Costs of Health and Social Care*[42] was the source of unit costs of all items of primary health-care resource use and outpatient contacts (see *Appendix 3*, *Table 48*). The number of health-care professional contacts recorded in the resource use questionnaires and baseline forms were multiplied by their respective unit costs.

The unit costs of medicines were based on drug tariff prices, as referenced in the *British National Formulary*[46] and the *Prescription Costs Analysis Data*[47] for NHS England. The cost of each medicine was calculated by multiplying the unit price by the daily quantity of prescribed medication (e.g. number of vials, ampoules, prefilled syringes, capsules or tablets) and by the number of days of treatment. If the dispensed medication was an oral suspension, the total quantity for the prescribed period was calculated and rounded up to the nearest whole bottle.

Health outcomes

The primary health outcome for the economic analysis was the first VPS failure (due to any cause) averted. A sensitivity analysis considered the first VPS failure (due to confirmed infection) averted, consistent with the primary clinical outcome.

The secondary economic health outcome measure was the QALY, calculated from responses to EuroQol-5 Dimensions (EQ-5D) questionnaires. The EQ-5D-3L-Proxy (parent or guardian) questionnaire was used for participants aged from 5 years to just under 18 years, and for participants aged > 18 years who lacked capacity to consent for themselves. The EQ-5D-Y was administered to participants aged from 8 years to just under 18 years. Adults were asked to complete the EQ-5D-3L questionnaire, and all participants aged ≥ 8 years were administered the EQ-VAS.

The EQ-5D-3L descriptive system includes five dimensions (mobility, self-care, usual activities, pain and anxiety); each dimension has three levels of morbidity (no problems, some problems and extreme problems), which are scored 1, 2 and 3, respectively. UK tariff[48] scores for the EQ-5D-3L questionnaire were applied to responses to the EQ-5D-3L, EQ-5D-Y and EQ-5D-3L-Proxy questionnaires, as no separate scoring systems are yet available for the youth and proxy versions.

Utility scores from each version of the EQ-5D questionnaires were combined to achieve the most complete data set by taking scores from trial participants, when available, and incorporating proxy responses.

In addition, the child version of the HOQ was administered to participants aged 8–18 years, and the parent proxy version was administered for participants aged from 5 years to just under 8 years. The HOQ is a Canadian 51-item outcome questionnaire designed specifically for use in paediatric hydrocephalus.[25,49] Responses to each item are given a score from 0 (worse health status) to 4 (better health status). A set combination of items make up three health dimensions: physical, socioemotional and cognitive. A final score is obtained by summing each item score and then dividing it by the highest possible summed score, which gives a utility value anchored at 0 (worse health state) or 1 (best health state).

Health outcome questionnaires were completed during clinic visits, or over the telephone at baseline (pre-operative assessment visit), at the early post-operative assessment, 12 weeks after randomisation and at the end of the trial.

Economic analyses

Analytic approach

Analyses included all randomised participants, consistent with the 'intention to treat' principle. All statistical tests were two-sided; the statistical significance level was set at 2.5% and CIs were calculated at 97.5% to adjust for multiplicity.

Data were examined for missingness. The appropriate method for dealing with missing cost data was dependent on the number of missing data and the likely mechanism of missingness.[50] Costs relating to hospitalisations were primarily sourced from PLICS data. If PLICS data were not available or missing, the use of hospital services was based on entries in CRFs, or otherwise from participants' resource use questionnaires.[51] In the base-case analysis, any remaining missing data were multiply imputed using the method of chained equations.[52] The number of imputed data sets was based on the fraction of missing information (FMI) value to limit the loss in power to no more than 1%, and to maximise model convergence. Imputed data sets were generated using predictive mean matching, from a set of imputation models that were constructed from all potential prognostic factors: sex, age (paediatrics aged from 0 to just under 16 years, adults aged 16–65 years and adults aged > 65 years), site, time spent in the trial, whether or not a first treatment failure had occurred and intervention group.

In the base-case analysis, costs and outcomes incurred in the second year were discounted at a rate of 3.5%, in accordance with the NICE *Guide to the Methods of Technology Appraisal 2013*.[53]

Cost analysis

Hospitalisations were costed from baseline to 24 months. Hospital admissions were included if the hospital episode start date commenced within the 0- to 24-month time horizon. Adjustments were made to apportion the costs of hospital stays that crossed baseline or that continued after the 24-month time horizon. Similarly, adjustments were made to courses of drug treatment that spanned the period preceding baseline or beyond the 24-month time horizon, to apportion costs to those administered during the 0- to 24-month time horizon only.

Participants' use of health care and Personal Social Services between randomised groups was described and tabulated, reporting mean resource use items for each intervention and differences between the intervention groups. The 97.5% CIs for differences in mean costs were calculated using bias-corrected and accelerated non-parametric bootstrap with 10,000 replications.

Total costs were analysed using a regression model to account for any imbalance in participants' characteristics between intervention groups, and to estimate the mean cost of VPS failure. Owing to the large sample, the near-normality of sample means was assumed and ordinary least squares regression was applied in the base case.[54] The regression was specified with total (discounted) per-patient costs as the dependent variable, and the stratifying variables [randomisation group, site (discrete), age (three categories), time in the trial (continuous, in days) and treatment failure] as predictors:

$$\text{Cost} = \beta_0 + \beta_{1\text{rand\_group}} + \beta_{2\text{treat\_fail}} + \beta_{3\text{age}} + \beta_{4\text{time\_in\_trial}} + \beta_{5\text{site}} + \text{e}. \quad (1)$$

Similarly, the mean outcome by intervention group was also calculated by ordinary least squares regression, specified with treatment failure (discounted) as the dependent variable, and total cost (discounted), site (discrete), age (three categories), time in the trial (continuous) and intervention group as predictors:

$$\text{Effect} = \beta_0 + \beta_{1\text{rand\_group}} + \beta_{2\text{total\_costs}} + \beta_{3\text{age}} + \beta_{4\text{time\_in\_trial}} + \beta_{5\text{site}} + \text{e}. \quad (2)$$

Cost-effectiveness analysis

In the base-case cost-effectiveness analysis, the outcome of interest was the incremental cost per (first) VPS failure (due to any cause) averted. Interventions were ranked according to their effectiveness (reverse order for interventions in the south-west quadrant of the cost-effectiveness plane). Dominated and extendedly dominated interventions were removed, and the incremental cost-effectiveness ratios (ICERs) were calculated for the remaining shunt catheters.

Sensitivity and scenario analyses

A number of sensitivity analyses were performed to assess the robustness of the base-case ICER to key assumptions and analytic approaches. These were (1) bivariate sensitivity analyses to vary the unit costs of antibiotic-impregnated and silver-impregnated VPSs, (2) applying different discount rates (0%, 1.5% and 6% per annum for both costs and outcomes), (3) using observed data for costs (no multiple imputation) and (4) using a different analytic approach for analysing costs [generalised linear models (GLMs), acknowledging the skewness in the underlying data]. The GLM regression was specified using a combination of families (gamma, Gaussian and Poisson) and links (log and square root). Appropriate link function was determined using the Akaike information criterion (AIC) and Bayesian information criterion (BIC) and the modified Park test to determine the distribution family.[55]

In addition, a stratified cost-effectiveness analysis was undertaken for the three age categories of paediatrics, adults aged 16–65 years and adults aged $\geq$ 65 years.

Alternative cost-effectiveness and utility analysis

Additional cost-effectiveness analyses were conducted based on the incremental cost per averted case of first shunt failure due to (1) confirmed infection, (2) a mechanical cause, (3) a functional reason and (4) patient factors. A cost–utility analysis was performed to estimate the incremental cost per QALY gained; this analysis was restricted to participants aged ≥ 5 years, as no utility data were collected for children aged < 5 years. Uncertainty in the incremental cost–utility ratio was considered using non-parametric bootstrap analysis, using 1000 replicates, and depicted in cost-effectiveness acceptability curves, which present the probability of each VPS catheter being cost-effective for given ceiling thresholds of costs per QALY.[56] The cost–utility analysis considered the reference threshold range of between £20,000 and £30,000 per QALY.[53]

All analyses were conducted using Stata® version 13 (StataCorp LP, College Station, TX, USA) and reported according to the Consolidated Health Economic Evaluation Reporting Standards.[57]

Results

Data completeness

The PLICS data were provided by 10 out of the 21 neurosurgical units. These related to 199 out of 536 participants allocated to the standard VPS, 207 out of 538 participants allocated to the antibiotic-impregnated VPS and 210 out of 531 participants allocated to the silver-impregnated VPS (*Table 25*). The reasons given by the 11 centres for not providing PLICS data included:

- They were short staffed and were unable to assign resources to pull the data together.
- One centre was procuring a new PLICS system and were unable to supply any patient-level information.
- Finance officers were unwilling to provide data; others agreed to provide data but they did not deliver by the deadline.
- Some trusts did not want to share the data or asked for data-sharing agreements, but these could not be arranged within the project timelines.

Resource use questionnaires were completed by 423 (27%) participants: 145 participants allocated to standard VPSs, 146 allocated to antibiotic-impregnated VPSs and 132 allocated to silver-impregnated VPSs. The costs of concomitant medications were available for 88% of trial participants: 466, 463 and 467 participants allocated to standard, antibiotic-impregnated and silver-impregnated VPSs, respectively. In relation to self-reported hospital stays, respondents rarely provided information that was amenable to being costed. For example, most respondents who answered 'yes' to the question 'Have you attended any hospital as an outpatient because of your hydrocephalus since your last BASICS study visit? (Please include reason and details of health-care professional seen)' provided no information on the reason for attending or the health-care professional seen, which limited our ability to cost episodes of hospital care.

Overall, however, the numbers of missing hospital cost data, resource use diaries and concomitant medication were balanced across the three intervention groups, and by age and sex (*Table 26*).

For the multiple imputation, and based on the variable with the highest FMI value (FMI 0.580), 50 data sets were imputed.[58]

Resource use and cost analysis

Table 27 presents observed, mean disaggregated health-care resource use from randomisation up to 24 months, by intervention group. There were no discernible differences between intervention groups with respect to participants' use of primary or secondary health care.

TABLE 25 Summary of data completeness[a] by type and intervention group

		Participants (*n*)					
		Aged ≥ 5 years (*N* = 1098)			All trial (*N* = 1594)		
Trial group	Variable	Complete	Incomplete (imputed)	Total	Complete	Incomplete (imputed)	Total
Standard VPS	Utility at baseline	240	129	369	N/A	N/A	N/A
	Utility early post operatively	233	136	369	N/A	N/A	N/A
	Utility at 12 weeks	190	179	369	N/A	N/A	N/A
	Utility at the end of the trial	189	180	369	N/A	N/A	N/A
	PLICS (total)	140	229	369	199	334	533
	Diaries (total)	91	278	369	145	388	533
	Concomitant medicines (total)	314	55	369	466	67	533
Antibiotic-impregnated VPS	Utility at baseline	244	125	369	N/A	N/A	N/A
	Utility early post operatively	231	138	369	N/A	N/A	N/A
	Utility at 12 weeks	174	195	369	N/A	N/A	N/A
	Utility at the end of the trial	179	190	369	N/A	N/A	N/A
	PLICS (total)	129	240	369	208	327	535
	Diaries (total)	98	271	369	146	389	535
	Concomitant medicines (total)	309	60	369	463	72	535
Silver-impregnated VPS	Utility at baseline	224	136	360	N/A	N/A	N/A
	Utility early post operatively	220	140	360	N/A	N/A	N/A
	Utility at 12 weeks	177	183	360	N/A	N/A	N/A
	Utility at the end of the trial	191	169	360	N/A	N/A	N/A
	PLICS (total)	130	230	360	210	316	526
	Diaries (total)	87	273	360	132	394	526
	Concomitant medicines (total)	310	50	360	467	59	526
Overall	Utility at baseline	708	390	1098	N/A	N/A	N/A
	Utility early post operatively	684	414	1098	N/A	N/A	N/A
	Utility at 12 weeks	541	557	1098	N/A	N/A	N/A
	Utility at the end of the trial	559	539	1098	N/A	N/A	N/A
	PLICS (total)	399	699	1098	617	977	1594
	Diaries (total)	276	822	1098	423	1171	1594
	Concomitant medicines (total)	933	165	1098	1396	198	1594

N/A, not applicable.

a The PLICS data were considered complete when at least one cost was reported as inpatient, outpatient or both. Diaries within CRFs were considered complete when at least one episode of health-care resource use was reported. Concomitant medications were considered complete when at least one prescription was reported. Responses to the EQ-5D-3L were considered complete (for each administration) if respondents had assigned a level to each of the five domains.

TABLE 26 Number of trial participants with complete data for PLICS, concomitant medications and diary responses, by intervention group, and their characteristics

Group or characteristic	PLICS data, *n* (%)	Concomitant medications, *n* (%)	Diaries, *n* (%)
Standard	199 (37.3)	466 (87.4)	145 (27.2)
Antibiotic impregnated	208 (38.9)	463 (86.5)	146 (27.3)
Silver impregnated	210 (39.9)	467 (88.8)	132 (25.1)
Paediatric	261 (42.3)	550 (39.4)	167 (39.5)
Adult aged 16–65 years	200 (32.5)	461 (33.0)	116 (27.4)
Adult aged ≥ 65 years	156 (25.3)	385 (27.6)	140 (33.1)
Male	303 (49.1)	698 (50.0)	205 (48.5)
Female	314 (51.0)	698 (50.0)	218 (51.5)

TABLE 27 Disaggregated health-care resource use from randomisation up to 24 months, by intervention group

	Trial group, mean count (range), *n* participants		
Item of resource use	Standard VPS	Antibiotic-impregnated VPS	Silver-impregnated VPS
GP visits	2.7 (0–25), 140	1.9 (0–10), 112	2.0 (0–9), 110
Nurse visits	2.8 (0–18), 37	2.5 (0–18), 44	1.4 (0–5), 29
Health visitor	3.0 (0–10), 27	5.3 (0–25), 20	3.4 (0–15), 26
Physiotherapy	4.0 (0–30), 32	4.5 (0–21), 34	3.9 (0–12), 38
Occupational therapist	3.7 (0–35), 20	3.4 (0–15), 21	2.0 (0–6), 25
Inpatient HRG			
AA13A	1.0 (0–1), 27	1.0 (0–1), 36	1.0 (0–2), 439
AA19A	1.4 (0–3), 7	1.5 (0–4), 8	1.5 (0–3), 10
AA25A	0.6 (0–3), 12	0.72 (0–3), 11	0.85 (0–2), 7
AA52C	1 (0–1), 12	1 (0–1), 9	0.83 (0–2), 12
PA44Z	2.3 (0–4), 3	3.0 (0–5), 4	4.0 (0–7), 3
PA42Z	6.7 (0–19), 4	6.7 (0–15), 4	3.0 (0–6), 4
AA52G	1.5 (0–3), 6	1.0 (0–1), 8	1.2 (0–3), 10
PM44Z	0.4 (0–4), 10	1 (0–1), 5	0.46 (0–6), 13
Outpatient HRG			
WF01A	5.7 (0–36), 63	5.7 (0–72), 67	5.5 (0–28), 60
WF01B	2.4 (0–16), 38	2.0 (0–9), 38	1.7 (0–5), 38
VB05Z	0.44 (0–5), 18	0.28 (0–11), 25	0.25 (0–22), 35
VB02Z	1.3 (0–3), 7	1.8 (0–4), 4	2.0 (0–3), 3
VB03Z	1.0 (0–1), 2	1.5 (0–4), 6	1.7 (0–2), 3
VB09Z	6.0 (0–6), 1	1.0 (0–1), 3	1.0 (0–1), 3
WF01C	1 (0–1), 5	0.77 (0–2), 9	0.62 (0–4), 8
BZ	1 (0–1), 8	0.5 (0–4), 6	1 (0–1), 1

Note
Listed are the most frequent items of resource use, including the top 16 HRGs (out of 463).

Based on the observed data, the majority of costs related to hospital inpatient procedures, followed by outpatient clinic visits and contacts with health-care professionals in primary care (*Table 28*). With the exception of GP costs, there were no significant differences in costs between the antibiotic- or silver-impregnated VPSs and the standard VPS catheter groups.

The adjusted base-case analysis yielded a total cost of £18,707 (97.5% CI £13,888 to £26,966) in the standard VPS group, £14,192 (97.5% CI £12,450 to £17,786) in the antibiotic-impregnated VPS group, and £17,385 (97.5% CI £14,649 to £22,355) in the silver-impregnated VPS group. Based on incremental analysis, the difference in 2-year costs between the silver-impregnated and the standard VPS groups was −£1322 (97.5% CI −£9295 to £5592), and was −£3192 (97.5% CI −£8382 to £1227) between the antibiotic-impregnated and the silver-impregnated VPSs (see *Appendix 3*, *Table 49*).

Overall, the cost of VPS failures was £8604 (97.5% CI £4696 to £12,511) due to any cause; £10,844 (97.5% CI £4267 to £17,436) due to confirmed infection; £5479 (97.5% CI £882 to £10,076) due to mechanical failure; £5149 (97.5% CI −£542 to £10,840) due to functional failure; and £7028 (97.5% CI −£5803 to £19,859) due to patient factors.

Economic health outcomes

The proportions of participants who experienced a first VPS failure (due to any cause) within 2 years were 130 out of 533, 132 out of 535 and 136 out of 526 in the standard, antibiotic-impregnated and silver-impregnated VPS groups, respectively. In the base-case analysis, with a 3.5% annual discount rate, the VPS failure rate was 23.3% (97.5% CI 19.1% to 27.3%) in the standard VPS group, 25.9% (97.5% CI 21.8% to 30.3%) in the antibiotic-impregnated VPS group and 25.4% (97.5% CI 20.9% to 29.6%) in the silver-impregnated VPS group.

The distribution of participants (or their parents' or guardians') responses to the EQ-5D questionnaires are presented in *Figure 6*. There was a low return rate of the EQ-5D questionnaire, with combined (EQ-5D-Y, EQ-5D-3L-Proxy and EQ-5D-3L) data available for only about half of the participants. Their responses suggested that there was a general improvement across all dimensions from baseline to the end of the trial, with no clear differences between intervention groups for any given dimension. Similarly, the response rates of participants, their parents or their guardians to the EQ-VAS, which are presented in *Appendix 3*, *Table 50*, were also low, but indicate a general trend for improvement from baseline to the end of the trial.

Quality of life, assessed using the Hydrocephalus Outcome Questionnaire

The return rate for the HOQ was low, and is summarised in *Appendix 3*, *Table 51*. Because of the low return rate, there were insufficient data to formally analyse the HOQ by mixed models, with the patient model not converging and the parent model output containing warnings that the final Hessian matrix not positive definite. For this reason, the patient questionnaire and the parent questionnaire are presented descriptively in *Appendix 3*, *Tables 52* and *53*.

Incremental analysis: base case

In the base-case analysis, both antibiotic-impregnated and silver-impregnated VPSs were located in the south-west quadrant of the cost-effectiveness plane; in relation to the standard VPS, they were less effective (associated with higher rates of first VPS failure due to any reason), but also less expensive, overall. The interpretation in the south-west quadrant is that interventions are more cost-effective with increasingly negative ICERs (larger savings associated with small health losses result in increasingly negative ICERs). Incrementally, silver-impregnated VPSs save £62,358 for each additional failure, compared with standard VPSs, and antibiotic-impregnated VPS catheters save £638,600 per additional failure, compared with silver-impregnated VPSs.

TABLE 28 Disaggregated 2-year costs from randomisation, by intervention group

Costs relating to	Trial group, mean (97.5% CI) (£)			Difference between antibiotic-impregnated and standard VPS, mean (97.5% CI) (£)	Difference between silver-impregnated and standard VPS, mean (97.5% CI) (£)
	Standard VPS	Antibiotic-impregnated VPS	Silver-impregnated VPS		
Inpatient visits	14,181 (10,618 to 20,557)	11,738 (9730 to 14,401)	14,481 (11,868 to 17,744)	−2442 (−8954 to 1933)	300 (−6242 to 4965)
Outpatient visits	2336 (1542 to 3651)	2117 (1499 to 2989)	2220 (1562 to 3442)	−219 (−1649 to 940)	−116 (−1559 to 1295)
GP visits	188 (108 to 373)	91 (71 to 121)	91 (66 to 129)	−97 (−280 to −11)	−97 (−277 to −7)
Nurse visits	133 (57 to 314)	97 (49 to 169)	60 (28 to 119)	−36 (−224 to 67)	−73 (−254 to 22)
Health visitor	303 (77 to 784)	131 (76 to 205)	287 (157 to 378)	−171 (−663 to 64)	−15 (−490 to 245)
Physiotherapy	500 (242 to 1110)	190 (121 to 279)	655 (356 to 1084)	−310 (−921 to −35)	155 (−472 to 666)
Occupational therapist	81 (18 to 184)	139 (60 to 243)	73 (15 to 175)	58 (−69 to 173)	−8 (−123 to 119)
Other health-care professionals	392 (211 to 817)	367 (189 to 682)	246 (190 to 328)	24 (−465 to 329)	−145 (−592 to 57)
Concomitant medications	203 (126 to 342)	125 (80 to 189)	272 (138 to 513)	−78 (−219 to 20)	68 (−110 to 313)

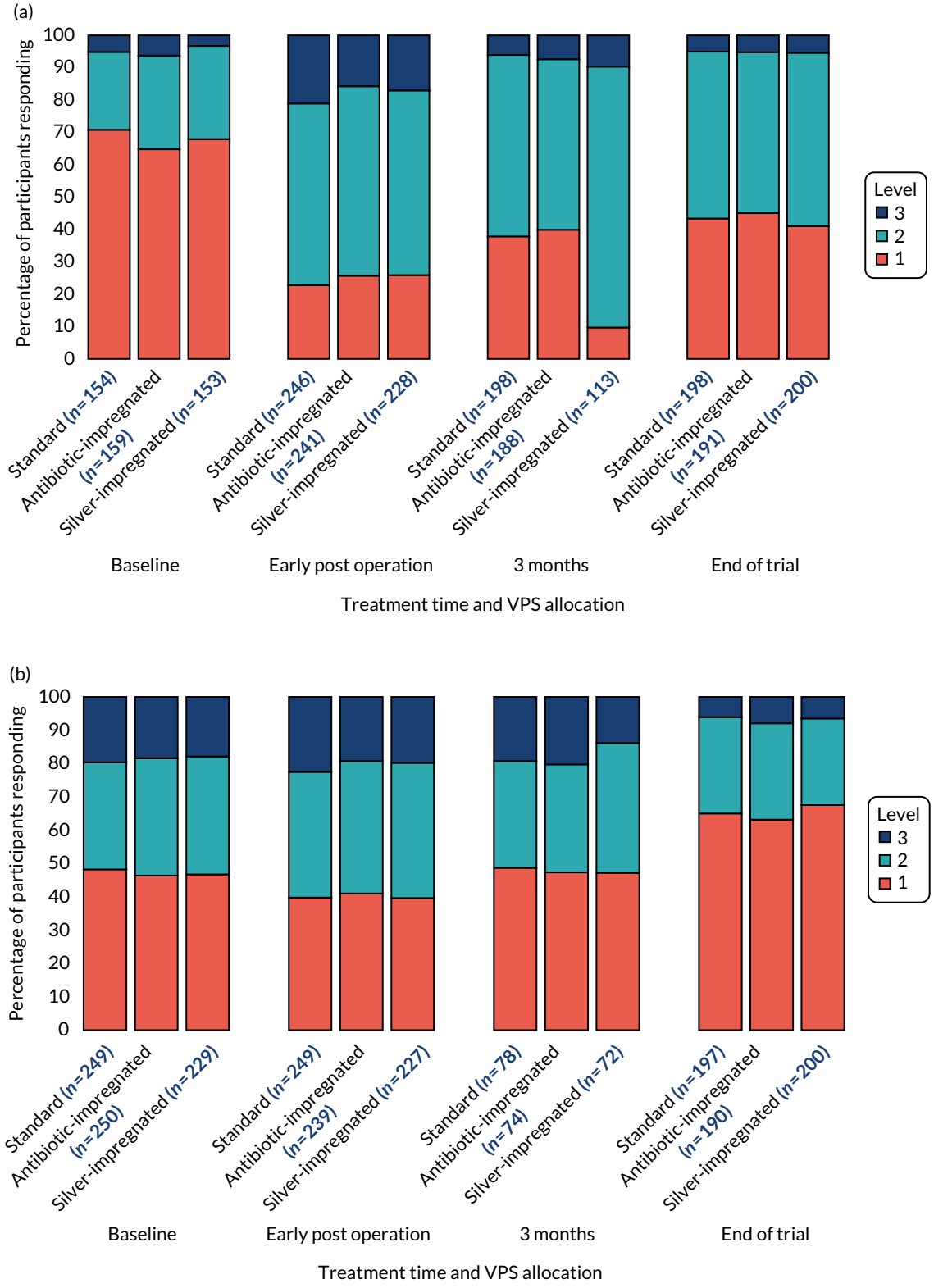

FIGURE 6 Distribution of participants' responses to each EQ-5D attribute, by treatment allocated and time. Levels range from 1 to 3, with 3 representing the most severe problem. The numbers of completed responses (*n*) are reported by intervention group. (a) Mobility; (b) self-care; (c) usual activities; (d) pain or discomfort; (e) anxiety or depression. (*continued*)

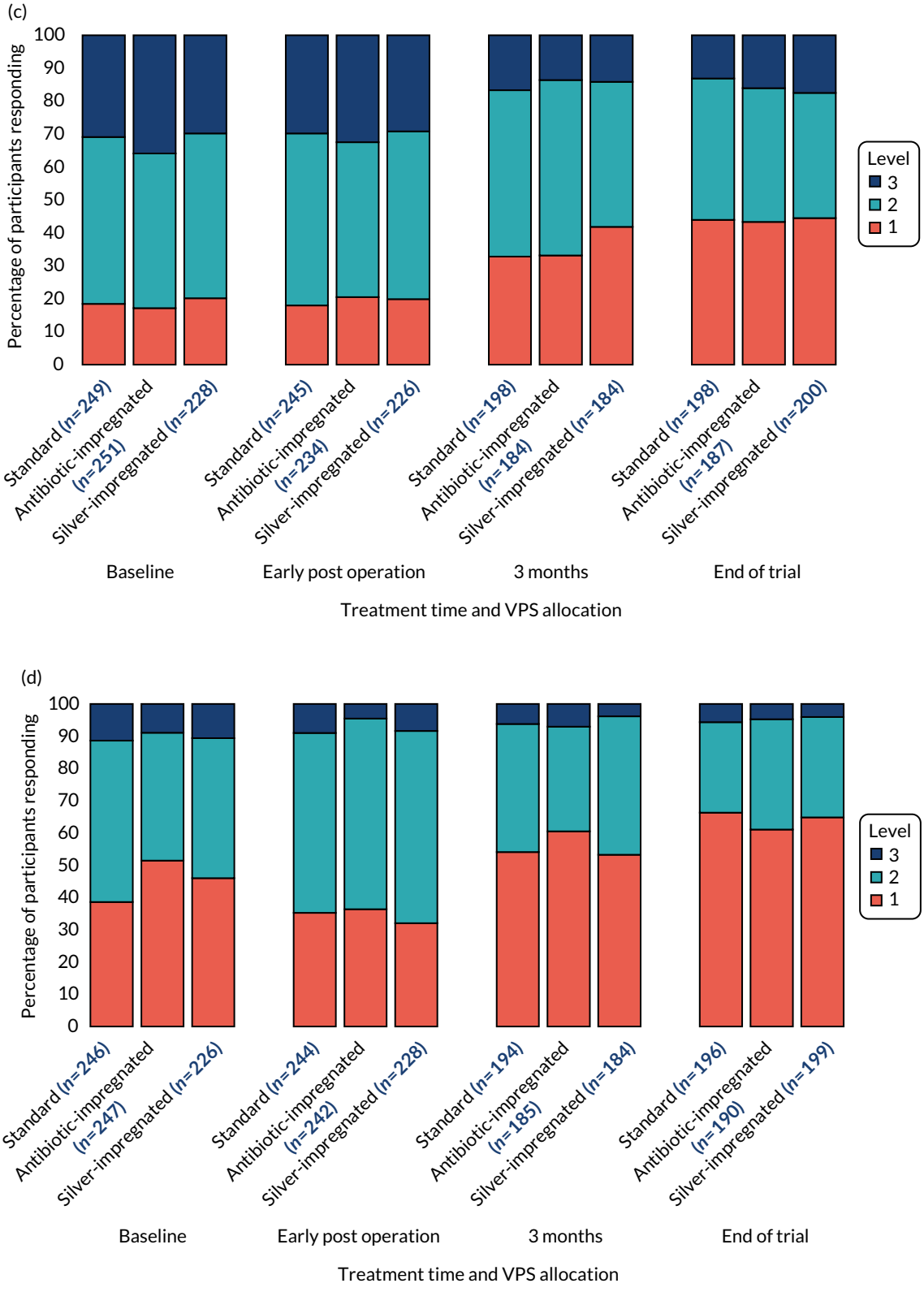

FIGURE 6 Distribution of participants' responses to each EQ-5D attribute, by treatment allocated and time. Levels range from 1 to 3, with 3 representing the most severe problem. The numbers of completed responses (*n*) are reported by intervention group. (a) Mobility; (b) self-care; (c) usual activities; (d) pain or discomfort; (e) anxiety or depression. (*continued*)

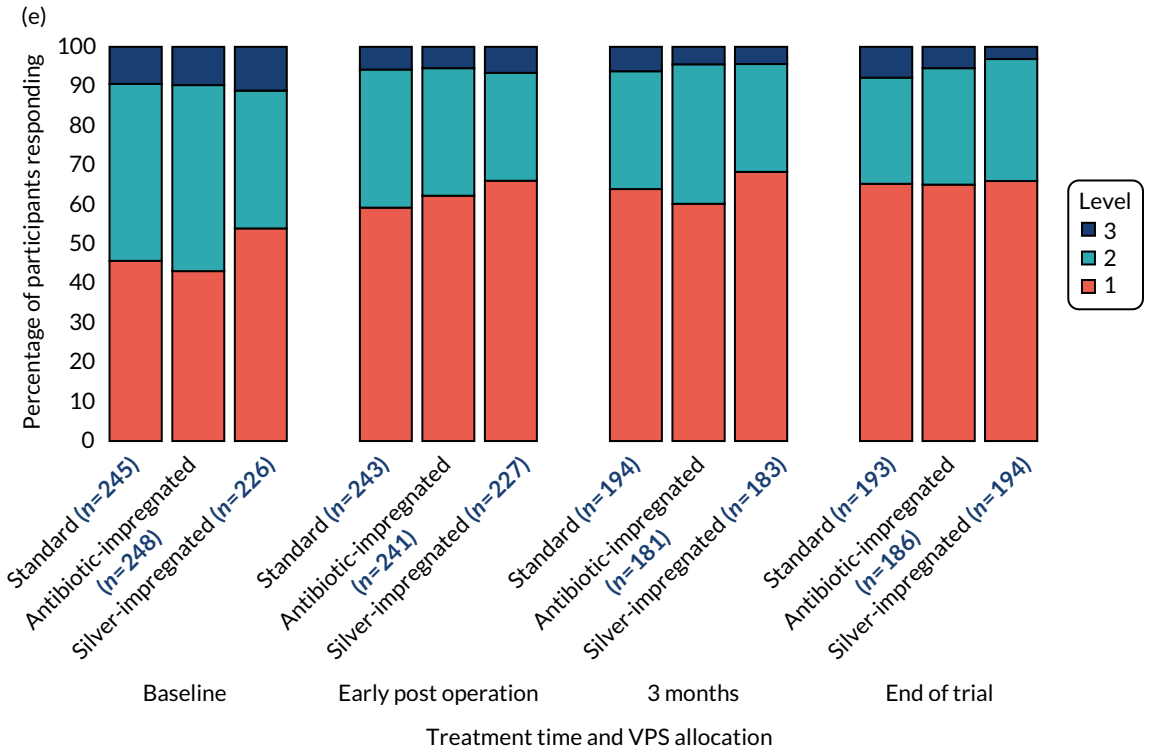

FIGURE 6 Distribution of participants' responses to each EQ-5D attribute, by treatment allocated and time. Levels range from 1 to 3, with 3 representing the most severe problem. The numbers of completed responses (*n*) are reported by intervention group. (a) Mobility; (b) self-care; (c) usual activities; (d) pain or discomfort; (e) anxiety or depression.

Sensitivity analyses

The ICERs were sensitive to changes in the unit costs of antibiotic-impregnated VPSs (*Table 29*). Compared with silver-impregnated VPSs, the incremental cost per first VPS failure became positive (north-east quadrant of the cost-effectiveness plane) when the cost of an antibiotic-impregnated VPS exceeded 10 times its current list price. The ICER (of antibiotic- vs. silver-impregnated VPSs) was insensitive to a change in the cost of silver-impregnated VPSs, even at 10% of the list price. However, a 35% reduction in cost, combined with a ninefold increase in the cost of antibiotic-impregnated VPSs, resulted in a positive ICER. In the comparison of silver-impregnated with standard VPSs, a fivefold increase in the cost of a silver-impregnated VPS resulted in a positive ICER (north-east quadrant of the cost-effectiveness plane), whereas no degree of reduction in the price of standard VPSs had a meaningful influence on the ICER.

The ICERs were stable to changes in discount rate (ranging from undiscounted to a discount rate of 6% per annum) and choice of regression modelling (*Table 30*). However, there were differences in cost-effectiveness when limiting the analysis to observed data, without multiple imputation. In this analysis, antibiotic-impregnated VPS dominated silver-impregnated VPS catheters, and saved £56,771 for each additional failure, compared with standard VPS catheters.

Based on the GLM, whereby the gamma family and log-link performed best (lowest AIC and BIC values and a coefficient close to 2 in the modified Park test), the ICERs were consistent with the base case, with a saving of £336,000 per additional VPS failure (due to any cause) with antibiotic-impregnated shunt catheters (compared with silver-impregnated VPSs), and a saving of £85,802 per additional VPS failure (due to any cause) with silver-impregnated VPS catheters (compared with standard VPSs).

TABLE 29 Results of the bivariate sensitivity analyses: the impact on the ICERs of changing the price of antibiotic-impregnated, silver-impregnated and standard VPSs

ICER vs. silver-impregnated VPS	**x-fold decrease in the price of a silver-impregnated VPS**									
x-fold increase in the price of an antibiotic-impregnated VPS	1	0.9	0.8	0.7	0.6	0.5	0.4	0.3	0.2	0.1
1	−638,600	−631,368	−624,135	−616,903	−609,670	−602,438	−595,206	−587,973	−580,741	−573,508
2	−561,800	−554,568	−547,335	−540,103	−532,870	−525,638	−518,406	−511,173	−503,941	−496,708
3	−485,000	−477,768	−470,535	−463,303	−456,070	−448,838	−441,606	−434,373	−427,141	−419,908
4	−408,200	−400,968	−393,735	−386,503	−379,270	−372,038	−364,806	−357,573	−350,341	−343,108
5	−331,400	−324,168	−316,935	−309,703	−302,470	−295,238	−288,006	−280,773	−273,541	−266,308
6	−254,600	−247,368	−240,135	−232,903	−225,670	−218,438	−211,206	−203,973	−196,741	−189,508
7	−177,800	−170,568	−163,335	−156,103	−148,870	−141,638	−134,406	−127,173	−119,941	−112,708
8	−101,000	−93,768	−86,535	−79,303	−72,070	−64,838	−57,606	−50,373	−43,141	−35,908
9	−24,200	−16,968	−9735	−2503	4730	11,962	19,194	26,427	33,659	40,892
10	52,600	59,832	67,065	74,297	81,530	88,762	95,994	103,227	110,459	117,692
ICER vs. standard VPS	**x–fold decrease in the price of a standard VPS**									
x-fold increase in the price of a silver-impregnated VPS	1	0.9	0.8	0.7	0.6	0.5	0.4	0.3	0.2	0.1
1	−62,358	−61,547	−60,736	−59,925	−59,113	−58,302	−57,491	−56,679	−55,868	−55,057
2	−45,301	−44,490	−43,678	−42,867	−42,056	−41,244	−40,433	−39,622	−38,810	−37,999
3	−28,243	−27,432	−26,621	−25,809	−24,998	−24,187	−23,375	−22,564	−21,753	−20,942
4	−11,186	−10,375	−9563	−8752	−7941	−7129	−6318	−5507	−4695	−3884
5	5872	6683	7494	8306	9117	9928	10,740	11,551	12,362	13,174
6	22,929	23,741	24,552	25,363	26,175	26,986	27,797	28,608	29,420	30,231
7	39,987	40,798	41,609	42,421	43,232	44,043	44,855	45,666	46,477	47,289
8	57,044	57,856	58,667	59,478	60,290	61,101	61,912	62,724	63,535	64,346
9	74,102	74,913	75,725	76,536	77,347	78,158	78,970	79,781	80,592	81,404
10	91,159	91,971	92,782	93,593	94,405	95,216	96,027	96,839	97,650	98,461

Note
Negative ICERs relate to incremental cost and outcome co-ordinates in the south-west quadrant of the cost-effectiveness plane.

TABLE 30 Results of the sensitivity analyses

VPS	Mean (97.5% CI)				ICER (£ per QALY)
	Total cost (£)	Proportion failure	Incremental cost	Incremental failure	
Base case					
Antibiotic-impregnated	14,192 (12,450 to 17,786)	0.259 (0.218 to 0.303)	−3192 (−8382 to 12,272)	0.005 (−0.046 to 0.063)	−638,600
Silver-impregnated	17,385 (14,649 to 22,355)	0.254 (0.209 to 0.296)	−1322 (−9295 to 5592)	0.021 (−0.035 to 0.078)	−62,358
Standard	18,707 (13,888 to 26,966)	0.233 (0.191 to 0.273)	–	–	–
0% discount rate					
Antibiotic-impregnated	14,331 (12,621 to 18,064)	0.260 (0.219 to 0.302)	−3212 (−8619 to 1534)	−0.006 (−0.048 to 0.061)	−535,333
Silver-impregnated	17,542 (14,768 to 22,523)	0.254 (0.209 to 0.298)	−1340 (−9454 to 5782)	−0.021 (−0.036 to 0.078)	−63,810
Standard	18,882 (14,015 to 27,224)	0.234 (0.192 to 0.275)	–	–	–
1.5% discount rate					
Antibiotic-impregnated	14,269 (12,515 to 17,989)	0.260 (0.219 to 0.301)	−3023 (−8575 to 1527)	−0.006 (−0.048 to 0.060)	−539,821
Silver-impregnated	17,473 (14,570 to 22,449)	0.254 (0.209 to 0.297)	−1332 (−9386 to 5764)	−0.021 (−0.035 to 0.078)	−63,429
Standard	18,805 (13,959 to 27,070)	0.233 (0.191 to 0.273)	–	–	–
6% discount rate					
Antibiotic-impregnated	14,099 (12,378 to 17,776)	0.258 (0.217 to 0.301)	−3179 (−8364 to 1224)	−0.005 (−0.046 to 0.062)	−635,800
Silver-impregnated	17,278 (14,551 to 22,242)	0.253 (0.208 to 0.295)	−1310 (−9184 to 5715)	−0.021 (−0.035 to 0.078)	−62,381
Standard	18,589 (13,802 to 26,721)	0.231 (0.190 to 0.271)	–	–	–
Observed data (without imputation)					
Silver-impregnated	6186 (5842 to 6530)	0.255 (0.247 to 0.258)	–	–	Dominated
Antibiotic-impregnated	5296 (4952 to 5640)	0.250 (0.243 to 0.258)	−545 (−1128 to 2215)	0.010 (−0.046 to 0.065)	−56,771
Standard	5841 (5497 to 6185)	0.241 (0.233 to 0.248)	–	–	–
Generalised linear modelling for costs					
Antibiotic-impregnated	15,012 (12,893 to 18,955)	0.259 (0.218 to 0.303)	−1680 (−8333 to 3033)	−0.005 (−0.046 to 0.063)	−336,000
Silver-impregnated	16,693 (14,397 to 20,888)	0.254 (0.209 to 0.296)	−1819 (−12813 to 4506)	−0.021 (−0.035 to 0.078)	−85,802
Standard	18,512 (13,766 to 26,178)	0.233 (0.191 to 0.273)	–	–	–

Note
Negative ICERs relate to incremental cost and outcome co-ordinates in the south-west quadrant of the cost-effectiveness plane.

Subgroup analyses

A stratified cost-effectiveness analysis indicated that cost-effectiveness was dependent on age (*Table 31*). In paediatrics, antibiotic-impregnated VPS catheters were dominant (south-east quadrant of the cost-effectiveness plane), with mean savings of £5312 and additional benefits of 0.004 VPS failures (due to any reason) averted. Put another way, for every 250 patients first receiving an antibiotic-impregnated instead of a standard VPS catheter, there would be one fewer case of VPS failure (due to any reason), and a cost-saving of £1,328,000.

For adults aged 16–65 years, silver-impregnated VPSs were the most cost-effective, with antibiotic-impregnated VPS catheters being extendedly dominated. In adults aged > 65 years, silver-impregnated VPSs save £29,375 for each additional failure, compared with standard VPSs, and antibiotic-impregnated VPSs save £786,375 per additional failure, compared with silver-impregnated VPSs.

TABLE 31 Results of subgroup analyses, defined by age categories

VPS	Mean (97.5% CI)				ICER (£ per QALY)
	Total cost (£)	Proportion of VPS failure	Incremental cost (£)	Incremental VPS failure	
Base case					
Antibiotic-impregnated	14,192 (12,450 to 17,786)	0.259 (0.218 to 0.303)	−3192 (−8382 to 12,272)	0.005 (−0.046 to 0.063)	−638,600
Silver-impregnated	17,385 (14,649 to 22,355)	0.254 (0.209 to 0.296)	−1322 (−9295 to 5592)	0.021 (−0.035 to 0.078)	−62,358
Standard	18,707 (13,888 to 26,966)	0.233 (0.191 to 0.273)	–	–	–
Paediatrics aged < 16 years					
Antibiotic-impregnated	14,859 (11,650 to 22,381)	0.362 (0.248 to 0.469)	−5312 (−16,289 to 2271)	0.004 (−0.107 to 0.102)	Dominant
Standard	20,171 (14,632 to 33,160)	0.365 (0.242 to 0.484)	–	–	–
Silver-impregnated	19,518 (15,338 to 28,372)	0.384 (0.256 to 0.493)	–	–	Dominated
Adults aged 16–65 years					
Antibiotic-impregnated	13,940 (9748 to 18,489)	0.306 (0.173 to 0.453)	−2651 (−8841 to 2058)	0.039 (−0.063 to 0.149)	Extendedly dominated
Silver-impregnated	16,591 (11,992 to 22,565)	0.266 (0.131 to 0.420)	−2845 (−10,188 to 4751)	0.027 (−0.076 to 0.140)	−105,370
Standard	19,437 (13,109 to 28,306)	0.239 (0.113 to 0.384)	–	–	–
Adults aged > 65 years					
Antibiotic-impregnated	14,730 (11,676 to 21,353)	0.123 (0.069 to 0.179)	−1881 (−8011 to 4666)	0.024 (−0.052 to 0.106)	−78,375
Silver-impregnated	16,611 (12,693 to 23,830)	0.099 (0.043 to 0.157)	−329 (−9205 to 6657)	0.011 (−0.059 to 0.089)	−29,375
Standard	16,941 (12,374 to 27,346)	0.088 (0.036 to 0.138)	–	–	–

Note
Negative ICERs relate to incremental cost and outcome co-ordinates in the south-west quadrant of the cost-effectiveness plane.

Alternative cost-effectiveness and cost–utility analyses

A cost-effectiveness analysis based on the incremental cost per confirmed infection averted indicated that silver-impregnated VPS catheters were dominated by standard VPSs, whereas antibiotic-impregnated VPS catheters were dominant, saving £4059 per 0.030 fewer infection-related VPS failures. Compared with standard VPSs, antibiotic-impregnated VPS catheters save £135,753 per VPS infection avoided (*Table 32*).

TABLE 32 Results of alternative cost-effectiveness and cost–utility analyses

VPS	Mean (97.5% CI)				ICER (£ per QALY)
	Total cost (£)	Outcome	Incremental cost (£)	Incremental outcome	
Confirmed infections					
Antibiotic-impregnated	14,446 (12,660 to 18,054)	0.027 (0.013 to 0.043)	−4059 (−12,567 to 1422)	−0.030 (−0.058 to −0.002)	Dominant
Standard	18,505 (13,872 to 27,274)	0.057 (0.035 to 0.083)	–	–	–
Silver-impregnated	17,331 (14,584 to 22,136)	0.057 (0.038 to 0.080)	–	–	Dominated
Mechanical failures					
Standard	14,110 (14,021 to 27,648)	0.092 (0.066 to 0.120)	–	–	–
Silver-impregnated	17,426 (14,682 to 22,445)	0.119 (0.088 to 0.154)	–	–	Dominated
Antibiotic-impregnated	18,749 (12,303 to 17,564)	0.134 (0.103 to 0.167)	–	–	Dominated
Functional failures					
Silver-impregnated	17,483 (14,767 to 22,396)	0.069 (0.047 to 0.092)	−1163 (−9349 to 5815)	−0.003 (−0.040 to 0.030)	387,667
Standard	18,646 (13,837 to 27,066)	0.072 (0.048 to 0.101)	–	–	–
Antibiotic-impregnated	14,157 (12,397 to 17,576)	0.084 (0.057 to 0.108)	−4488 (−12,919 to 960)	0.011 (−0.027 to 0.049)	−374,000
Patient factors					
Antibiotic-impregnated	14,196 (12,438 to 17,648)	0.008 (0.001 to 0.018)	−4441 (−12,825 to 987)	−0.0006 (−0.015 to 0.012)	7,401,667
Standard	18,638 (13,983 to 27,464)	0.009 (0.001 to 0.018)	–	–	–
Silver-impregnated	17,451 (14,712 to 22,543)	0.009 (0.001 to 0.019)	1186 (−9255 to 5694)	−0.0002 (−0.011 to 0.010)	−3,953,333
Cost–utility analysis based on imputed data					
Silver-impregnated	9115 (7596 to 12,682)	1.319 (1.207 to 1.365)	183 (−3035 to 3854)	0.096 (−0.488 to 0.188)	1904
Standard	8932 (7301 to 11,980)	1.223 (1.136 to 1.298)	–	–	–
Antibiotic-impregnated	9643 (7545 to 11,736)	1.250 (1.163 to 1.336)	–	–	Dominated

Note
Negative ICERs relate to incremental cost and outcome co-ordinates in the south-west quadrant of the cost-effectiveness plane.

For the cost-effectiveness measure of incremental cost per mechanical failure averted, both silver-impregnated and antibiotic-impregnated VPS catheters were dominated by standard VPSs, as they were associated with higher rates of mechanical failures and higher costs than standard VPSs. With regards to functional VPS failures, antibiotic-impregnated VPS catheters are both less effective and less expensive than standard VPSs, whereas silver-impregnated shunt catheters cost an additional £387,667 per additional functional failure averted. The opposite was observed when considering the incremental cost per VPS failure due to patient-related factors, although failure rates due to patient influences are much lower, and the reporting of this outcome was less reliable. Antibiotic-impregnated VPS catheters cost an additional £7.4M per failure averted, whereas silver-impregnated VPS catheters save £3.9M per additional failure, each in comparison with standard shunt catheters.

In the cost–utility analysis of trial participants aged ≥ 5 years, and based on multiple imputation to account for missing data, antibiotic-impregnated VPS catheters were dominated by silver-impregnated VPS. Compared with standard VPSs, silver-impregnated VPSs are £183 more costly, and yield 0.096 additional QALYs overall, resulting in an incremental cost of £1904 per QALY gained. The cost-effectiveness acceptability curve showing the probability of each VPS catheter being cost-effective, by a range of cost-per-QALY thresholds, is depicted in *Figure 7*.

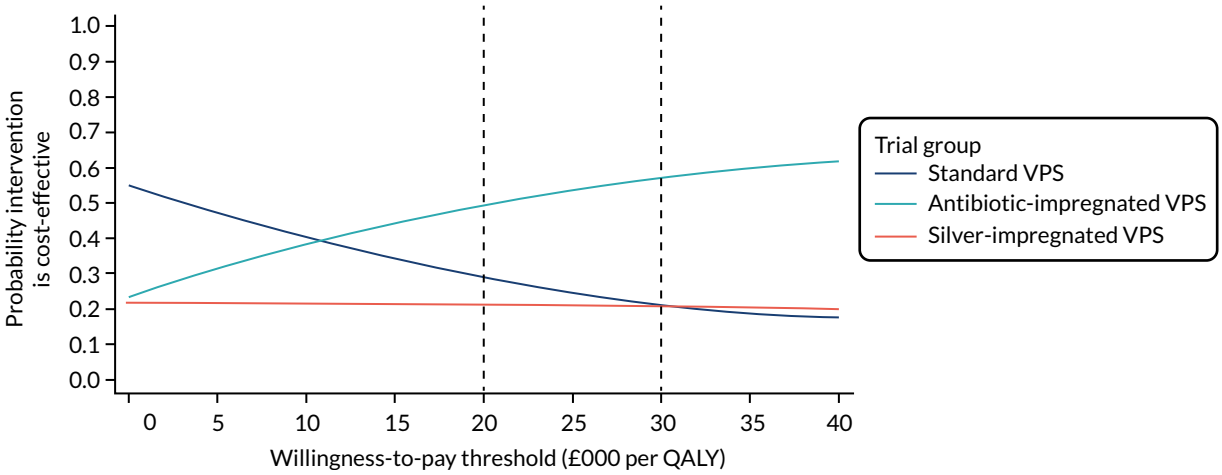

FIGURE 7 Cost-effectiveness acceptability curves indicating the probability of each VPS catheter being cost-effective (based on the incremental cost per QALY gained) for a range of threshold (willingness-to-pay) values. Vertical lines indicate the usual NICE threshold range[53] of £20,000–30,000 per QALY.

Chapter 5 Discussion

Summary of findings

In this trial of patients with hydrocephalus who were undergoing insertion of their first permanent VPS, the infection rates were 6.0% in the standard VPS group, 2.2% in the antibiotic-impregnated VPS group and 5.9% in the silver-impregnated VPS group. Compared with standard VPSs, antibiotic-impregnated VPSs were associated with a significantly lower rate of infection, whereas silver-impregnated VPSs were not. This effect was present across all age categories. There is significant economic benefit for every shunt infection averted. There were notable differences in infection rates for differing aetiologies of hydrocephalus and between different age groups.

Clinical effectiveness

The BASICS trial provides definitive evidence favouring the use of antibiotic-impregnated VPSs to reduce infection. A previously reported underpowered randomised trial[15] demonstrated a trend favouring antibiotic-impregnated over standard VPSs, but did not show a statistically significant difference between the two groups in the risk of infection (RR 0.38, 95% CI 0.11 to 1.30). Silver-impregnated shunt catheters have been evaluated only in a randomised trial of EVDs,[22] which found a reduction in infection from 21.4% (30/140) with standard shunt catheters to 12.3% (17/138) ($p = 0.043$) with silver-impregnated shunt catheters, although this is much higher than the UK national reported infection rate (9.3%) for EVDs.[59] The BASICS trial was conceived to evaluate both antibiotic-impregnated and silver-impregnated VPSs before the widespread introduction of these products into routine practice, despite a lack of evidence. The results of this trial will inform neurosurgery practice and choice of VPS for insertion, to the benefit of patients.

In this trial, the classification of VPS infection was determined by the central review committee. The proportion of culture-positive infections was 68.8% in the standard VPS group, 50.0% in antibiotic-impregnated VPS group and 80.6% in silver-impregnated VPS group; there was a lower rate of culture-positive infection with antibiotic-impregnated VPSs than with either the standard-impregnated or the silver-impregnated VPS. The analysis allowed for culture-negative infections to be included when there was sufficient supporting clinical evidence of VPS infection. We postulate that the presence of antibiotic-impregnated shunt catheters reduced the ability to culture organisms in infected VPSs. This trial would have shown an even greater effect in favour of antibiotic-impregnated VPSs if we had included culture-positive infections only.

The reduction of types of infections seen is consistent with the expected microbiological spectrum of the antibiotic-impregnated VPSs, which are especially active against Gram-positive organisms, and were incorporated to prevent staphylococcus species infections. The culture results show a large reduction in staphylococcal infection with antibiotic-impregnated VPSs, compared with the standard and silver-impregnated VPSs, which accounts for the majority of the infections prevented and supports the biological plausibility as clindamycin and rifampicin are preferentially active against Gram-positive organisms. All three VPS types have a similar number of Gram-negative infections, which the antibiotics were not expected to reduce.

It should be noted that the overall VPS failure rate was the same for all groups, although infection was reduced in the antibiotic-impregnated VPS arm. When infection is removed as a cause, the clean non-infected revision rates were slightly higher in the antibiotic-impregnated VPS group. In the post hoc analysis, the only pattern that could be found was a higher rate of valve change in the antibiotic-impregnated VPS group than in the standard and silver-impregnated VPS groups when analysing the components of the shunt that were changed and/or blocked at surgery, as reported by the operating surgeon on the CRF. Interestingly, the valve itself is not impregnated and is common to all shunt types. Unfortunately, in most cases, the valves were not sent for culture as it was not part of most units' protocol at clean shunt revision. Of note, there were no increased revisions for any group for peritoneal shunt catheters. One of the concerns voiced by some of the surgeons was that silver-impregnated peritoneal shunt catheters were more rigid than the other types, and that this might lead to more peritoneal catheter revisions. This was not borne out in the results.

The reasons for the higher non-infective blockages in the antibiotic-impregnated VPS group are not known. One hypothesis is that the antibiotic-impregnated shunt catheters convert an 'infected' shunt revision to an apparently 'clean' shunt revision in the following ways:

- Low virulent pathogens are restricted to a biofilm in the valve, not causing a CSF change as there is no ventriculitis and not isolated from the revision CSF as the planktonic bacteria are low in number or not able to grow in the presence of the eluted antibiotics.
- A sufficient change in CSF composition and flow (such as debris or high protein) to promote a blockage in the system such as the valve, which is probably the most vulnerable to content of CSF in terms of blockage in view of the intricate mechanical valve mechanisms. This study has not been powered or designed to answer this question directly, but, in future research, this question will be important.

Of note, from a patient well-being and health economic standpoint, a mechanical clean shunt revision, such as a valve change, will have a minor effect on the patient and a minor cost to the NHS. A clean revision for valve change typically involves an overnight stay only, no brain operation (as the ventricular shunt catheter is not changed) and none of the health implications of suffering from clinical meningitis. In contrast, a shunt infection will involve two brain operations: a first operation to remove the whole shunt system and to insert a temporary ventricular shunt catheter (an average of 2 weeks in a hospital bed for both intravenous and intrathecal antibiotics, and the health implications of clinical meningitis) and a second operation to re-insert a whole new shunt system including a ventricular shunt catheter.

In addition to the above, if a patient has ventricular shunt catheter change at shunt revision [as opposed to valve change or peritoneal shunt catheter change, (not a brain operation)], they will lose their driving licence for 6 months because of the increased risk of epilepsy after ventricular shunt catheter revision (as it is a brain operation).

Cost effectiveness

Complications associated with VPS failures are expensive to manage.[32–38] Consequently, the use of VPS catheters, which result in fewer complications, even if more expensive to purchase, could be cost-effective or yield cost savings to the NHS. The economic analysis within the BASICS trial estimated that, although antibiotic-impregnated shunt catheters are about twice the price of standard silicone shunt catheters, this upfront cost could be justified by the reduced infection rate and associated cost savings of further surgery and prolonged hospital care. Based on the primary economic outcome of incremental cost per VPS failure (due to any cause) averted, there appeared to be large potential savings for additional cases of VPS failures with silver- and antibiotic-impregnated VPSs compared with standard VPSs. This conservative estimate does not assume equivalence, despite no difference between groups in VPS failure rate. Had a cost-minimisation analysis been considered appropriate, the saving per patient having an antibiotic-impregnated rather than a standard VPS would be £4515 (97.5% CI £140 to £9170).

In this context, the secondary outcome based on the incremental cost per confirmed infection averted is more relevant, as well as for comparison with previous such analyses, which use the same outcome measure. Notably, antibiotic-impregnated VPS catheters were dominant, saving £4059 per 0.030 fewer infection-related VPS failures. Compared with standard VPSs, antibiotic-impregnated VPS catheters save £135,753 per VPS infection avoided. In terms of determining technical efficiency, no cost-effectiveness threshold is necessary, given the dominance of antibiotic-impregnated VPS catheters.

For the purposes of informing decisions on allocative efficiency, the cost–utility analysis of participants aged ≥ 5 years indicated that antibiotic-impregnated VPSs were dominant, whereas the incremental cost per QALY gained with silver-impregnated VPSs was £1904, which is within the threshold applied by NICE for the determination of cost-effectiveness. However, the cost–utility analysis was limited, with respect to missing data and the exclusion of participants who were at the highest risk of VPS infections.

The analyses are robust to a range of assumptions and analytic approaches. Important subgroup analyses indicate differences in cost-effectiveness by age. The risk of infection in the BASICS trial was highest in paediatrics; it was lower for adults and was particularly low for the elderly. Some patterns also emerged with the aetiology of hydrocephalus; for example, congenital causes and post-haemorrhagic hydrocephalus (both prevalent in the paediatric age group) resulted in much higher infection rates than those observed for other aetiologies seen in older patients. Although the primary economic analysis was based on all-cause VPS failures, subgroup analyses demonstrated higher cost-effectiveness in paediatrics than in adult populations.

Generalisability and cost impact

In the context of the NHS, there should be a major health benefit and cost-saving impact by routinely adopting antibiotic-impregnated VPSs for all first-time VPS insertions for hydrocephalus.

Clearly, in paediatrics, for whom the effect of reduction in shunt infections is greatest, the economic benefit will also be the most significant. For example, for every 100 paediatric new VPS insertions, using antibiotic-impregnated rather than standard shunt catheters should avert up to six or seven shunt infections, which translates to a potential cost saving of between £814,000 and £950,000. Even in those aged > 65 years, averting one infection per 100 shunts could potentially save £135,753.

Such savings may well translate to equivalent health economies, such as the in the USA, but clearly the potential value and savings will vary in different health models internationally.

Strengths and limitations

The strengths of this trial are that (1) infections were centrally classified by a panel blinded to treatment allocation, thereby removing the risk of treating-surgeon bias; (2) participant retention was very high owing to the nature of the intervention and the primary outcome (patients with infected VPSs are always re-admitted to hospital); (3) patient withdrawal was low ($n = 53$, 3.3%) so it is unlikely that events were missed; (4) participants were recruited across the whole of the UK and the Republic of Ireland to encompass all ages and socioeconomic classes; and (5) the trial sample size was large.

Some limitations of the trial should be noted. First, it was not possible to blind the treating neurosurgeon to the VPS type, because the physical appearance of each shunt catheter is distinctive. Participants were blinded to the shunt catheter type, and shunt catheter type was not recorded in patient records. The majority of VPS revisions and removals for infection happen as emergencies and are managed by the emergency neurosurgery team. Therefore, the likelihood of the same neurosurgeon who inserted the VPS being involved in the decision to remove the VPS was low,

given the work rotas of neurosurgical staff. Furthermore, there was high agreement (95.7%) in the classification of VPS infection between treating surgeons and the central review panel, suggesting that any bias that the treating surgeon may have had did not affect the study conclusion. Second, ventriculoatrial and ventriculopleural shunts were excluded, although we postulate that the results are translatable to patients undergoing these procedures. Finally, the return rate for patient-reported outcomes was low, thereby limiting the analysis of the impact of VPS infection.

Limitations to the economic evaluation include a lack of detailed costing for revisions, and failure to obtain Hospital Episode Statistics data from NHS Digital, as per protocol. Reliance on PLICS data mitigated these limitations, but, as with other data on costs, there was a high degree of missingness due to some centres not being able to share electronic data and patient questionnaires not being returned. This was addressed using robust methods (multiple imputation), but still may have introduced bias to the analysis.

Safety

The data suggest that there is no increased health risk in using impregnated shunt catheters. There were no serious AEs. All of the AEs that were seen were expected events predominantly related to expected shunt revisions and/or due to re-admission for expected known complications associated with VPS surgery; no differences were seen between catheter types.

Implications for practice and health care

From a patient perspective and that of the treating clinician, the hospital and the health service, every effort to reduce shunt infection should be made, and health technologies such as antibiotic-impregnated shunt catheters, with their potential to reduce VPS infections, deserve proper evaluation through appropriately planned and powered trials.

Having demonstrated a marked reduction in such infections, with all of the potentially catastrophic and life-changing health sequalae that result from each infection, the BASICS trial has provided evidence to support that the adoption of antibiotic-impregnated shunt catheters is justified in all patients receiving their first VPS in the UK. The increased upfront cost of the impregnated shunt catheters is offset by the added health economic benefit demonstrated in the health economic analysis and in a previous publication.[39] The benefits and implications, both from an efficacy and health economic point of view, are most pronounced in younger patients.

A wider discussion and analysis, particularly from a health economics point of view, is required when considering recommendations and implications globally.

Conclusions

In conclusion, antibiotic-impregnated shunt catheters significantly reduce the VPS infection rate and the probability of infection, compared with standard silicone shunt catheters in all age groups, whereas silver-impregnated shunt catheters do not. The routine use of these shunt catheters would result in a significant cost saving to the NHS.

These results support the use of antibiotic-impregnated shunt catheters in the treatment of patients undergoing insertion of a first VPS for hydrocephalus.

Implications for future research

To our knowledge, the BASICS trial is the largest-ever prospective randomised trial for VPSs in hydrocephalus worldwide.

A critical value-added aspect of the BASICS trial was the development of systematic clinical sample collection (of CSF and blood) from participants undergoing VPS insertion. We have established a unique neurosurgical patient sample collection, which will enable us to identify surrogate markers of VPS infection in CSF or blood using molecular techniques (transcriptomics/proteomics); to assess whether or not infection may be associated with shunt failure cases (by detection of pathogen nucleic acid via next-generation sequencing); and to begin to explore whether or not host differences contribute to the different rates of infection in children, compared with adults. Proteomic analysis of CSF has already been undertaken to identify a series of candidate surrogate markers of neurosurgical infection. These candidate markers are now being re-tested among the BASICS trial samples to assess their accuracy in identifying confirmed infection. The BASICS trial sample collection, stored at the University of Liverpool, is a valuable resource to help answer the ongoing questions around VPS infection identified in the BASICS trial (as outlined in this paragraph) and to support future additional studies.

A large number of data was collected regarding aetiology, surgical techniques, types of valves and the technology used, which can guide future management and trials. We plan to undertake further analysis exploring patterns related to mechanical shunt failure. This is led by the results and will, therefore, be post hoc. We also plan to create a detailed shunt failure model and predictive score. Failure and infection rates across different aetiologies of hydrocephalus will be analysed further.

Surgical techniques and factors that potentially affect failure rates will be further analysed, such as the use of neuronavigation and the placement of the ventricular shunt catheter, surgical site infection information collected at the time of surgery and seniority of the surgeon. This may feed further questions and prospective randomised studies.

From a methodological perspective, the economic evaluation was significantly affected by missing data. However, organisational familiarity with the procedures and requirements for accessing routine data, post General Data Protection Regulation,[60] should facilitate Hospital Episode Statistics data access from NHS Digital in future trials. Acute trusts are now mandated to produce PLICS data, and early engagement with hospital finance offices should resolve many of the difficulties that were faced in the BASICS trial. Poor response rates to questionnaires is a common problem in self-reported resource use. Further research into methods to mitigate this ought to focus not just on technical solutions, but also on operational solutions, including a broader appreciation that achieving complete data on economic outcomes should be regarded as having equal importance to achieving complete data on primary clinical end points. This may be especially relevant for time-to-event analyses, in which costs and disutilities are most likely to accrue after such events.

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Contributions of authors

Conor L Mallucci (https://orcid.org/0000-0002-5509-0547) (Chief Investigator and Consultant Neurosurgeon) developed the trial protocol in collaboration with co-investigators. He oversaw the delivery of the trial, prepared trial update reports and oversaw clinical aspects of the statistical analysis plan and clinical interpretation of the trial data. He co-led the preparation of the final report (drafting, reviewing and editing). He was chairperson of the TMG and a member of the central review panel.

Michael D Jenkinson (https://orcid.org/0000-0003-4587-2139) (Co-Chief Investigator and Consultant Neurosurgeon) developed the funding application and trial protocol in collaboration with co-investigators. He contributed to clinical interpretation of the trial data and to the preparation of the final report (drafting, reviewing and editing).

Elizabeth J Conroy (https://orcid.org/0000-0003-4858-727X) (Trial Statistician) contributed to protocol development and data capture methods, wrote the statistical analysis plan, undertook the final statistical analysis under the supervision of **Carrol Gamble**, prepared data for reports throughout the trial, prepared data tables and figures for final report and co-led the preparation of the final report.

John C Hartley (https://orcid.org/0000-0003-0503-5985) (Trial Microbiologist) contributed to protocol development, data capture methods, central classification of infections, preparation and review of progress and final reports.

Michaela Brown (https://orcid.org/0000-0002-7772-271X) (Senior Statistician) contributed to protocol development and data capture methods, proposed statistical analysis methods, approved the statistical analysis plan and oversaw trial monitoring activities.

Tracy Moitt (https://orcid.org/0000-0002-5579-996X) (Senior Trials Manager) contributed to protocol development, gave guidance and support on all aspects of governance and trial delivery and supported the preparation of progress reports. She also contributed to the final report (drafting and reviewing).

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Tom Kearns (https://orcid.org/0000-0001-5416-8376) (Trial Co-ordinator) contributed to protocol development, all aspects of governance and study delivery and preparation of progress reports. He also contributed to the final report (reviewing).

Michael J Griffiths (https://orcid.org/0000-0003-1851-6155) (Senior Lecturer in Paediatric Neurology) co-ordinated and developed the sample collection substudy; contributed to protocol development; oversaw sample recruitment, collection and storage; and contributed to the preparation of the final report (reviewing, editing).

Giovanna Culeddu (https://orcid.org/0000-0001-5032-4255) (Study Health Economist) contributed to protocol development and data capture methods, undertook the economic analysis under the supervision of Dyfrig Hughes and contributed to the final report (drafting).

Tom Solomon (https://orcid.org/0000-0001-7266-6547) (Professor of Neurology) helped devise the trial, assisted with obtaining grant funding and reviewed the final report.

Dyfrig Hughes (https://orcid.org/0000-0001-8247-7459) (Senior Health Economist) led the economic evaluation, contributed to protocol development and data capture methods and contributed to the writing of the report (drafting, reviewing and editing).

Carrol Gamble (https://orcid.org/0000-0002-3021-1955) (Statistical Lead) led trial design and developed the funding application, trial protocol and data capture methods in collaboration with co-investigators. She led blind review of the data and supervised the final analysis. She also contributed to the preparation of the final report (drafting, reviewing and editing).

All authors were members of the TMG.

Publications

Jenkinson MD, Gamble C, Hartley JC, Hickey H, Hughes D, Blundell M, *et al.* The British antibiotic and silver-impregnated catheters for ventriculoperitoneal shunts multi-centre randomised controlled trial (the BASICS trial): study protocol. *Trials* 2014;**15**:4.

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Data-sharing statement

All requests for data should be sent to the corresponding author. Access to available anonymised data may be granted following review.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 2 Clinical effectiveness study: additional data

TABLE 33 Recruitment rates by centre

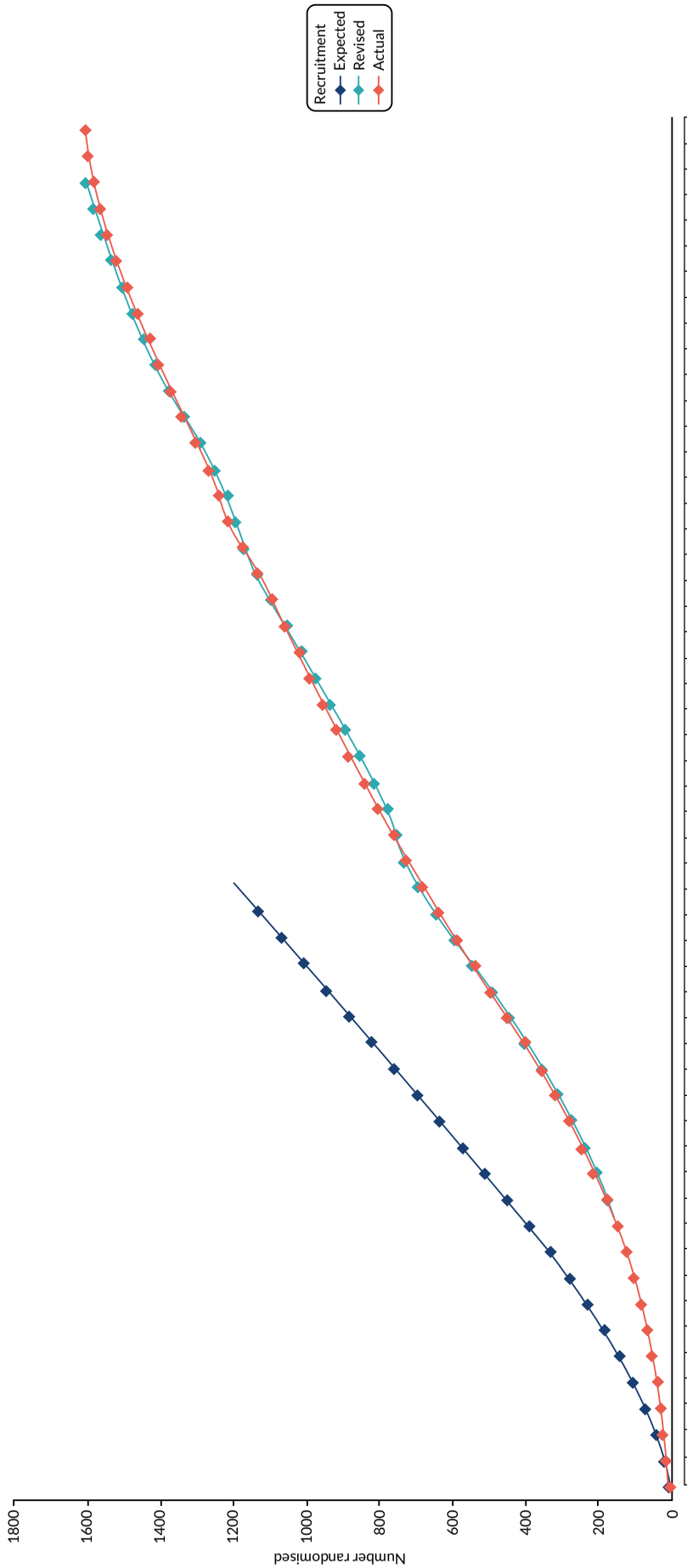
Centre code	Date of centre opening[a]	Date of centre closure	Initial planned total recruitment (*n*)	Date of first randomisation	Date of last randomisation	Number randomised
0243	26 June 2013	9 October 2017	70	26 June 2013	12 September 2017	119
0114	3 July 2013	30 September 2017	115	5 July 2013	15 September 2017	175
0578	24 July 2013	9 October 2017	100	25 July 2013	9 October 2017	155
0232	1 October 2013	28 August 2015	50	29 December 2013	12 August 2015	22
0249	7 October 2013	31 August 2017	100	16 October 2013	4 August 2017	71
0400	8 October 2013	30 September 2017	80	23 October 2013	4 July 2017	82
0213	1 November 2013	30 September 2017	90	27 November 2013	13 September 2017	141
0248	21 November 2013	30 September 2017	50	16 December 2013	10 May 2017	41
0133	10 December 2013	31 August 2016	40	28 January 2014	24 June 2016	30
0007	21 January 2014	30 September 2017	60	7 February 2014	13 September 2017	85
0246	12 March 2014	30 September 2017	65	29 April 2014	22 September 2017	48
0352	1 April 2014	30 September 2017	65	7 April 2014	20 September 2017	129
0030	29 April 2014	30 September 2017	115	17 June 2014	22 September 2017	92
0185	17 June 2014	30 September 2017	65	26 June 2014	10 July 2017	188
0161	25 September 2014	30 September 2017	60	25 September 2014	15 December 2016	36
0361	1 October 2014	31 August 2016	20	31 October 2014	3 September 2015	5
0393	1 October 2014	31 August 2016	20	4 March 2015	14 January 2016	8
0006	7 January 2015	30 September 2017	0	30 January 2015	19 May 2017	22
9999	23 February 2015	30 September 2017	35	23 February 2015	5 June 2017	69
0672	1 April 2015	30 September 2017	0	16 April 2015	4 September 2017	73
0004	20 October 2015	30 September 2017	0	6 November 2015	9 September 2016	14
All centres	26 June 2013	9 October 2017	1200	26 June 2013	9 October 2017	1605

a Table ordered by date of centre opening.

TABLE 34 Screening summary by centre

Centre code[a]	Number of patients screened[b] (*n*)	Ineligible,[c] *n* (%)	Consent not sought,[d] *n* (%)	Consent not provided (a), *n* (%)	Consented but not randomised (b), *n* (%)	Randomised (c), *n* (%)	Consent rate (%) $\frac{b+c}{a+b+c}$
0243	194	47 (24.2)	5 (2.6)	18 (9.3)	5 (2.6)	119 (61.3)	87.3
0114	508	197 (38.8)	68 (13.4)	55 (10.8)	13 (2.6)	175 (34.4)	77.4
0578	223	33 (14.8)	14 (6.3)	14 (6.3)	7 (3.1)	155 (69.5)	92.0
0232	70	32 (45.7)	9 (12.9)	4 (5.7)	3 (4.3)	22 (31.4)	86.2
0249	164	26 (15.9)	28 (17.1)	35 (21.3)	3 (1.8)	71 (43.3)	67.9
0400	266	87 (32.7)	62 (23.3)	26 (9.8)	8 (3.0)	82 (30.8)	77.6
0213	327	105 (32.1)	52 (15.9)	26 (8.0)	3 (0.9)	141 (43.1)	84.7
0248	130	54 (41.5)	11 (8.5)	21 (16.2)	2 (1.5)	41 (31.5)	67.2
0133	105	26 (24.8)	28 (26.7)	21 (20.0)	0 (0.0)	30 (28.6)	58.8
0007	184	12 (6.5)	59 (32.1)	22 (12.0)	6 (3.3)	85 (46.2)	80.5
0246	200	129 (64.5)	12 (6.0)	9 (4.5)	2 (1.0)	48 (24.0)	84.7
0352	238	65 (27.3)	18 (7.6)	20 (8.4)	1 (0.4)	129 (54.2)	86.7
0030	199	71 (35.7)	11 (5.5)	21 (10.6)	3 (1.5)	92 (46.2)	81.9
0185	225	3 (1.3)	17 (7.6)	10 (4.4)	7 (3.1)	188 (83.6)	95.1
0161	53	1 (1.9)	1 (1.9)	15 (28.3)	0 (0.0)	36 (67.9)	70.6
0361	8	1 (12.5)	2 (25.0)	0 (0.0)	0 (0.0)	5 (62.5)	100.0
0393	11	0 (0.0)	0 (0.0)	2 (18.2)	1 (9.1)	8 (72.7)	81.8
0006	36	10 (27.8)	3 (8.3)	1 (2.8)	0 (0.0)	22 (61.1)	95.7
9999	144	34 (23.6)	13 (9.0)	26 (18.1)	2 (1.4)	69 (47.9)	73.2
0672	176	62 (35.2)	19 (10.8)	21 (11.9)	1 (0.6)	73 (41.5)	77.9
0004	44	25 (56.8)	3 (6.8)	2 (4.5)	0 (0.0)	14 (31.8)	87.5

a Table ordered by date of centre opening.
b Patients could be screened multiple times. This table presents the most recent screening per patient.
c Eligible: yes/no; not known for two patients.
d Consent sought: yes/no; not known for seven patients.



	June 2013	July 2013	August 2013	September 2013	October 2013	November 2013	December 2013	January 2014	February 2014	March 2014	April 2014	May 2014	June 2014	July 2014	August 2014	September 2014	October 2014	November 2014	December 2014	January 2015	February 2015	March 2015	April 2015	May 2015	June 2015	July 2015	August 2015	September 2015	October 2015	November 2015	December 2015	January 2016	February 2016	March 2016	April 2016	May 2016	June 2016	July 2016	August 2016	September 2016	October 2016	November 2016	December 2016	January 2017	February 2017	March 2017	April 2017	May 2017	June 2017	July 2017	August 2017	September 2017	October 2017
Expected	5	19	43	72	105	142	183	229	279	332	389	449	510	573	636	698	761	824	886	949	1012	1074	1137	1200	736	696	646	596	546	496	446	396	355	314	276	241	208	177	283	322	356	399	451	497	537	584	636	681	728	765	807	841	887	918	957	992	1025	1061	1094	1135	1178	1218	1243	1271	1306	1346	1376	1403	1429	1459	1476	1506	1536	1566	1586	1606
Revised																									736	696	646	596	546	496	446	396	355	314	276	241	208	177	219	249	283	322	356	399	451	497	537	584	636	681	728	765	807	841	887	918	957	992	1025	1061	1094	1135	1178	1218	1243	1271	1306	1346	1376	1403	1429	1459	1476	1506	1536	1566	1586	1606	1605
Actual	1	15	24	31	40	53	70	83	103	126	147	177	219	249	283	322	356	396	451	497	537	584	636	681	728	765	807	841	887	918	957	992	1025	1061	1094	1135	1178	1218	1243	1271	1306	1346	1376	1403	1429	1459	1487	1521	1548	1566	1586	1606	1605	1606	

FIGURE 8 Recruitment graph.

TABLE 35 Reasons participants received other (not allocated) VPS

Reason	Trial group, *n* (%)			Total (*N* = 16), *n* (%)
	Standard VPS (*N* = 6)	Antibiotic-impregnated VPS (*N* = 7)	Silver-impregnated VPS (*N* = 3)	
Allocated VPS not available	1 (16.7)	1 (14.3)	0 (0.0)	2 (12.5)
Allocated catheter not available	3 (50.0)	1 (14.3)	0 (0.0)	4 (25.0)
Allocated shunt not available	0 (0.0)	1 (14.3)	0 (0.0)	1 (6.3)
Allocated shunt too short	0 (0.0)	1 (14.3)	1 (33.3)	2 (12.5)
Allocated tubing not available	0 (0.0)	1 (14.3)	0 (0.0)	1 (6.3)
Catheter too firm; difficult to remove if required	0 (0.0)	0 (0.0)	1 (33.3)	1 (6.3)
Consultant felt that allocated shunt would affect quality of future scans	0 (0.0)	1 (14.3)	0 (0.0)	1 (6.3)
Miscommunication within the trial team	0 (0.0)	1 (14.3)	1 (33.3)	2 (12.5)
No long catheter available for allocated VPS	1 (16.7)	0 (0.0)	0 (0.0)	1 (6.3)
Technical difficulties	1 (16.7)	0 (0.0)	0 (0.0)	1 (6.3)

The terms catheter, shunt and tube signify shunt catheter.

TABLE 36 Reasons participants did not receive a VPS

Reason	Trial group, *n* (%)			Total (*N* = 4), *n* (%)
	Standard VPS (*N* = 0)	Antibiotic-impregnated VPS (*N* = 2)	Silver-impregnated VPS (*N* = 2)	
MRI brain reviewed (done pre surgery); decision made to cancel surgery as ventricle size had reduced	0 (0.0)	0 (0.0)	1 (50.0)	1 (25.0)
Unsuccessful ventricular shunt catheter insertion	0 (0.0)	1 (50.0)	0 (0.0)	1 (25.0)
Abnormal ECG; surgery abandoned	0 (0.0)	0 (0.0)	1 (50.0)	1 (25.0)
Pus found intraoperatively; EVD inserted	0 (0.0)	1 (50.0)	0 (0.0)	1 (25.0)

ECG, electrocardiogram; MRI, magnetic resonance imaging.

TABLE 37 Protocol deviations

Deviation	Trial group, *n* (%)			Total (*N* = 1605), *n* (%)
	Standard VPS (*N* = 536)	Antibiotic-impregnated VPS (*N* = 538)	Silver-impregnated VPS (*N* = 531)	
Any protocol deviation	134 (25.0)	146 (27.1)	159 (29.9)	439 (27.4)
Major deviations				
PD1: consent not obtained	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PD2: patient has had at least one previous indwelling VPS	2 (0.4)	2 (0.4)	1 (0.2)	5 (0.3)
PD3: patient had an active CSF infection at the time of VPS insertion	3 (0.6)	1 (0.2)	3 (0.6)	7 (0.4)
PD4: patient had an allergy to the antibiotics with which one of the randomised shunts is impregnated	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PD5: patient could have an allergy to the silver with which one of the randomised shunts is impregnated	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PD6: patient did not receive allocated intervention	0 (0.0)	2 (0.4)	2 (0.4)	4 (0.2)
PD7A: CSF samples not taken or sent for culture at time of VPS insertion	16 (3.0)	12 (2.2)	19 (3.6)	47 (2.9)
PD7B: CSF samples not taken or sent for culture at time shunt revision/removal	6 (1.1)	3 (0.6)	5 (0.9)	14 (0.9)
PD7C: shunt components not taken for culture at shunt revision/removal	99 (18.5)	108 (20.1)	113 (21.3)	320 (19.9)
At least one major deviation	112 (20.9)	120 (22.3)	131 (24.7)	363 (22.6)
Minor deviations				
PD8: patient had multiloculated hydrocephalus, necessitating multiple VPSs or neuroendoscopy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PD9: patient had ventriculoatrial or ventriculopleural shunt planned	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PD10: patient prematurely withdrew from follow-up	14 (2.6)	22 (4.1)	17 (3.2)	53 (3.3)
PD11: patient missed scheduled assessments (early post-operative assessment)	1 (0.2)	2 (0.4)	6 (1.1)	9 (0.6)
PD12: randomisation envelope opened out of sequence	12 (2.2)	9 (1.7)	10 (1.9)	31 (1.9)
PD13: unblinding occurred	11 (2.1)	6 (1.1)	15 (2.8)	32 (2.0)
At least one minor deviation	38 (7.1)	37 (6.9)	45 (8.5)	120 (7.5)

PD, protocol deviation.

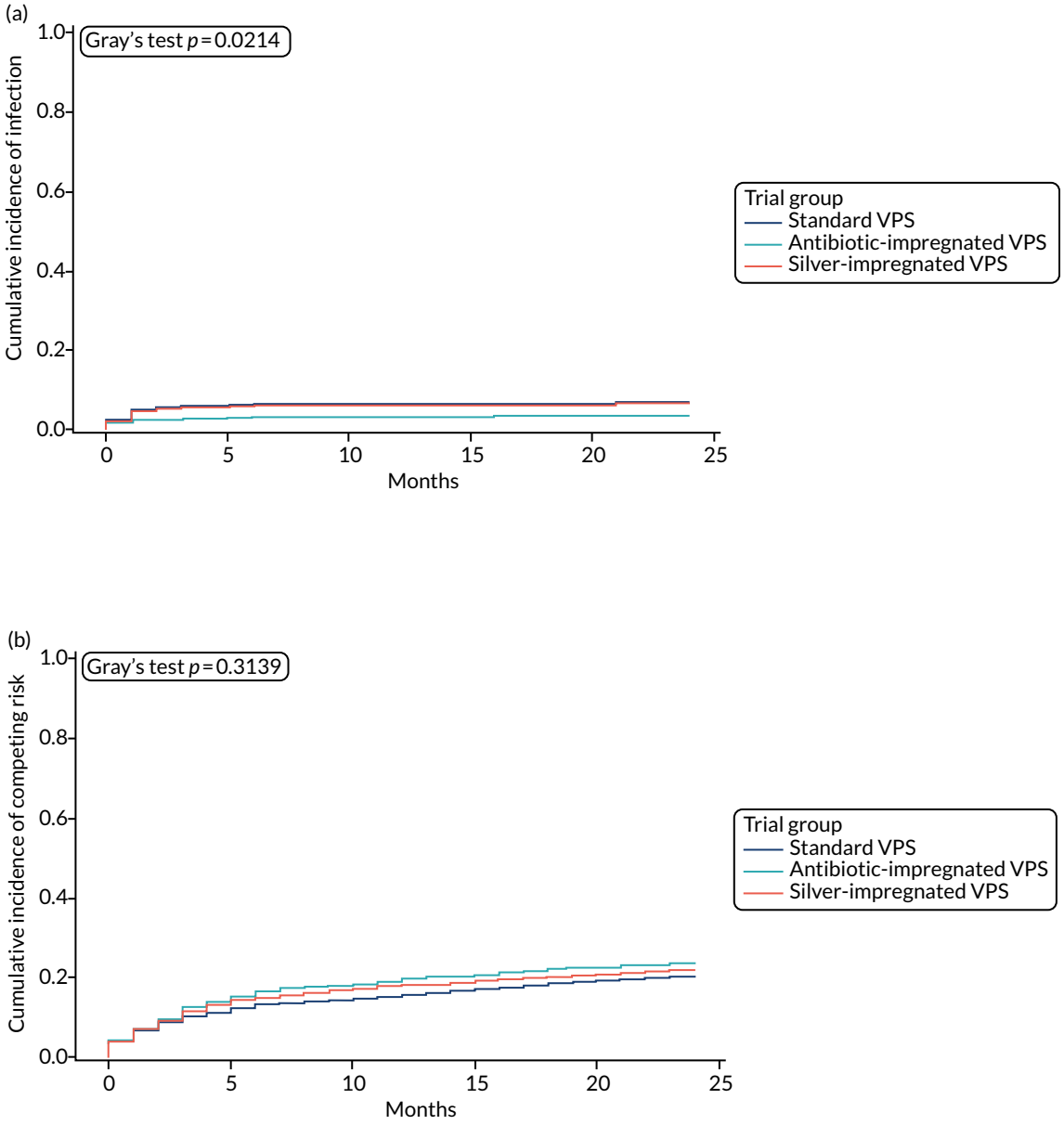


FIGURE 9 Cumulative incidence plots of revisions for infection and competing risk as classified by treating surgeon, by VPS group and age group. (a) Infection by VPS group; (b) competing risk by VPS group; (c) infection by age group; (d) competing risk by age group. (*continued*)

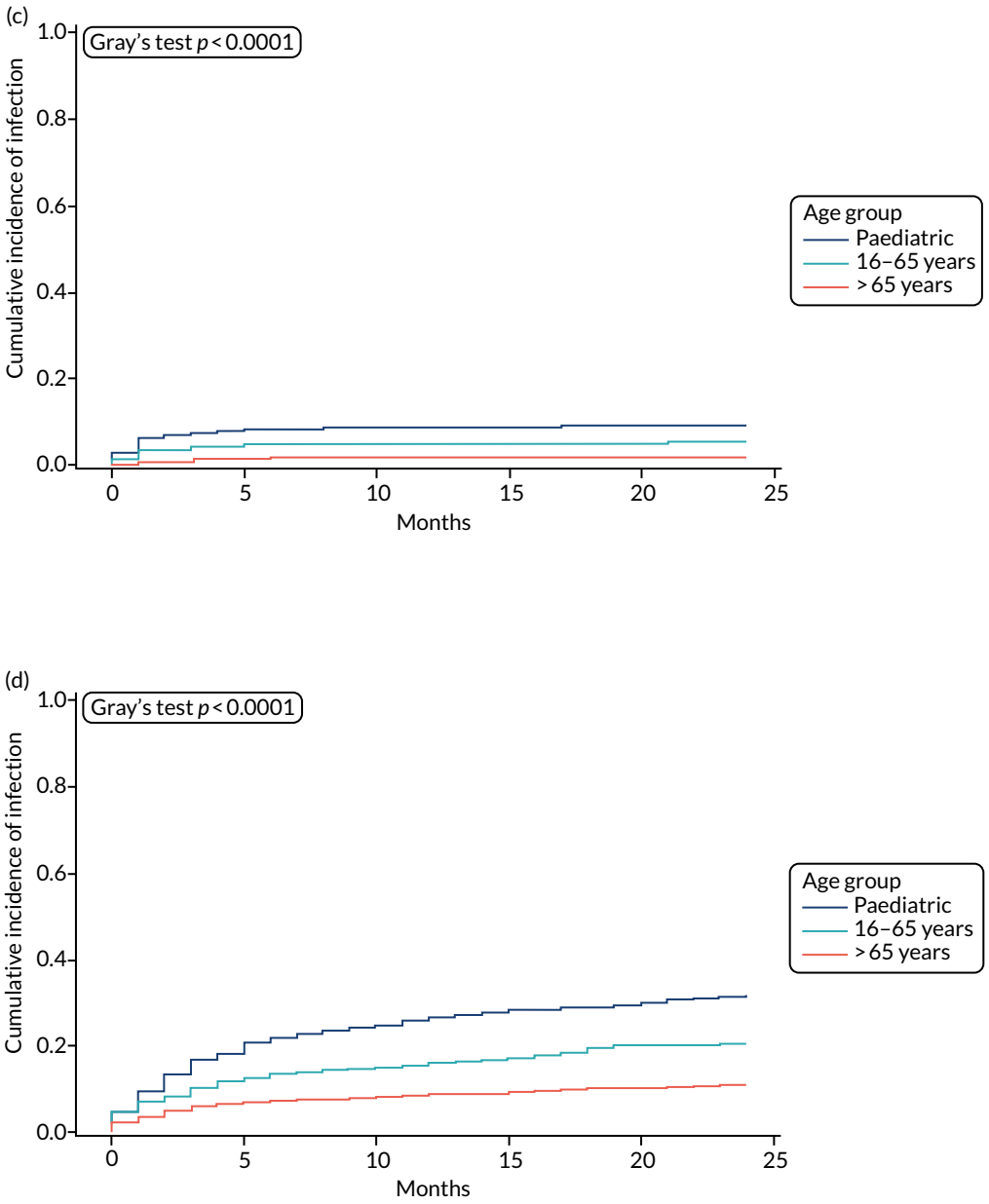


FIGURE 9 Cumulative incidence plots of revisions for infection and competing risk as classified by treating surgeon, by VPS group and age group. (a) Infection by VPS group; (b) competing risk by VPS group; (c) infection by age group; (d) competing risk by age group.

TABLE 38 Line listings of infection type, organism cultured and level of sensitivities

Infection	Type of infection	Organism cultured	Sample (*n*)	Antibiotic sensitivities: Sensitivity	Resistance	Partial sensitivity	Sensitivities unknown	Antibiotics unknown
(A) Line listings of infections associated with the standard VPS (n = 23)								
1	A 'definite – culture positive' infection	*Staphylococcus capitas*	1	Vancomycin				
2	A 'definite – culture positive' infection	Coagulase-negative staphylococcus	1					Yes
		Serratia species	[a]					Yes
		Staphylococcus capitas	1		Clarithromycin, doxycycline, erythromycin, flucloxacillin, Fucidin® (Leo Pharma A/S, Ballerup, Denmark)			
3	A 'probable – culture uncertain' infection	*Staphylococcus epidermidis*	1					Yes
4	A 'definite – culture positive' infection	*Pseudomonas aeruginosa*	1			Meropenem		
			2			Meropenem		
			3	Meropenem				
5	A 'definite – culture positive' infection	*Staphylococcus epidermidis*	1	Vancomycin	Ciprofloxacin, clindamycin, flucloxacillin, gentamicin, rifampicin, trimethoprim			
			2	Fusidic acid; vancomycin	Erythromycin, flucloxacillin, penicillin			
6	A 'definite – culture positive' infection	*Klebsiella pneumoniae*	1	Co-amoxiclav (Augmentin®; GlaxoSmithKline plc, London, UK)	Amoxicillin, ampicillin			
7	A 'definite – culture positive' infection	*Staphylococcus aureus*	1	Cefuroxime, flucloxacillin				
8	A 'definite – culture positive' infection	Coagulase-negative staphylococcus	1	Flucloxacillin	Vancomycin			

Infection	Type of infection	Organism cultured	Sample (*n*)	Antibiotic sensitivities				
				Sensitivity	Resistance	Partial sensitivity	Sensitivities unknown	Antibiotics unknown
9	A 'definite – culture positive' infection	*Staphylococcus aureus*	1	Flucloxacillin, vancomycin				
			2	Flucloxacillin				
			3	Flucloxacillin, vancomycin				
10	A 'definite – culture positive' infection	Coagulase-negative staphylococcus	1	Vancomycin				
11	A 'definite – culture positive' infection	*Klebsiella pneumoniae*	1	Cefotaxime, gentamicin				
12	A 'definite – culture positive' infection	Coagulase-negative staphylococcus	1	Vancomycin				
			2	Vancomycin				
			3	Vancomycin				
13	A 'definite – culture positive' infection	*Staphylococcus hominis*	1		Penicillin			
			2	Gentamicin, linezolid, rifampicin, vancomycin	Erythromycin, Fucidin, penicillin			
		Staphylococcus aureus	1	Amikacin, flucloxacillin, gentamicin, rifampicin, teicoplanin, vancomycin				
			2	Erythromycin, flucloxacillin, gentamicin, linezolid, penicillin, rifampicin				
			3	Erythromycin, flucloxacillin, Fucidin, gentamicin, linezolid, penicillin, rifampicin, vancomycin				
14	A 'definite – culture positive' infection	*Staphylococcus epidermidis*	1	Amikacin, vancomycin	Flucloxacillin			
15	A 'definite – culture positive' infection	Coagulase-negative staphylococcus	1					Yes
16	A 'definite – culture positive' infection	*Staphylococcus* species mixed	1					Yes
			2					Yes

continued

TABLE 38 Line listings of infection type, organism cultured and level of sensitivities (*continued*)

Infection	Type of infection	Organism cultured	Sample (*n*)	Antibiotic sensitivities				
				Sensitivity	Resistance	Partial sensitivity	Sensitivities unknown	Antibiotics unknown
17	A 'definite – culture positive' infection	*Staphylococcus aureus*	1	Flucloxacillin				
			2	Flucloxacillin				
18	A 'definite – culture positive' infection	*Klebsiella pneumoniae*	1	Meropenem				
			2	Meropenem				
19	A 'definite – culture positive' infection	*Staphylococcus epidermidis*	1	Vancomycin				
			2	Vancomycin				
			3	Vancomycin				
20	A 'definite – culture positive' infection	*Serratia marcescens*	1	Gentamicin, meropenem				
21	A 'definite – culture positive' infection	*Staphylococcus aureus*	1			Chloramphenicol		
			2			Erythromycin, flucloxacillin		
			3			Chloramphenicol, teicoplanin, vancomycin		
			4			Chloramphenicol, teicoplanin, vancomycin		
			5			Chloramphenicol, teicoplanin, vancomycin		
22	A 'definite – culture positive' infection	*Staphylococcus aureus*	1	Vancomycin				
			3	Vancomycin				
		Staphylococcus capitas	2			Vancomycin		
23	A 'definite – culture positive' infection	*Streptococcus salivaris*	1	Vancomycin	Cefotaxime, penicillin			

Infection	Type of infection	Organism cultured	Sample (*n*)	Antibiotic sensitivities: Sensitivity	Resistance	Partial sensitivity	Sensitivities unknown	Antibiotics unknown
(B) Line listings of infections associated with the antibiotic-impregnated VPSs* (n = *6)								
1	A 'definite – culture positive' infection	*Pseudomonas aeruginosa*	1			Ciprofloxacin, gentamicin, piperacillin/ tazobactam		
2	A 'definite – culture positive' infection	*Propionibacterium* species	1	Penicillin				
3	A 'definite – culture positive' infection	Coagulase-negative staphylococcus	1	Vancomycin				
4	A 'definite – culture positive' infection	*Escherichia coli*	1	Cefotaxime				
5	A 'definite – culture positive' infection	*Enterobacter cloacae*	1	Cefotaxime, ciprofloxacin				
6	A 'definite – culture positive' infection	*Proteus mirabilis*	1	Cefuroxime				
(C) Line listings of infections associated with silver-impregnated VPSs* (n = *27)								
1	A 'definite – culture positive' infection	*Staphylococcus epidermidis*	1					
2	A 'definite – culture positive' infection	*Staphylococcus capitas*	1					
3	A 'definite – culture positive' infection	*Streptococcus mitis*	1	Penicillin, vancomycin				
			2	Penicillin, vancomycin				
4	A 'definite – culture positive' infection	*Staphylococcus aureus*	1	Erythromycin, flucloxacillin, vancomycin				
5	A 'probable – culture uncertain' infection	*Staphylococcus aureus*	1	Flucloxacillin, Vancomycin	Trimethoprim			

continued

TABLE 38 Line listings of infection type, organism cultured and level of sensitivities (*continued*)

Infection	Type of infection	Organism cultured	Sample (*n*)	Antibiotic sensitivities				
				Sensitivity	Resistance	Partial sensitivity	Sensitivities unknown	Antibiotics unknown
6	A 'definite – culture positive' infection	*Staphylococcus epidermidis*	1	Erythromycin, rifampicin, vancomycin	Flucloxacillin, penicillin			
			2	Erythromycin, rifampicin, vancomycin	Flucloxacillin, penicillin			
			3	Rifampicin, vancomycin	Flucloxacillin			
7	A 'definite – culture positive' infection	*Escherichia coli*	1	Colomycin® (Teva Pharmaceutical Industries Ltd, Petah Tikva, Israel) (colistin), meropenem	Amoxicillin, ceftazidime, cefuroxime, ciprofloxacin, co-amoxiclav (Augmentin), co-trimoxazole, gentamicin			
8	A 'definite – culture positive' infection	*Staphylococcus aureus*	1	Clarithromycin, erythromycin, flucloxacillin, rifampicin				
			2					Yes
			3	Flucloxacillin, rifampicin				
			4	Clarithromycin, erythromycin, rifampicin				
9	A 'definite – culture positive' infection	*Enterobacter cloacae*	1					
			2					
			3					
			4					
			5					
10	A 'definite – culture positive' infection	*Enterobacter cloacae*	1					
11	A 'definite – culture positive' infection	*Staphylococcus aureus*	1	Flucloxacillin				

Infection	Type of infection	Organism cultured	Sample (*n*)	Antibiotic sensitivities				
				Sensitivity	Resistance	Partial sensitivity	Sensitivities unknown	Antibiotics unknown
12	A 'definite – culture positive' infection	*Staphylococcus aureus*	1				Flucloxacillin, vancomycin	
			2	Flucloxacillin, vancomycin				
13	A 'definite – culture positive' infection	*Staphylococcus aureus*	1	Vancomycin	Flucloxacillin			
14	A 'definite – culture positive' infection	*Staphylococcus aureus*	1	Vancomycin				
15	A 'definite – culture positive' infection	*Escherichia coli*	1	Cefotaxime, gentamicin, meropenem				
			2	Cefotaxime, gentamicin, meropenem				
16	A 'probable – culture uncertain' infection	*Enterococcus faecalis*	1	Amoxicillin, teicoplanin, vancomycin				
17	A 'definite – culture positive' infection	Coagulase-negative staphylococcus	1	Vancomycin				
			2	Vancomycin				
18	A 'definite – culture positive' infection	*Staphylococcus aureus*	1	Flucloxacillin				
19	A 'definite – culture positive' infection	*Enterococcus faecalis*	1	Ampicillin, gentamicin, vancomycin				
20	A 'definite – culture positive' infection	Coagulase-negative staphylococcus	1	Amikacin, erythromycin, flucloxacillin, linezolid				
21	A 'definite – culture positive' infection	Coagulase-negative staphylococcus	1	Amikacin, cefotaxime, linezolid, rifampicin				
22	A 'definite – culture positive' infection	*Staphylococcus aureus*	1	Flucloxacillin, rifampicin, teicoplanin, vancomycin				
23	A 'definite – culture positive' infection	*Propionibacterium acnes*	1					Yes
			2					Yes

continued

TABLE 38 Line listings of infection type, organism cultured and level of sensitivities (*continued*)

				Antibiotic sensitivities				
Infection	Type of infection	Organism cultured	Sample (*n*)	Sensitivity	Resistance	Partial sensitivity	Sensitivities unknown	Antibiotics unknown
24	A 'definite – culture positive' infection	*Propionibacterium acnes*	1	Ciprofloxacin, penicillin, vancomycin				
25	A 'definite – culture positive' infection	*Citrobacter* species	1	Flucloxacillin				
		Staphylococcus aureus	1	Flucloxacillin				
			2	Vancomycin				
26	A 'definite – culture positive' infection	*Staphylococcus aureus*	1	Ciprofloxacin, flucloxacillin, gentamicin, rifampicin, vancomycin				
			2	Ceftriaxone				
27	A 'definite – culture positive' infection	*Staphylococcus epidermidis*	1	Chloramphenicol, teicoplanin, vancomycin	Penicillin			
			2		Clindamycin, daptomycin, flucloxacillin, Fucidin, gentamicin, tetracycline			
			3					Yes
			4					Yes
			5					Yes
			6	Chloramphenicol, vancomycin				
			7	Chloramphenicol, vancomycin				

A, standard VPS; B, antibiotic-impregnated VPS; C, silver-impregnated VPS.
a An organism is cultured but there is no sample.

TABLE 39 Classifications of infection and no infection by assessor type

	Reason for revision (treating surgeon), *n* (%)	
Reason for revision (central panel)	**Infection**	**No infection**
Infection	68 (17.1)	7 (1.8)
No infection	10 (2.5)	313 (78.6)

TABLE 40 Summary of revision rates by centre

			Revisions	
Centre code	**Centre demographic**	**Primary outcome set (*N*)**	***n***	**% (97.5% CI)**
0393	Paediatric only	8	6	75.0 (40.7 to 100.0)
9999	Paediatric only	68	34	50.0 (36.4 to 63.6)
0243	Paediatric only	118	56	47.5 (37.2 to 57.8)
0248	Paediatric only	40	19	47.5 (29.8 to 65.2)
0246	Paediatric only	47	20	42.6 (26.4 to 58.7)
0006	Adults only	22	9	40.9 (17.4 to 64.4)
0361	Adults only	5	2	40.0 (0.0 to 89.1)
0249	Paediatric only	71	23	32.4 (20.0 to 44.8)
0400	Adults only	81	25	30.9 (19.4 to 42.4)
0133	Paediatric only	30	8	26.7 (8.6 to 44.8)
0578	Adults only	154	40	26.0 (18.1 to 33.9)
0352	Both adults and paediatrics	128	30	23.4 (15.1 to 31.8)
0030	Both adults and paediatrics	91	21	23.1 (13.2 to 33.3)
0114	Both adults and paediatrics	175	35	20.0 (13.2 to 26.8)
0161	Both adults and paediatrics	36	6	16.7 (2.8 to 30.6)
0213	Both adults and paediatrics	140	23	16.4 (9.4 to 23.4)
0004	Adults only	14	2	14.3 (0.0 to 35.2)
0007	Both adults and paediatrics	84	12	14.3 (5.7 to 22.8)
0672	Adults only	73	8	11.0 (2.8 to 19.1)
0185	Both adults and paediatrics	188	18	9.6 (4.8 to 14.4)
0232	Adults only	21	1	4.8 (0.0 to 15.2)

Note
Table sorted by revision rate (highest rate to lowest rate).

TABLE 41 Summary of infection rates by centre

Centre code	Centre demographic	Primary outcome set (*N*)	Infection	
			n	% (97.5% CI)
0393	Paediatric only	8	2	25.0 (0.0 to 59.3)
0361	Adults only	5	1	20.0 (0.0 to 60.1)
0243	Paediatric only	118	13	11.0 (4.6 to 17.5)
0248	Paediatric only	40	4	10.0 (0.0 to 20.6)
0006	Adults only	22	2	9.1 (0.0 to 22.8)
0249	Paediatric only	71	6	8.5 (1.1 to 15.8)
9999	Paediatric only	68	5	7.4 (0.3 to 14.4)
0161	Both adults and paediatrics	36	2	5.6 (0.0 to 14.1)
0578	Adults only	154	8	5.2 (1.2 to 9.2)
0400	Adults only	81	4	4.9 (0.0 to 10.3)
0030	Both adults and paediatrics	91	4	4.4 (0.0 to 9.2)
0246	Paediatric only	47	2	4.3 (0.0 to 10.9)
0672	Adults only	73	3	4.1 (0.0 to 9.3)
0007	Both adults and paediatrics	84	3	3.6 (0.0 to 8.1)
0213	Both adults and paediatrics	140	5	3.6 (0.1 to 7.1)
0133	Paediatric only	30	1	3.3 (0.0 to 10.7)
0352	Both adults and paediatrics	128	4	3.1 (0.0 to 6.6)
0114	Both adults and paediatrics	175	3	1.7 (0.0 to 3.9)
0185	Both adults and paediatrics	188	3	1.6 (0.0 to 3.6)
0004	Adults only	14	0	0.0 (0.0 to 0.0)
0232	Adults only	21	0	0.0 (0.0 to 0.0)

Note
Table sorted by infection rate (highest rate to lowest rate).

TABLE 42 Summary of aetiologies, and type of aetiologies, of the hydrocephalus by VPS group

Summary of aetiology by VPS group	Clean insertion,[a] *n* (%)	Revision required		Reason for revision				
		No revision, *n* (%)	Revision,[b] *n* (%)	Failure due to patient, *n* (%)	Functional shunt failure, *n* (%)	Mechanical shunt failure, *n* (%)	Failure due to infection, *n* (%)	Failure – no infection,[c] *n* (%)
Total number of patients	1594	1196	398	14	121	185	78	320
Congenital malformations								
Patients with congenital malformations								
Overall	294 (18.4)	181 (61.6)	113 (38.4)	2 (0.7)	36 (12.2)	48 (16.3)	27 (9.2)	86 (29.3)
Standard VPS	95 (17.8)	62 (65.3)	33 (34.7)	1 (1.1)	13 (13.7)	11 (11.6)	8 (8.4)	25 (26.3)
Antibiotic-impregnated VPS	93 (17.4)	57 (61.3)	36 (38.7)	0 (0.0)	13 (14.0)	17 (18.3)	6 (6.5)	30 (32.3)
Silver-impregnated VPS	106 (20.2)	62 (58.5)	44 (41.5)	1 (0.9)	10 (9.4)	20 (18.9)	13 (12.3)	31 (29.2)
Type(s) of congenital malformation								
Aqueduct stenosis								
Overall	68 (23.1)	46 (67.6)	22 (32.4)	0 (0.0)	8 (11.8)	7 (10.3)	7 (10.3)	15 (22.1)
Standard VPS	21 (22.1)	15 (71.4)	6 (28.6)	0 (0.0)	4 (19.0)	1 (4.8)	1 (4.8)	5 (23.8)
Antibiotic-impregnated VPS	15 (16.1)	9 (60.0)	6 (40.0)	0 (0.0)	2 (13.3)	3 (20.0)	1 (6.7)	5 (33.3)
Silver-impregnated VPS	32 (30.2)	22 (68.8)	10 (31.3)	0 (0.0)	2 (6.3)	3 (9.4)	5 (15.6)	5 (15.6)
Dandy–Walker								
Overall	7 (2.4)	6 (85.7)	1 (14.3)	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)	1 (14.3)
Standard VPS	2 (2.1)	1 (50.0)	1 (50.0)	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)	1 (50.0)
Antibiotic-impregnated VPS	3 (3.2)	3 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Silver-impregnated VPS	2 (1.9)	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

continued

TABLE 42 Summary of aetiologies, and type of aetiologies, of the hydrocephalus by VPS group (*continued*)

Summary of aetiology by VPS group	Clean insertion,[a] *n* (%)	Revision required		Reason for revision				
		No revision, *n* (%)	Revision,[b] *n* (%)	Failure due to patient, *n* (%)	Functional shunt failure, *n* (%)	Mechanical shunt failure, *n* (%)	Failure due to infection, *n* (%)	Failure – no infection,[c] *n* (%)
Chiari								
Overall	62 (21.1)	43 (69.4)	19 (30.6)	0 (0.0)	7 (11.3)	7 (11.3)	5 (8.1)	14 (22.6)
Standard VPS	23 (24.2)	17 (73.9)	6 (26.1)	0 (0.0)	4 (17.4)	0 (0.0)	2 (8.7)	4 (17.4)
Antibiotic-impregnated VPS	22 (23.7)	15 (68.2)	7 (31.8)	0 (0.0)	3 (13.6)	4 (18.2)	0 (0.0)	7 (31.8)
Silver-impregnated VPS	17 (16.0)	11 (64.7)	6 (35.3)	0 (0.0)	0 (0.0)	3 (17.6)	3 (17.6)	3 (17.6)
Spina bifida								
Overall	111 (37.8)	62 (55.9)	49 (44.1)	1 (0.9)	11 (9.9)	25 (22.5)	12 (10.8)	37 (33.3)
Standard VPS	35 (36.8)	19 (54.3)	16 (45.7)	1 (2.9)	3 (8.6)	7 (20.0)	5 (14.3)	11 (31.4)
Antibiotic-impregnated VPS	34 (36.6)	22 (64.7)	12 (35.3)	0 (0.0)	4 (11.8)	7 (20.6)	1 (2.9)	11 (32.4)
Silver-impregnated VPS	42 (39.6)	21 (50.0)	21 (50.0)	0 (0.0)	4 (9.5)	11 (26.2)	6 (14.3)	15 (35.7)
Other								
Overall	72 (24.5)	38 (52.8)	34 (47.2)	1 (1.4)	12 (16.7)	13 (18.1)	8 (11.1)	26 (36.1)
Standard VPS	27 (28.4)	18 (66.7)	9 (33.3)	0 (0.0)	4 (14.8)	4 (14.8)	1 (3.7)	8 (29.6)
Antibiotic-impregnated VPS	23 (24.7)	11 (47.8)	12 (52.2)	0 (0.0)	4 (17.4)	4 (17.4)	4 (17.4)	8 (34.8)
Silver-impregnated VPS	22 (20.8)	9 (40.9)	13 (59.1)	1 (4.5)	4 (18.2)	5 (22.7)	3 (13.6)	10 (45.5)
Not known								
Overall	1 (0.3)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Standard VPS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Antibiotic-impregnated VPS	1 (1.1)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Silver-impregnated VPS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Summary of aetiology by VPS group	Clean insertion,[a] *n* (%)	Revision required		Reason for revision				
		No revision, *n* (%)	Revision,[b] *n* (%)	Failure due to patient, *n* (%)	Functional shunt failure, *n* (%)	Mechanical shunt failure, *n* (%)	Failure due to infection, *n* (%)	Failure – no infection,[c] *n* (%)
Number of types per patient with congenital malformations								
0								
Overall	1 (0.3)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Standard VPS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Antibiotic-impregnated VPS	1 (1.1)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Silver-impregnated VPS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1								
Overall	268 (91.2)	166 (61.9)	102 (38.1)	2 (0.7)	33 (12.3)	44 (16.4)	23 (8.6)	79 (29.5)
Standard VPS	83 (87.4)	55 (66.3)	28 (33.7)	1 (1.2)	10 (12.0)	10 (12.0)	7 (8.4)	21 (25.3)
Antibiotic-impregnated VPS	87 (93.5)	52 (59.8)	35 (40.2)	0 (0.0)	13 (14.9)	16 (18.4)	6 (6.9)	29 (33.3)
Silver-impregnated VPS	98 (92.5)	59 (60.2)	39 (39.8)	1 (1.0)	10 (10.2)	18 (18.4)	10 (10.2)	29 (29.6)
2								
Overall	23 (7.8)	13 (56.5)	10 (43.5)	0 (0.0)	3 (13.0)	4 (17.4)	3 (13.0)	7 (30.4)
Standard VPS	11 (11.6)	6 (54.5)	5 (45.5)	0 (0.0)	3 (27.3)	1 (9.1)	1 (9.1)	4 (36.4)
Antibiotic-impregnated VPS	5 (5.4)	4 (80.0)	1 (20.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	1 (20.0)
Silver-impregnated VPS	7 (6.6)	3 (42.9)	4 (57.1)	0 (0.0)	0 (0.0)	2 (28.6)	2 (28.6)	2 (28.6)
3								
Overall	2 (0.7)	1 (50.0)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)
Standard VPS	1 (1.1)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Antibiotic-impregnated VPS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Silver-impregnated VPS	1 (0.9)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)

continued

TABLE 42 Summary of aetiologies, and type of aetiologies, of the hydrocephalus by VPS group (*continued*)

Summary of aetiology by VPS group	Clean insertion,[a] *n* (%)	Revision required		Reason for revision				
		No revision, *n* (%)	Revision,[b] *n* (%)	Failure due to patient, *n* (%)	Functional shunt failure, *n* (%)	Mechanical shunt failure, *n* (%)	Failure due to infection, *n* (%)	Failure – no infection,[c] *n* (%)
Acquired hydrocephalus								
Patients with acquired hydrocephalus								
Overall	819 (51.4)	615 (75.1)	204 (24.9)	9 (1.1)	54 (6.6)	102 (12.5)	39 (4.8)	165 (20.1)
Standard VPS	274 (51.4)	201 (73.4)	73 (26.6)	3 (1.1)	22 (8.0)	27 (9.9)	21 (7.7)	52 (19.0)
Antibiotic-impregnated VPS	266 (49.7)	207 (77.8)	59 (22.2)	2 (0.8)	15 (5.6)	37 (13.9)	5 (1.9)	54 (20.3)
Silver-impregnated VPS	279 (53.0)	207 (74.2)	72 (25.8)	4 (1.4)	17 (6.1)	38 (13.6)	13 (4.7)	59 (21.1)
Type(s) of acquired hydrocephalus								
Cysts (colloid or arachoid)								
Overall	32 (3.9)	24 (75.0)	8 (25.0)	0 (0.0)	4 (12.5)	3 (9.4)	1 (3.1)	7 (21.9)
Standard VPS	11 (4.0)	8 (72.7)	3 (27.3)	0 (0.0)	2 (18.2)	0 (0.0)	1 (9.1)	2 (18.2)
Antibiotic-impregnated VPS	13 (4.9)	10 (76.9)	3 (23.1)	0 (0.0)	2 (15.4)	1 (7.7)	0 (0.0)	3 (23.1)
Silver-impregnated VPS	8 (2.9)	6 (75.0)	2 (25.0)	0 (0.0)	0 (0.0)	2 (25.0)	0 (0.0)	2 (25.0)
Trauma								
Overall	30 (3.7)	25 (83.3)	5 (16.7)	1 (3.3)	1 (3.3)	3 (10.0)	0 (0.0)	5 (16.7)
Standard VPS	12 (4.4)	10 (83.3)	2 (16.7)	1 (8.3)	1 (8.3)	0 (0.0)	0 (0.0)	2 (16.7)
Antibiotic-impregnated VPS	7 (2.6)	6 (85.7)	1 (14.3)	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)	1 (14.3)
Silver-impregnated VPS	11 (3.9)	9 (81.8)	2 (18.2)	0 (0.0)	0 (0.0)	2 (18.2)	0 (0.0)	2 (18.2)

Summary of aetiology by VPS group	Clean insertion,[a] *n* (%)	Revision required		Reason for revision				
		No revision, *n* (%)	Revision,[b] *n* (%)	Failure due to patient, *n* (%)	Functional shunt failure, *n* (%)	Mechanical shunt failure, *n* (%)	Failure due to infection, *n* (%)	Failure – no infection,[c] *n* (%)
Tumour: benign								
Overall	124 (15.1)	96 (77.4)	28 (22.6)	2 (1.6)	9 (7.3)	14 (11.3)	3 (2.4)	25 (20.2)
Standard VPS	40 (14.6)	33 (82.5)	7 (17.5)	0 (0.0)	3 (7.5)	4 (10.0)	0 (0.0)	7 (17.5)
Antibiotic-impregnated VPS	35 (13.2)	26 (74.3)	9 (25.7)	1 (2.9)	3 (8.6)	5 (14.3)	0 (0.0)	9 (25.7)
Silver-impregnated VPS	49 (17.6)	37 (75.5)	12 (24.5)	1 (2.0)	3 (6.1)	5 (10.2)	3 (6.1)	9 (18.4)
Tumour: malignant								
Overall	133 (16.2)	105 (78.9)	28 (21.1)	2 (1.5)	6 (4.5)	14 (10.5)	6 (4.5)	22 (16.5)
Standard VPS	38 (13.9)	29 (76.3)	9 (23.7)	1 (2.6)	1 (2.6)	5 (13.2)	2 (5.3)	7 (18.4)
Antibiotic-impregnated VPS	54 (20.3)	45 (83.3)	9 (16.7)	1 (1.9)	2 (3.7)	4 (7.4)	2 (3.7)	7 (13.0)
Silver-impregnated VPS	41 (14.7)	31 (75.6)	10 (24.4)	0 (0.0)	3 (7.3)	5 (12.2)	2 (4.9)	8 (19.5)
Post haemorrhagic/intracranial haemorrhage								
Overall	337 (41.1)	244 (72.4)	93 (27.6)	2 (0.6)	21 (6.2)	45 (13.4)	25 (7.4)	68 (20.2)
Standard VPS	118 (43.1)	81 (68.6)	37 (31.4)	0 (0.0)	9 (7.6)	12 (10.2)	16 (13.6)	21 (17.8)
Antibiotic-impregnated VPS	102 (38.3)	76 (74.5)	26 (25.5)	0 (0.0)	5 (4.9)	18 (17.6)	3 (2.9)	23 (22.5)
Silver-impregnated VPS	117 (41.9)	87 (74.4)	30 (25.6)	2 (1.7)	7 (6.0)	15 (12.8)	6 (5.1)	24 (20.5)
Infection: meningitis								
Overall	32 (3.9)	23 (71.9)	9 (28.1)	0 (0.0)	2 (6.3)	5 (15.6)	2 (6.3)	7 (21.9)
Standard VPS	13 (4.7)	9 (69.2)	4 (30.8)	0 (0.0)	1 (7.7)	2 (15.4)	1 (7.7)	3 (23.1)
Antibiotic-impregnated VPS	9 (3.4)	7 (77.8)	2 (22.2)	0 (0.0)	1 (11.1)	1 (11.1)	0 (0.0)	2 (22.2)
Silver-impregnated VPS	10 (3.6)	7 (70.0)	3 (30.0)	0 (0.0)	0 (0.0)	2 (20.0)	1 (10.0)	2 (20.0)

continued

TABLE 42 Summary of aetiologies, and type of aetiologies, of the hydrocephalus by VPS group (*continued*)

		Revision required		Reason for revision				
Summary of aetiology by VPS group	**Clean insertion,[a] *n* (%)**	**No revision, *n* (%)**	**Revision,[b] *n* (%)**	**Failure due to patient, *n* (%)**	**Functional shunt failure, *n* (%)**	**Mechanical shunt failure, *n* (%)**	**Failure due to infection, *n* (%)**	**Failure – no infection,[c] *n* (%)**
Infection: cerebral abscess								
Overall	8 (1.0)	7 (87.5)	1 (12.5)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	1 (12.5)
Standard VPS	6 (2.2)	5 (83.3)	1 (16.7)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	1 (16.7)
Antibiotic-impregnated VPS	1 (0.4)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Silver-impregnated VPS	1 (0.4)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infection: other								
Overall	21 (2.6)	17 (81.0)	4 (19.0)	0 (0.0)	0 (0.0)	4 (19.0)	0 (0.0)	4 (19.0)
Standard VPS	8 (2.9)	5 (62.5)	3 (37.5)	0 (0.0)	0 (0.0)	3 (37.5)	0 (0.0)	3 (37.5)
Antibiotic-impregnated VPS	6 (2.3)	5 (83.3)	1 (16.7)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	1 (16.7)
Silver-impregnated VPS	7 (2.5)	7 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other factors								
Overall	140 (17.1)	99 (70.7)	41 (29.3)	3 (2.1)	16 (11.4)	17 (12.1)	5 (3.6)	36 (25.7)
Standard VPS	47 (17.2)	34 (72.3)	13 (27.7)	1 (2.1)	8 (17.0)	1 (2.1)	3 (6.4)	10 (21.3)
Antibiotic-impregnated VPS	49 (18.4)	37 (75.5)	12 (24.5)	1 (2.0)	3 (6.1)	8 (16.3)	0 (0.0)	12 (24.5)
Silver-impregnated VPS	44 (15.8)	28 (63.6)	16 (36.4)	1 (2.3)	5 (11.4)	8 (18.2)	2 (4.5)	14 (31.8)

Summary of aetiology by VPS group	Clean insertion,[a] *n* (%)	Revision required		Reason for revision				
		No revision, *n* (%)	Revision,[b] *n* (%)	Failure due to patient, *n* (%)	Functional shunt failure, *n* (%)	Mechanical shunt failure, *n* (%)	Failure due to infection, *n* (%)	Failure – no infection,[c] *n* (%)
Number of types per patient with acquired hydrocephalus								
0								
Overall	1 (0.1)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Standard VPS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Antibiotic-impregnated VPS	1 (0.4)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Silver-impregnated VPS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1								
Overall	782 (95.5)	590 (75.4)	192 (24.6)	8 (1.0)	50 (6.4)	98 (12.5)	36 (4.6)	156 (19.9)
Standard VPS	257 (93.8)	189 (73.5)	68 (26.5)	3 (1.2)	20 (7.8)	26 (10.1)	19 (7.4)	49 (19.1)
Antibiotic-impregnated VPS	254 (95.5)	199 (78.3)	55 (21.7)	1 (0.4)	14 (5.5)	35 (13.8)	5 (2.0)	50 (19.7)
Silver-impregnated VPS	271 (97.1)	202 (74.5)	69 (25.5)	4 (1.5)	16 (5.9)	37 (13.7)	12 (4.4)	57 (21.0)
2								
Overall	33 (4.0)	22 (66.7)	11 (33.3)	1 (3.0)	3 (9.1)	4 (12.1)	3 (9.1)	8 (24.2)
Standard VPS	15 (5.5)	11 (73.3)	4 (26.7)	0 (0.0)	1 (6.7)	1 (6.7)	2 (13.3)	2 (13.3)
Antibiotic-impregnated VPS	11 (4.1)	7 (63.6)	4 (36.4)	1 (9.1)	1 (9.1)	2 (18.2)	0 (0.0)	4 (36.4)
Silver-impregnated VPS	7 (2.5)	4 (57.1)	3 (42.9)	0 (0.0)	1 (14.3)	1 (14.3)	1 (14.3)	2 (28.6)
3								
Overall	3 (0.4)	2 (66.7)	1 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	1 (33.3)
Standard VPS	2 (0.7)	1 (50.0)	1 (50.0)	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)	1 (50.0)
Antibiotic-impregnated VPS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Silver-impregnated VPS	1 (0.4)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

continued

TABLE 42 Summary of aetiologies, and type of aetiologies, of the hydrocephalus by VPS group (*continued*)

Summary of aetiology by VPS group	Clean insertion,[a] *n* (%)	Revision required		Reason for revision				
		No revision, *n* (%)	Revision,[b] *n* (%)	Failure due to patient, *n* (%)	Functional shunt failure, *n* (%)	Mechanical shunt failure, *n* (%)	Failure due to infection, *n* (%)	Failure – no infection,[c] *n* (%)
Idiopathic condition								
Patients with idiopathic condition								
Overall	496 (31.1)	408 (82.3)	88 (17.7)	4 (0.8)	32 (6.5)	38 (7.7)	14 (2.8)	74 (14.9)
Standard VPS	169 (31.7)	145 (85.8)	24 (14.2)	3 (1.8)	5 (3.0)	11 (6.5)	5 (3.0)	19 (11.2)
Antibiotic-impregnated VPS	177 (33.1)	142 (80.2)	35 (19.8)	0 (0.0)	15 (8.5)	17 (9.6)	3 (1.7)	32 (18.1)
Silver-impregnated VPS	150 (28.5)	121 (80.7)	29 (19.3)	1 (0.7)	12 (8.0)	10 (6.7)	6 (4.0)	23 (15.3)
Type(s) of idiopathic condition								
Idiopathic 'normal pressure' hydrocephalus of the elderly								
Overall	361 (72.8)	325 (90.0)	36 (10.0)	1 (0.3)	15 (4.2)	16 (4.4)	4 (1.1)	32 (8.9)
Standard VPS	119 (70.4)	110 (92.4)	9 (7.6)	1 (0.8)	3 (2.5)	4 (3.4)	1 (0.8)	8 (6.7)
Antibiotic-impregnated VPS	135 (76.3)	118 (87.4)	17 (12.6)	0 (0.0)	8 (5.9)	8 (5.9)	1 (0.7)	16 (11.9)
Silver-impregnated VPS	107 (71.3)	97 (90.7)	10 (9.3)	0 (0.0)	4 (3.7)	4 (3.7)	2 (1.9)	8 (7.5)
IIH								
Overall	98 (19.8)	63 (64.3)	35 (35.7)	2 (2.0)	10 (10.2)	16 (16.3)	7 (7.1)	28 (28.6)
Standard VPS	38 (22.5)	27 (71.1)	11 (28.9)	1 (2.6)	1 (2.6)	5 (13.2)	4 (10.5)	7 (18.4)
Antibiotic-impregnated VPS	32 (18.1)	19 (59.4)	13 (40.6)	0 (0.0)	5 (15.6)	7 (21.9)	1 (3.1)	12 (37.5)
Silver-impregnated VPS	28 (18.7)	17 (60.7)	11 (39.3)	1 (3.6)	4 (14.3)	4 (14.3)	2 (7.1)	9 (32.1)
Other								
Overall	38 (7.7)	20 (52.6)	18 (47.4)	1 (2.6)	7 (18.4)	7 (18.4)	3 (7.9)	15 (39.5)
Standard VPS	13 (7.7)	8 (61.5)	5 (38.5)	1 (7.7)	1 (7.7)	3 (23.1)	0 (0.0)	5 (38.5)
Antibiotic-impregnated VPS	10 (5.6)	5 (50.0)	5 (50.0)	0 (0.0)	2 (20.0)	2 (20.0)	1 (10.0)	4 (40.0)
Silver-impregnated VPS	15 (10.0)	7 (46.7)	8 (53.3)	0 (0.0)	4 (26.7)	2 (13.3)	2 (13.3)	6 (40.0)

Summary of aetiology by VPS group	Clean insertion,[a] *n* (%)	Revision required		Reason for revision				
		No revision, *n* (%)	Revision,[b] *n* (%)	Failure due to patient, *n* (%)	Functional shunt failure, *n* (%)	Mechanical shunt failure, *n* (%)	Failure due to infection, *n* (%)	Failure – no infection,[c] *n* (%)
Number of types per patient with idiopathic condition								
0								
Overall	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Standard VPS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Antibiotic-impregnated VPS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Silver-impregnated VPS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1								
Overall	495 (99.8)	408 (82.4)	87 (17.6)	4 (0.8)	32 (6.5)	37 (7.5)	14 (2.8)	73 (14.7)
Standard VPS	168 (99.4)	145 (86.3)	23 (13.7)	3 (1.8)	5 (3.0)	10 (6.0)	5 (3.0)	18 (10.7)
Antibiotic-impregnated VPS	177 (100.0)	142 (80.2)	35 (19.8)	0 (0.0)	15 (8.5)	17 (9.6)	3 (1.7)	32 (18.1)
Silver-impregnated VPS	150 (100.0)	121 (80.7)	29 (19.3)	1 (0.7)	12 (8.0)	10 (6.7)	6 (4.0)	23 (15.3)
2								
Overall	1 (0.2)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	1 (100.0)
Standard VPS	1 (0.6)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	1 (100.0)
Antibiotic-impregnated VPS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Silver-impregnated VPS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

a Clean insertion = no revision + revision.
b Revision = failure due to patient + functional shunt failure + mechanical shunt failure + failure due to infection.
c Failure – no infection = failure due to patient + functional shunt failure + mechanical shunt failure.

TABLE 43 Summary of valve type and operative approach by VPS group

Summary of operative approach/valve type	Clean insertion,[a] *n* (%)	Revision required		Reason for revision				
		No revision, *n* (%)	Revision,[b] *n* (%)	Failure due to patient, *n* (%)	Functional shunt failure, *n* (%)	Mechanical shunt failure, *n* (%)	Failure due to infection, *n* (%)	Failure – no infection,[c] *n* (%)
Total number of patients	1594	1196	398	14	121	185	78	320
Use of guidance system								
Patients for whom guidance system used for ventricular shunt catheter placement								
Overall	653 (41.0)	489 (74.9)	164 (25.1)	7 (1.1)	45 (6.9)	78 (11.9)	34 (5.2)	130 (19.9)
Standard VPS	225 (42.2)	174 (77.3)	51 (22.7)	2 (0.9)	9 (4.0)	24 (10.7)	16 (7.1)	35 (15.6)
Antibiotic-impregnated VPS	218 (40.7)	164 (75.2)	54 (24.8)	3 (1.4)	17 (7.8)	29 (13.3)	5 (2.3)	49 (22.5)
Silver-impregnated VPS	210 (39.9)	151 (71.9)	59 (28.1)	2 (1.0)	19 (9.0)	25 (11.9)	13 (6.2)	46 (21.9)
Type of guidance system								
Electromagnetic								
Overall	413 (63.2)	309 (74.8)	104 (25.2)	4 (1.0)	26 (6.3)	50 (12.1)	24 (5.8)	80 (19.4)
Standard VPS	147 (65.3)	120 (81.6)	27 (18.4)	1 (0.7)	5 (3.4)	12 (8.2)	9 (6.1)	18 (12.2)
Antibiotic-impregnated VPS	138 (63.3)	99 (71.7)	39 (28.3)	1 (0.7)	12 (8.7)	22 (15.9)	4 (2.9)	35 (25.4)
Silver-impregnated VPS	128 (61.0)	90 (70.3)	38 (29.7)	2 (1.6)	9 (7.0)	16 (12.5)	11 (8.6)	27 (21.1)
Ultrasonography								
Overall	128 (19.6)	88 (68.8)	40 (31.3)	3 (2.3)	16 (12.5)	14 (10.9)	7 (5.5)	33 (25.8)
Standard VPS	38 (16.9)	22 (57.9)	16 (42.1)	1 (2.6)	4 (10.5)	5 (13.2)	6 (15.8)	10 (26.3)
Antibiotic-impregnated VPS	40 (18.3)	33 (82.5)	7 (17.5)	2 (5.0)	2 (5.0)	3 (7.5)	0 (0.0)	7 (17.5)
Silver-impregnated VPS	50 (23.8)	33 (66.0)	17 (34.0)	0 (0.0)	10 (20.0)	6 (12.0)	1 (2.0)	16 (32.0)
Optical								
Overall	46 (7.0)	37 (80.4)	9 (19.6)	0 (0.0)	2 (4.3)	6 (13.0)	1 (2.2)	8 (17.4)
Standard VPS	16 (7.1)	13 (81.3)	3 (18.8)	0 (0.0)	0 (0.0)	2 (12.5)	1 (6.3)	2 (12.5)
Antibiotic-impregnated VPS	19 (8.7)	15 (78.9)	4 (21.1)	0 (0.0)	2 (10.5)	2 (10.5)	0 (0.0)	4 (21.1)
Silver-impregnated VPS	11 (5.2)	9 (81.8)	2 (18.2)	0 (0.0)	0 (0.0)	2 (18.2)	0 (0.0)	2 (18.2)

Summary of operative approach/valve type	Clean insertion,[a] *n* (%)	Revision required		Reason for revision				
		No revision, *n* (%)	Revision,[b] *n* (%)	Failure due to patient, *n* (%)	Functional shunt failure, *n* (%)	Mechanical shunt failure, *n* (%)	Failure due to infection, *n* (%)	Failure – no infection,[c] *n* (%)
Stereotactic frame								
Overall	63 (9.6)	52 (82.5)	11 (17.5)	0 (0.0)	1 (1.6)	8 (12.7)	2 (3.2)	9 (14.3)
Standard VPS	22 (9.8)	17 (77.3)	5 (22.7)	0 (0.0)	0 (0.0)	5 (22.7)	0 (0.0)	5 (22.7)
Antibiotic-impregnated VPS	20 (9.2)	16 (80.0)	4 (20.0)	0 (0.0)	1 (5.0)	2 (10.0)	1 (5.0)	3 (15.0)
Silver-impregnated VPS	21 (10.0)	19 (90.5)	2 (9.5)	0 (0.0)	0 (0.0)	1 (4.8)	1 (4.8)	1 (4.8)
Not known								
Overall	3 (0.5)	3 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Standard VPS	2 (0.9)	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Antibiotic-impregnated VPS	1 (0.5)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Silver-impregnated VPS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Placement of proximal shunt catheter								
Frontal								
Overall	134 (8.4)	93 (69.4)	41 (30.6)	0 (0.0)	13 (9.7)	15 (11.2)	13 (9.7)	28 (20.9)
Standard VPS	49 (9.2)	33 (67.3)	16 (32.7)	0 (0.0)	5 (10.2)	4 (8.2)	7 (14.3)	9 (18.4)
Antibiotic-impregnated VPS	48 (9.0)	35 (72.9)	13 (27.1)	0 (0.0)	4 (8.3)	7 (14.6)	2 (4.2)	11 (22.9)
Silver-impregnated VPS	37 (7.0)	25 (67.6)	12 (32.4)	0 (0.0)	4 (10.8)	4 (10.8)	4 (10.8)	8 (21.6)
Parietal, occipital or parietal/occipital								
Overall	1453 (91.2)	1100 (75.7)	353 (24.3)	14 (1.0)	107 (7.4)	167 (11.5)	65 (4.5)	288 (19.8)
Standard VPS	481 (90.2)	369 (76.7)	112 (23.3)	5 (1.0)	35 (7.3)	46 (9.6)	26 (5.4)	86 (17.9)
Antibiotic-impregnated VPS	486 (90.8)	368 (75.7)	118 (24.3)	4 (0.8)	39 (8.0)	62 (12.8)	13 (2.7)	105 (21.6)
Silver-impregnated VPS	486 (92.4)	363 (74.7)	123 (25.3)	5 (1.0)	33 (6.8)	59 (12.1)	26 (5.3)	97 (20.0)

continued

TABLE 43 Summary of valve type and operative approach by VPS group (*continued*)

Summary of operative approach/valve type	Clean insertion,[a] *n* (%)	Revision required		Reason for revision				
		No revision, *n* (%)	Revision,[b] *n* (%)	Failure due to patient, *n* (%)	Functional shunt failure, *n* (%)	Mechanical shunt failure, *n* (%)	Failure due to infection, *n* (%)	Failure – no infection,[c] *n* (%)
Combination								
Overall	3 (0.2)	2 (66.7)	1 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	1 (33.3)
Standard VPS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Antibiotic-impregnated VPS	1 (0.2)	0 (0.0)	1 (100.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)
Silver-impregnated VPS	2 (0.4)	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not known								
Overall	4 (0.3)	1 (25.0)	3 (75.0)	0 (0.0)	0 (0.0)	3 (75.0)	0 (0.0)	3 (75.0)
Standard VPS	3 (0.6)	1 (33.3)	2 (66.7)	0 (0.0)	0 (0.0)	2 (66.7)	0 (0.0)	2 (66.7)
Antibiotic-impregnated VPS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Silver-impregnated VPS	1 (0.2)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	1 (100.0)
Type of valve								
Fixed								
Overall	935 (58.7)	652 (69.7)	283 (30.3)	10 (1.1)	91 (9.7)	126 (13.5)	56 (6.0)	227 (24.3)
Standard VPS	320 (60.0)	228 (71.3)	92 (28.8)	3 (0.9)	28 (8.8)	37 (11.6)	24 (7.5)	68 (21.3)
Antibiotic-impregnated VPS	304 (56.8)	212 (69.7)	92 (30.3)	3 (1.0)	32 (10.5)	47 (15.5)	10 (3.3)	82 (27.0)
Silver-impregnated VPS	311 (59.1)	212 (68.2)	99 (31.8)	4 (1.3)	31 (10.0)	42 (13.5)	22 (7.1)	77 (24.8)
Programmable								
Overall	627 (39.3)	525 (83.7)	102 (16.3)	4 (0.6)	26 (4.1)	52 (8.3)	20 (3.2)	82 (13.1)
Standard VPS	202 (37.9)	172 (85.1)	30 (14.9)	2 (1.0)	8 (4.0)	13 (6.4)	7 (3.5)	23 (11.4)
Antibiotic-impregnated VPS	219 (40.9)	182 (83.1)	37 (16.9)	1 (0.5)	12 (5.5)	19 (8.7)	5 (2.3)	32 (14.6)
Silver-impregnated VPS	206 (39.2)	171 (83.0)	35 (17.0)	1 (0.5)	6 (2.9)	20 (9.7)	8 (3.9)	27 (13.1)

Summary of operative approach/valve type	Clean insertion,[a] *n* (%)	Revision required		Reason for revision				
		No revision, *n* (%)	Revision,[b] *n* (%)	Failure due to patient, *n* (%)	Functional shunt failure, *n* (%)	Mechanical shunt failure, *n* (%)	Failure due to infection, *n* (%)	Failure – no infection,[c] *n* (%)
Not known								
Overall	32 (2.0)	19 (59.4)	13 (40.6)	0 (0.0)	4 (12.5)	7 (21.9)	2 (6.3)	11 (34.4)
Standard VPS	11 (2.1)	3 (27.3)	8 (72.7)	0 (0.0)	4 (36.4)	2 (18.2)	2 (18.2)	6 (54.5)
Antibiotic-impregnated VPS	12 (2.2)	9 (75.0)	3 (25.0)	0 (0.0)	0 (0.0)	3 (25.0)	0 (0.0)	3 (25.0)
Silver-impregnated VPS	9 (1.7)	7 (77.8)	2 (22.2)	0 (0.0)	0 (0.0)	2 (22.2)	0 (0.0)	2 (22.2)

a Clean insertion = no revision + revision.
b Revision = failure due to patient + functional shunt failure + mechanical shunt failure + failure due to infection.
c Failure – no infection = failure due to patient + functional shunt failure + mechanical shunt failure.

TABLE 44 Summary of components replaced at revision by VPS group

Summary of shunt components replaced	Failure – no infection,[a] *n* (%)	Reason for revision for no infection		
		Failure due to patient, *n* (%)	Functional shunt failure *n* (%)	Mechanical shunt failure, *n* (%)
Total number of patients	320	14	121	185
Was a complete new shunt inserted?				
No				
Overall	268 (83.8)	12 (4.5)	99 (36.9)	157 (58.6)
Standard VPS	84 (86.6)	5 (6.0)	35 (41.7)	44 (52.4)
Antibiotic-impregnated VPS	97 (82.9)	3 (3.1)	33 (34.0)	61 (62.9)
Silver-impregnated VPS	87 (82.1)	4 (4.6)	31 (35.6)	52 (59.8)
If no, which component was replaced?				
Ventricular shunt catheter only				
Overall	72 (26.9)	0 (0.0)	22 (30.6)	50 (69.4)
Standard VPS	21 (25.0)	0 (0.0)	7 (33.3)	14 (66.7)
Antibiotic-impregnated VPS	27 (27.8)	0 (0.0)	11 (40.7)	16 (59.3)
Silver-impregnated VPS	24 (27.6)	0 (0.0)	4 (16.7)	20 (83.3)
Peritoneal shunt catheter only				
Overall	31 (11.6)	3 (9.7)	5 (16.1)	23 (74.2)
Standard VPS	12 (14.3)	1 (8.3)	4 (33.3)	7 (58.3)
Antibiotic-impregnated VPS	12 (12.4)	0 (0.0)	1 (8.3)	11 (91.7)
Silver-impregnated VPS	7 (8.0)	2 (28.6)	0 (0.0)	5 (71.4)
Valve only				
Overall	76 (28.4)	3 (3.9)	35 (46.1)	38 (50.0)
Standard VPS	20 (23.8)	0 (0.0)	10 (50.0)	10 (50.0)
Antibiotic-impregnated VPS	33 (34.0)	2 (6.1)	13 (39.4)	18 (54.5)
Silver-impregnated VPS	23 (26.4)	1 (4.3)	12 (52.2)	10 (43.5)
Combination				
Overall	38 (14.2)	1 (2.6)	19 (50.0)	18 (47.4)
Standard VPS	15 (17.9)	1 (6.7)	8 (53.3)	6 (40.0)
Antibiotic-impregnated VPS	11 (11.3)	0 (0.0)	5 (45.5)	6 (54.5)
Silver-impregnated VPS	12 (13.8)	0 (0.0)	6 (50.0)	6 (50.0)
Not known				
Overall	51 (19.0)	5 (9.8)	18 (35.3)	28 (54.9)
Standard VPS	16 (19.0)	3 (18.8)	6 (37.5)	7 (43.8)
Antibiotic-impregnated VPS	14 (14.4)	1 (7.1)	3 (21.4)	10 (71.4)
Silver-impregnated VPS	21 (24.1)	1 (4.8)	9 (42.9)	11 (52.4)

a Failure – no infection = failure due to patient + functional shunt failure + mechanical shunt failure.

TABLE 45 Summary of AEs related to the VPS

Summary of AEs	VPS									
	Standard VPS (531 patients)		Antibiotic-impregnated VPS (545 patients)		Silver-impregnated VPS (525 patients)		Other VPS (136 patients)		Total[a] (1601 patients)	
	Events (*n*)	Patients experiencing an AE, *n* (%)	Events (*n*)	Patients experiencing an AE, *n* (%)	Events (*n*)	Patients experiencing an AE, *n* (%)	Events (*n*)	Patients experiencing an AE, *n* (%)	Events (*n*)	Patients experiencing an AE, *n* (%)
Total	201	135 (25.4)	210	136 (25.0)	191	134 (36.4)	52	35 (25.7)	654	413 (25.8)
Expected AEs related to the VPS										
Ventricular shunt catheter obstruction	21	20 (3.8)	39	31 (5.7)	29	26 (5.0)	7	7 (5.1)	96	79 (4.9)
Shunt infection[b]	40	39 (7.3)	17	16 (2.9)	24	24 (4.6)	9	9 (6.6)	90	88 (5.5)
Shunt valve obstructionc	15	12 (2.3)	25	22 (4.0)	18	17 (3.2)	7	7 (5.1)	65	52 (3.2)
Valve change for symptomatic over/underdrainage	13	12 (2.3)	19	19 (3.5)	16	15 (2.9)	6	5 (3.7)	54	50 (3.1)
CSF leak	16	16 (3.0)	17	14 (2.6)	16	12 (2.3)	4	3 (2.2)	53	45 (2.8)
Wound infection[b,c]	13	10 (1.9)	11	11 (2.0)	16	14 (2.7)	3	2 (1.5)	43	37 (2.3)
Distal shunt catheter obstruction	16	15 (2.8)	10	9 (1.7)	12	10 (1.9)	3	3 (2.2)	41	36 (2.2)
Seizures (early, post operatively, delayed)	13	12 (2.3)	7	7 (1.3)	9	9 (1.7)	1	1 (0.7)	30	29 (1.8)
Migration of shunt	10	7 (1.3)	6	5 (0.9)	7	6 (1.1)	1	1 (0.7)	24	18 (1.1)
Subdural haematoma from excessive CSF drainage	4	4 (0.8)	10	10 (1.8)	6	6 (1.1)	0	0 (0.0)	20	20 (1.2)
Misplacement of distal shunt catheter	4	3 (0.6)	7	6 (1.1)	5	5 (1.0)	0	0 (0.0)	16	14 (0.9)
Misplacement of ventricular shunt catheter	3	3 (0.6)	5	5 (0.9)	4	4 (0.8)	1	1 (0.7)	13	13 (0.8)
Disconnection of shunt	1	1 (0.2)	3	3 (0.6)	3	3 (0.6)	2	2 (1.5)	9	9 (0.6)
Wound dehiscence	1	1 (0.2)	4	4 (0.7)	3	3 (0.6)	0	0 (0.0)	8	8 (0.5)

continued

TABLE 45 Summary of AEs related to the VPS (*continued*)

Summary of AEs	VPS									
	Standard VPS (531 patients)		Antibiotic-impregnated VPS (545 patients)		Silver-impregnated VPS (525 patients)		Other VPS (136 patients)		Total[a] (1601 patients)	
	Events (*n*)	Patients experiencing an AE, *n* (%)	Events (*n*)	Patients experiencing an AE, *n* (%)	Events (*n*)	Patients experiencing an AE, *n* (%)	Events (*n*)	Patients experiencing an AE, *n* (%)	Events (*n*)	Patients experiencing an AE, *n* (%)
Independent abdominal infections	5	4 (0.8)	0	0 (0.0)	1	1 (0.2)	0	0 (0.0)	6	5 (0.3)
Intracranial haemorrhage	1	1 (0.2)	4	3 (0.6)	1	1 (0.2)	0	0 (0.0)	6	5 (0.3)
Brain injury related to procedure with new neurologic deficit	0	0 (0.0)	0	0 (0.0)	5	4 (0.8)	0	0 (0.0)	5	4 (0.2)
Fracture of shunt	2	2 (0.4)	1	1 (0.2)	2	2 (0.4)	0	0 (0.0)	5	5 (0.3)
Bowel perforation as a result of shunt surgery	0	0 (0.0)	2	2 (0.4)	2	2 (0.4)	0	0 (0.0)	4	4 (0.2)
Extra-axial fluid collections	3	3 (0.6)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	3	3 (0.2)
Tunnelling injury (organ, viscus, lung, vascular)	1	1 (0.2)	1	1 (0.2)	0	0 (0.0)	0	0 (0.0)	2	2 (0.1)
Abdominal hernia	1	1 (0.2)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.1)
Loculation of ventricles	0	0 (0.0)	0	0 (0.0)	1	1 (0.2)	0	0 (0.0)	1	1 (0.1)
Malabsorption	0	0 (0.0)	0	0 (0.0)	1	1 (0.2)	0	0 (0.0)	1	1 (0.1)
Pseudocysts	0	0 (0.0)	1	1 (0.2)	0	0 (0.0)	0	0 (0.0)	1	1 (0.1)
Sunken fontanelle	0	0 (0.0)	1	1 (0.2)	0	0 (0.0)	0	0 (0.0)	1	1 (0.1)
Vascular injury to brain pseudoaneurysm	0	0 (0.0)	1	1 (0.2)	0	0 (0.0)	0	0 (0.0)	1	1 (0.1)
Unexpected AEs related to the VPS										
Vomiting	4	3 (0.6)	1	1 (0.2)	1	1 (0.2)	2	2 (1.5)	8	6 (0.4)
Headaches	1	1 (0.2)	3	3 (0.6)	0	0 (0.0)	1	1 (0.7)	5	4 (0.2)
Abdominal pain	0	0 (0.0)	2	2 (0.4)	2	2 (0.4)	0	0 (0.0)	4	4 (0.2)
Distended abdomen	2	2 (0.4)	0	0 (0.0)	1	1 (0.2)	0	0 (0.0)	3	3 (0.2)

Summary of AEs	VPS									
	Standard VPS (531 patients)		Antibiotic-impregnated VPS (545 patients)		Silver-impregnated VPS (525 patients)		Other VPS (136 patients)		Total[a] (1601 patients)	
	Events (*n*)	Patients experiencing an AE, *n* (%)	Events (*n*)	Patients experiencing an AE, *n* (%)	Events (*n*)	Patients experiencing an AE, *n* (%)	Events (*n*)	Patients experiencing an AE, *n* (%)	Events (*n*)	Patients experiencing an AE, *n* (%)
Lethargy	1	1 (0.2)	0	0 (0.0)	1	1 (0.2)	1	1 (0.7)	3	3 (0.2)
Swelling at shunt site	0	0 (0.0)	2	1 (0.2)	1	1 (0.2)	0	0 (0.0)	3	2 (0.1)
Functional valve problems	1	1 (0.2)	0	0 (0.0)	1	1 (0.2)	0	0 (0.0)	2	2 (0.1)
Irritability	1	1 (0.2)	0	0 (0.0)	0	0 (0.0)	1	1 (0.7)	2	2 (0.1)
Blank spells	0	0 (0.0)	1	1 (0.2)	0	0 (0.0)	0	0 (0.0)	1	1 (0.1)
Blurred vision	0	0 (0.0)	1	1 (0.2)	0	0 (0.0)	0	0 (0.0)	1	1 (0.1)
Difficult to cannulate, catheter too short	0	0 (0.0)	0	0 (0.0)	1	1 (0.2)	0	0 (0.0)	1	1 (0.1)
Distal shunt catheter extra peritoneal	1	1 (0.2)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.1)
Externalisation of VPS	0	0 (0.0)	0	0 (0.0)	1	1 (0.2)	0	0 (0.0)	1	1 (0.1)
Fluid leaking from ears	1	1 (0.2)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.1)
Foreign body removed from shunt surgery site	1	1 (0.2)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.1)
Intracranial pressure bolt insertion	0	0 (0.0)	0	0 (0.0)	1	1 (0.2)	0	0 (0.0)	1	1 (0.1)
Intra-abdonimal collection	0	0 (0.0)	1	1 (0.2)	0	0 (0.0)	0	0 (0.0)	1	1 (0.1)
Itching at shunt site	0	0 (0.0)	1	1 (0.2)	0	0 (0.0)	0	0 (0.0)	1	1 (0.1)
Losing balance	1	1 (0.2)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.1)
Memory loss	0	0 (0.0)	1	1 (0.2)	0	0 (0.0)	0	0 (0.0)	1	1 (0.1)
Nausea and vomiting	0	0 (0.0)	1	1 (0.2)	0	0 (0.0)	0	0 (0.0)	1	1 (0.1)
Nausea	1	1 (0.2)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.1)

continued

TABLE 45 Summary of AEs related to the VPS (*continued*)

Summary of AEs	VPS									
	Standard VPS (531 patients)		Antibiotic-impregnated VPS (545 patients)		Silver-impregnated VPS (525 patients)		Other VPS (136 patients)		Total[a] (1601 patients)	
	Events (*n*)	Patients experiencing an AE, *n* (%)	Events (*n*)	Patients experiencing an AE, *n* (%)	Events (*n*)	Patients experiencing an AE, *n* (%)	Events (*n*)	Patients experiencing an AE, *n* (%)	Events (*n*)	Patients experiencing an AE, *n* (%)
Numbness	1	1 (0.2)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.1)
Pneumocephalus	0	0 (0.0)	1	1 (0.2)	0	0 (0.0)	0	0 (0.0)	1	1 (0.1)
Poor feeding	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.7)	1	1 (0.1)
Pseudomeningocoele	1	1 (0.2)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.1)
Pyrexia	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.7)	1	1 (0.1)
Seizure	0	0 (0.0)	1	1 (0.2)	0	0 (0.0)	0	0 (0.0)	1	1 (0.1)
Shutting-down episodes	0	0 (0.0)	1	1 (0.2)	0	0 (0.0)	0	0 (0.0)	1	1 (0.1)
Skull fracture associated with VPS migration	0	0 (0.0)	1	1 (0.2)	0	0 (0.0)	0	0 (0.0)	1	1 (0.1)
Tremor in hand	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.7)	1	1 (0.1)
Ventriculer shunt catheter coiled and kinked	1	1 (0.2)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.1)
Vision bubbles	0	0 (0.0)	1	1 (0.2)	0	0 (0.0)	0	0 (0.0)	1	1 (0.1)

a Table ordered by total number of events column (most common to least common) within expected and unexpected events.
b Shunt and wound infections include all revisions; infections as an outcome in the efficacy analyses are a subset of these.
c Wound infections as AEs include VPS superficial incisional infections (without CSF or tubing involvement) and VPS deep incisional infection; only VPS deep incisional infections are considered infections as an outcome in the efficacy analyses and, therefore, are a subset of these.

Appendix 3 Health economics study: additional data

TABLE 46 Unit costs of elective and day-case inpatient hospital attendances for the most frequent HRG codes (top 15 out of 281)

HRG code	HRG name	Attendance	Unit cost (£)	Source
AA13A	Intermediate intracranial procedures except trauma with cerebral degenerations or miscellaneous disorders of nervous system, with CCs	Elective/day case	4888.00	*NHS National Tariff Payment System*[45]
PA42Z	Brain tumours with length of stay of ≥ 1 day	Elective/day case	3052.00	*NHS National Tariff Payment System*[45]
AA19A	Minor intracranial procedures except trauma with cerebral degenerations or miscellaneous disorders of nervous system, with CCs	Elective/day case	2041.00	*NHS National Tariff Payment System*[45]
AA52G	Very major intracranial procedures, aged ≤ 18 years an, with a CC score of 0–3	Elective/day case	6210.00	*NHS Reference Costs 2015 to 2016*[44]
PA44Z	Neoplasm diagnoses with length of stay of 0 days	Elective/day case	533.00	*NHS National Tariff Payment System*[45]
AA25A	Cerebral Degenerations or miscellaneous disorders of nervous system, with CCs	Elective/day case	1269.00	*NHS National Tariff Payment System*[45]
AA52C	Very major intracranial procedures, aged ≤ 18 years, with a CC score of 0–3	Elective/day case	6210.00	*NHS Reference Costs 2015 to 2016*[44]
PM44Z	Paediatric neoplasm diagnoses with length of stay of 0 days	Elective/day case	1373.00	*NHS Reference Costs 2015 to 2016*[44]
AA13B	Intermediate intracranial procedures except trauma with cerebral degenerations or miscellaneous disorders of nervous system without CCs	Elective/day case	4409.00	*NHS National Tariff Payment System*[45]
PA01A	Nervous system disorders with CCs	Elective/day case	1056.00	*NHS National Tariff Payment System*[45]
AA21A	Minor intracranial procedures except trauma with other diagnoses with CCs	Elective/day case	1489.00	*NHS National Tariff Payment System*[45]
AA52D	Very major intracranial procedures, aged ≥ 19 years, with a CC score of 0–3	Elective/day case	7907.00	*NHS Reference Costs 2015 to 2016*[44]
PR01C	Paediatric nervous system disorders with a CC score of 2–4	Elective/day case	2417.00	*NHS Reference Costs 2015 to 2016*[44]
PA28A	Feeding difficulties and vomiting, without CCs	Elective/day case	2190.00	*NHS National Tariff Payment System*[45]
AA54A	Intermediate intracranial procedures, aged ≥ 19 years, with a CC score of ≥ 4	Elective/day case	5787.00	*NHS Reference Costs 2015 to 2016*[44]

CC, complication or comorbidity.

TABLE 47 Unit costs of hospital outpatient attendances, ordered by the most frequent HRG codes (top 15 out of 122 HRG codes and 162 treatment function codes)

HRG	Treatment function code	HRG name	Unit cost (£)	Source
WF01A	150	Neurosurgery	188.00	*NHS Reference Costs 2015 to 2016*[44]
WF01A	218	Paediatric neurosurgery	179.00	*NHS Reference Costs 2015 to 2016*[44]
WF01A	300	General medicine	164.00	*NHS Reference Costs 2015 to 2016*[44]
WF01A	400	Neurology	161.00	*NHS Reference Costs 2015 to 2016*[44]
WF01A	216	Paediatric ophthalmology	115.00	*NHS Reference Costs 2015 to 2016*[44]
WF01A	420	Paediatrics	180.00	*NHS Reference Costs 2015 to 2016*[44]
WF01A	252	Paediatric endocrinology	229.00	*NHS Reference Costs 2015 to 2016*[44]
WF01A	260	Paediatric medical oncology	243.00	*NHS Reference Costs 2015 to 2016*[44]
WF01A	218	Paediatric neurosurgery	179.00	*NHS Reference Costs 2015 to 2016*[44]
WF01A	251	Paediatric gastroenterology	195.00	*NHS Reference Costs 2015 to 2016*[44]
WF01A	100	General surgery	123.00	*NHS Reference Costs 2015 to 2016*[44]
WF01A	258	Paediatric respiratory medicine	204.00	*NHS Reference Costs 2015 to 2016*[44]
WF01A	290	Community paediatrics	265.00	*NHS Reference Costs 2015 to 2016*[44]
WF01B	150	Neurosurgery	236.00	*NHS Reference Costs 2015 to 2016*[44]
WF01B	400	Neurology	217.00	*NHS Reference Costs 2015 to 2016*[44]
WF01B	290	Community paediatrics	376.00	*NHS Reference Costs 2015 to 2016*[44]
WF01B	216	Paediatric ophthalmology	119.00	*NHS Reference Costs 2015 to 2016*[44]
WF01B	320	Cardiology	156.00	*NHS Reference Costs 2015 to 2016*[44]
WF01B	252	Paediatric endocrinology	330.00	*NHS Reference Costs 2015 to 2016*[44]
WF01B	218	Paediatric neurosurgery	255.00	*NHS Reference Costs 2015 to 2016*[44]
WF01B	303	Clinical haematology	223.00	*NHS Reference Costs 2015 to 2016*[44]
WF01B	214	Paediatric trauma and orthopaedics	136.00	*NHS Reference Costs 2015 to 2016*[44]
WF01B	314	Rehabilitation service	248.00	*NHS Reference Costs 2015 to 2016*[44]
WF01B	130	Ophthalmology	110.00	*NHS Reference Costs 2015 to 2016*[44]
WF01B	171	Paediatric surgery	185.00	*NHS Reference Costs 2015 to 2016*[44]
WF01B	180	A&E	157.00	*NHS Reference Costs 2015 to 2016*[44]
WF01B	713	Psychotherapy	158.00	*NHS Reference Costs 2015 to 2016*[44]
WF01B	191	Pain management	177.00	*NHS Reference Costs 2015 to 2016*[44]
WF02A	216	Paediatric ophthalmology	102.00	*NHS Reference Costs 2015 to 2016*[44]
WF02A	214	Paediatric trauma and orthopaedics	142.00	*NHS Reference Costs 2015 to 2016*[44]
WF02A	260	Paediatric medical oncology	258.00	*NHS Reference Costs 2015 to 2016*[44]
WF02A	421	Paediatric neurology	375.00	*NHS Reference Costs 2015 to 2016*[44]
WF02A	218	Paediatric neurosurgery	170.00	*NHS Reference Costs 2015 to 2016*[44]
WF02A	258	Paediatric respiratory medicine	176.00	*NHS Reference Costs 2015 to 2016*[44]
WF02A	251	Paediatric gastroenterology	251.00	*NHS Reference Costs 2015 to 2016*[44]

TABLE 47 Unit costs of hospital outpatient attendances, ordered by the most frequent HRG codes (top 15 out of 122 HRG codes and 162 treatment function codes) (*continued*)

HRG	Treatment function code	HRG name	Unit cost (£)	Source
WF02A	256	Paediatric infectious diseases	269.00	*NHS Reference Costs 2015 to 2016*[44]
WF02A	252	Paediatric endocrinology	230.00	*NHS Reference Costs 2015 to 2016*[44]
WF02A	253	Paediatric clinical haematology	328.00	*NHS Reference Costs 2015 to 2016*[44]
WF02A	219	Paediatric plastic surgery	145.00	*NHS Reference Costs 2015 to 2016*[44]

TABLE 48 Unit costs of consultations with health-care professionals

Consultation	Unit cost (£)	Source
GP surgery visit (per 9.22-minute consultation)	38.00	PSSRU 2017[42]
Nurse at surgery (per 9-minute consultation)	5.40	PSSRU 2017[42]
Telephone triage: GP led (per call)	14.75	PSSRU 2017[42]
Telephone triage: nurse led (per call)	7.90	PSSRU 2017[42]
Prescription	29.20	PSSRU 2017[42]
Paediatric consult (per consultation)	196.00	PSSRU 2017[42]
Physiotherapy (per consultation)	86.00	PSSRU 2017[42]
Continence nurse (per consultation)	80.00	*NHS Reference Costs 2015 to 2016*[44]
Specialist nurse, adult, face to face (per consultation)	77.00	*NHS Reference Costs 2015 to 2016*[44]
District nurse	38.00	*NHS Reference Costs 2015 to 2016*[44]
Doctor: home visit (per visit)	87.46	PSSRU 2017[42]
Consultant psychiatrist (per consultation)	108.00	PSSRU 2017[42]
Health visitor (per consultation)	53.00	*NHS Reference Costs 2015 to 2016*[44]
School nurse (per consultation)	54.00	*NHS Reference Costs 2015 to 2016*[44]
Occupational therapist (per consultation)	79.00	*NHS Reference Costs 2015 to 2016*[44]
Speech therapist, adult (per consultation)	88.00	*NHS Reference Costs 2015 to 2016*[44]
Dietitian (per consultation)	81.00	*NHS Reference Costs 2015 to 2016*[44]
Speech therapist, child (per consultation)	94.00	*NHS Reference Costs 2015 to 2016*[44]
Clinical psychologist (per consultation)	144.70	*NHS Reference Costs 2015 to 2016*[44]
Care work and social care (per intervention)	54.00	PSSRU 2017[42]
Social worker (per intervention)	54.00	PSSRU 2017[42]
Community nurse (per consultation)	89.00	*NHS Reference Costs 2015 to 2016*[44]
Shunt nurse specialist (per consultation)	77.00	*NHS Reference Costs 2015 to 2016*[44]

PSSRU, Personal Social Services Research Unit.

TABLE 49 Adjusted total (24-month, discounted) costs: results of the ordinary least squares regression based on imputed data

Variable	Coefficient (£)	*p*-value	97.5% CI (£)
Intercept	28,796.83	0.000	10,845.34 to 46,748.32
Antibiotic-impregnated VPS	−4514.67	0.030	−9169.53 to 140.19
Silver-impregnated VPS	−1322.34	0.557	−6456.95 to 3812.27
Treatment failure	8603.91	0.000	4696.00 to 12,511.82
Age: 16–65 years	−3670.40	0.113	−8886.24 to 1545.44
Age: > 65 years	−2872.09	0.227	−8233.51 to 2489.33
Time in trial (days)	−7.09	0.129	−17.61 to 3.43
Centre			
A	33.59	0.997	−23,137.15 to 23,204.33
B	−901.01	0.906	−18,118.44 to 16,316.41
C	732.23	0.922	−16,116.42 to 17,580.88
D	−8262.26	0.289	−25,868.11 to 9343.59
E	−1615.54	0.856	−21,698.98 to 18,467.90
F	−8657.07	0.282	−26,785.97 to 9471.82
G	−11,152.65	0.147	−28,493.21 to 6187.91
H	−5695.04	0.477	−23,805.53 to 12,415.46
I	638.42	0.943	−19,533.70 to 20,810.55
J	−1701.73	0.825	−19,070.15 to 15,666.69
K	−4921.65	0.543	−23,203.33 to 13,360.04
L	−4898.48	0.561	−23,919.14 to 14,122.18
M	−6878.41	0.374	−24,346.42 to 10,589.60
N	−7992.50	0.295	−25,226.53 to 9241.53
O	1158.21	0.940	−33,654.62 to 35,971.04
P	−2290.29	0.846	−28,875.46 to 24,294.88
Q	−5408.04	0.485	−22,913.22 to 12,097.13
R	−7347.52	0.336	−24,590.30 to 9895.26
S	−1171.56	0.878	−18,447.40 to 16,104.27
T	−5911.51	0.460	−23,978.95 to 12,155.93

TABLE 50 Responses to the EQ-VAS questionnaire, by version and intervention group

	Trial group					
	Standard VPS		Antibiotic-impregnated VPS		Silver-impregnated VPS	
EQ-VAS	*n*	Mean (97.5% CI)	*n*	Mean (97.5% CI)	*n*	Mean (97.5% CI)
Youth version (8–18 years)						
Baseline	8	43.25 (13.73 to 72.75)	10	58.00 (40.18 to 75.81)	4	72.75 (46.59 to 98.90)
Early post operatively	12	65.33 (50.33 to 80.32)	10	68.90 (49.42 to 88.37)	8	65.75 (45.56 to 85.93)
12 weeks	9	80.77 (64.42 to 97.13)	8	79.25 (63.31 to 95.18)	8	81.37 (66.28 to 96.46)
End of trial	7	70.14 (45.79 to 94.48)	6	80.00 (55.49 to 104.50)	6	84.00 (50.87 to 117.12)
Adult version						
Baseline	182	54.12 (50.70 to 57.54)	171	56.79 (53.34 to 60.24)	162	55.79 (51.94 to 59.64)
Early post operatively	173	61.15 (57.99 to 64.30)	168	61.49 (58.33 to 64.65)	157	60.29 (56.50 to 64.08)
12 weeks	145	67.34 (63.68 to 71.00)	137	67.09 (63.27 to 70.91)	133	69.20 (64.94 to 73.45)
End of trial	155	68.15 (64.71 to 71.59)	159	67.53 (63.84 to 71.22)	155	71.71 (68.20 to 75.23)
Proxy version						
Baseline	57	36.75 (29.46 to 44.04)	63	38.55 (31.56 to 45.54)	55	43.43 (36.25 to 50.61)
Early post operatively	62	46.38 (39.35 to 53.41)	61	50.22 (43.32 to 57.13)	59	54.15 (47.53 to 60.76)
12 weeks	42	61.45 (52.86 to 70.03)	39	63.00 (54.47 to 71.52)	38	65.10 (56.11 to 74.09)
End of trial	34	64.61 (57.12 to 72.10)	22	57.27 (43.28 to 71.25)	39	58.87 (50.16 to 67.18)
Combined						
Baseline	247	50.32 (47.11 to 53.53)	246	52.92 (49.76 to 56.08)	224	52.98 (49.66 to 56.30)
Early post operatively	246	57.22 (54.23 to 60.20)	240	58.90 (55.95 to 61.84)	225	58.00 (54.75 to 61.24)
12 weeks	194	65.94 (62.58 to 69.30)	187	65.95 (62.59 to 69.31)	183	67.86 (64.14 to 71.58)
End of trial	196	67.00 (63.85 to 70.14)	187	66.43 (62.94 to 69.93)	200	68.90 (65.53 to 72.27)

TABLE 51 Summary of HOQ return by time point

Questionnaire	Trial group: Standard VPS					Antibiotic-impregnated VPS					Silver-impregnated VPS					Total				
	N returned form expected	Baseline, *n* (%)	Early post operatively, *n* (%)	12 weeks, *n* (%)	End of trial, *n* (%)	*N* returned form expected	Baseline, *n* (%)	Early post operatively, *n* (%)	12 weeks, *n* (%)	End of trial, *n* (%)	*N* returned form expected	Baseline, *n* (%)	Early post operatively, *n* (%)	12 weeks, *n* (%)	End of trial, *n* (%)	*N* returned form expected	Baseline, *n* (%)	Early post operatively, *n* (%)	12 weeks, *n* (%)	End of trial, *n* (%)
HOQ patient	25	7 (28.0)	14 (56.0)	8 (32.0)	5 (20.0)	27	7 (25.9)	7 (25.9)	4 (14.8)	5 (18.5)	18	5 (27.8)	8 (44.4)	8 (44.4)	7 (38.9)	70	19 (27.1)	29 (41.4)	20 (28.6)	17 (24.3)
HOQ parent	11	4 (36.4)	5 (45.5)	6 (54.5)	2 (18.2)	12	8 (66.7)	8 (66.7)	7 (58.3)	2 (16.7)	11	6 (54.5)	8 (72.7)	6 (54.5)	3 (27.3)	34	18 (52.9)	21 (61.8)	19 (55.9)	7 (20.6)

TABLE 52 The HOQ – patient questionnaire

Scale	Trial group: Standard VPS				Antibiotic-impregnated VPS				Silver-impregnated VPS				Total			
	Baseline	Early post operatively	12 weeks	End of trial	Baseline	Early post operatively	12 weeks	End of trial	Baseline	Early post operatively	12 weeks	End of trial	Baseline	Early post operatively	12 weeks	End of trial
Physical health																
Completed item, *n* (% completed)	7 (100.0)	14 (100.0)	8 (100.0)	5 (100.0)	7 (100.0)	7 (100.0)	4 (100.0)	5 (100.0)	5 (100.0)	8 (100.0)	8 (100.0)	7 (100.0)	19 (100.0)	29 (100.0)	20 (100.0)	17 (100.0)
Median (IQR)	0.6 (0.4–0.8)	0.7 (0.6–0.9)	0.8 (0.7–1.0)	0.7 (0.7–0.8)	0.8 (0.3–0.8)	0.8 (0.6–0.9)	0.8 (0.7–0.9)	0.7 (0.7–1.0)	0.6 (0.2–0.8)	0.7 (0.5–0.9)	0.9 (0.5–1.0)	0.9 (0.9–1.0)	0.6 (0.3–0.8)	0.8 (0.6–0.9)	0.9 (0.7–1.0)	0.9 (0.7–1.0)
Socioemotional health																
Completed item, *n* (% completed)	6 (85.7)	14 (100.0)	8 (100.0)	5 (100.0)	7 (100.0)	6 (85.7)	3 (75.0)	5 (100.0)	5 (100.0)	8 (100.0)	8 (100.0)	7 (100.0)	18 (94.7)	28 (96.6)	19 (95.0)	17 (100.0)
Median (IQR)	0.8 (0.7–0.9)	0.8 (0.8–0.9)	0.8 (0.8–0.9)	0.8 (0.7–0.9)	0.7 (0.4–0.9)	0.8 (0.3–0.9)	0.8 (0.7–0.8)	0.9 (0.7–0.9)	0.4 (0.4–0.9)	0.8 (0.6–1.0)	0.8 (0.6–0.9)	0.9 (0.7–1.0)	0.8 (0.4–0.9)	0.8 (0.7–0.9)	0.8 (0.7–0.9)	0.9 (0.7–0.9)
Cognitive health																
Completed item, *n* (% completed)	5 (71.4)	14 (100.0)	8 (100.0)	5 (100.0)	7 (100.0)	6 (85.7)	3 (75.0)	5 (100.0)	5 (100.0)	8 (100.0)	8 (100.0)	6 (85.7)	17 (89.5)	28 (96.6)	19 (95.0)	16 (94.1)
Median (IQR)	0.8 (0.7–0.8)	0.8 (0.7–0.9)	0.9 (0.6–0.9)	0.7 (0.6–0.9)	0.8 (0.4–0.9)	0.8 (0.6–0.9)	0.8 (0.4–0.8)	0.8 (0.7–0.8)	0.3 (0.2–1.0)	0.8 (0.4–1.0)	0.8 (0.6–0.9)	0.9 (0.8–0.9)	0.8 (0.3–0.9)	0.8 (0.6–0.9)	0.8 (0.6–0.9)	0.8 (0.7–0.9)
Total health																
Completed item, *n* (% completed)	6 (85.7)	14 (100.0)	8 (100.0)	5 (100.0)	7 (100.0)	6 (85.7)	4 (100.0)	5 (100.0)	5 (100.0)	8 (100.0)	8 (100.0)	7 (100.0)	18 (94.7)	28 (96.6)	20 (100.0)	17 (100.0)
Median (IQR)	0.8 (0.7–0.8)	0.8 (0.7–0.8)	0.8 (0.8–0.9)	0.7 (0.7–0.8)	0.7 (0.4–0.9)	0.7 (0.6–0.9)	0.7 (0.7–0.8)	0.8 (0.6–0.9)	0.4 (0.3–0.9)	0.8 (0.5–0.9)	0.8 (0.6–0.9)	0.9 (0.8–1.0)	0.7 (0.4–0.8)	0.8 (0.6–0.9)	0.8 (0.7–0.9)	0.8 (0.7–0.9)

IQR, interquartile range.

TABLE 53 The HOQ – parent questionnaire

	Trial group															
	Standard VPS				Antibiotic-impregnated VPS				Silver-impregnated VPS				Total			
Scale	Baseline	Early post operatively	12 weeks	End of trial	Baseline	Early post operatively	12 weeks	End of trial	Baseline	Early post operatively	12 weeks	End of trial	Baseline	Early post operatively	12 weeks	End of trial
Physical health																
Completed item, *n* (% completed)	4 (100.0)	5 (100.0)	6 (100.0)	2 (100.0)	8 (100.0)	8 (100.0)	7 (100.0)	2 (100.0)	6 (100.0)	8 (100.0)	6 (100.0)	3 (100.0)	18 (100.0)	21 (100.0)	19 (100.0)	7 (100.0)
Median (IQR)	0.3 (0.1–0.5)	0.1 (0.0–0.4)	0.5 (0.3–0.8)	0.7 (0.6–0.8)	0.5 (0.3–0.8)	0.5 (0.3–0.7)	0.6 (0.3–0.9)	0.6 (0.6–0.6)	0.6 (0.4–0.7)	0.5 (0.5–0.8)	0.7 (0.4–0.9)	0.6 (0.5–1.0)	0.5 (0.3–0.7)	0.5 (0.3–0.6)	0.6 (0.3–0.9)	0.6 (0.6–0.8)
Socioemotional health																
Completed item, *n* (% completed)	2 (50.0)	3 (60.0)	6 (100.0)	2 (100.0)	7 (87.5)	7 (87.5)	6 (85.7)	2 (100.0)	6 (100.0)	8 (100.0)	6 (100.0)	3 (100.0)	15 (83.3)	18 (85.7)	18 (94.7)	7 (100.0)
Median (IQR)	0.7 (0.5–0.8)	0.5 (0.1–0.8)	0.6 (0.5–0.8)	0.8 (0.8–0.8)	0.8 (0.7–0.9)	0.7 (0.6–0.9)	0.6 (0.6–0.7)	0.7 (0.6–0.8)	0.8 (0.7–0.9)	0.8 (0.6–0.9)	0.8 (0.7–0.9)	0.9 (0.6–0.9)	0.8 (0.7–0.9)	0.7 (0.5–0.9)	0.7 (0.5–0.8)	0.8 (0.6–0.9)
Cognitive health																
Completed item, *n* (% completed)	3 (75.0)	2 (40.0)	5 (83.3)	2 (100.0)	7 (87.5)	6 (75.0)	4 (57.1)	2 (100.0)	6 (100.0)	8 (100.0)	6 (100.0)	3 (100.0)	16 (88.9)	16 (76.2)	15 (78.9)	7 (100.0)
Median (IQR)	0.2 (0.0–0.6)	0.4 (0.2–0.6)	0.4 (0.2–0.4)	0.2 (0.1–0.2)	0.6 (0.5–0.9)	0.6 (0.4–0.7)	0.4 (0.3–0.7)	0.6 (0.2–1.0)	0.7 (0.3–0.8)	0.7 (0.2–0.9)	0.7 (0.0–0.9)	0.3 (0.1–1.0)	0.6 (0.3–0.8)	0.6 (0.2–0.9)	0.4 (0.2–0.9)	0.2 (0.1–1.0)
Total health																
Completed item, *n* (% completed)	3 (75.0)	3 (60.0)	6 (100.0)	2 (100.0)	7 (87.5)	6 (75.0)	6 (85.7)	2 (100.0)	6 (100.0)	8 (100.0)	6 (100.0)	3 (100.0)	16 (88.9)	17 (81.0)	18 (94.7)	7 (100.0)
Median (IQR)	0.5 (0.1–0.6)	0.5 (0.1–0.6)	0.5 (0.4–0.7)	0.6 (0.6–0.6)	0.7 (0.6–0.8)	0.7 (0.5–0.8)	0.6 (0.5–0.7)	0.7 (0.5–0.8)	0.7 (0.5–0.8)	0.6 (0.5–0.9)	0.7 (0.5–0.9)	0.7 (0.5–0.9)	0.7 (0.5–0.8)	0.6 (0.5–0.8)	0.6 (0.5–0.8)	0.6 (0.5–0.8)

IQR, interquartile range.

EME
HS&DR
HTA
PGfAR
PHR

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