# Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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## 1. Trial committees and list of investigators

Committee membership

### Trial Steering Committee (TSC) independent members:

Deborah Stocken (chair)

John R.W. Kestle

Craig Williams

Abhaya Kulkarni

Gill Yaz

### Independent Data Monitoring Committee (IDMC) members:

Peter J.A. Hutchinson (chair)

Andrew Vail

Carmel Curtis

#### Trial writing group

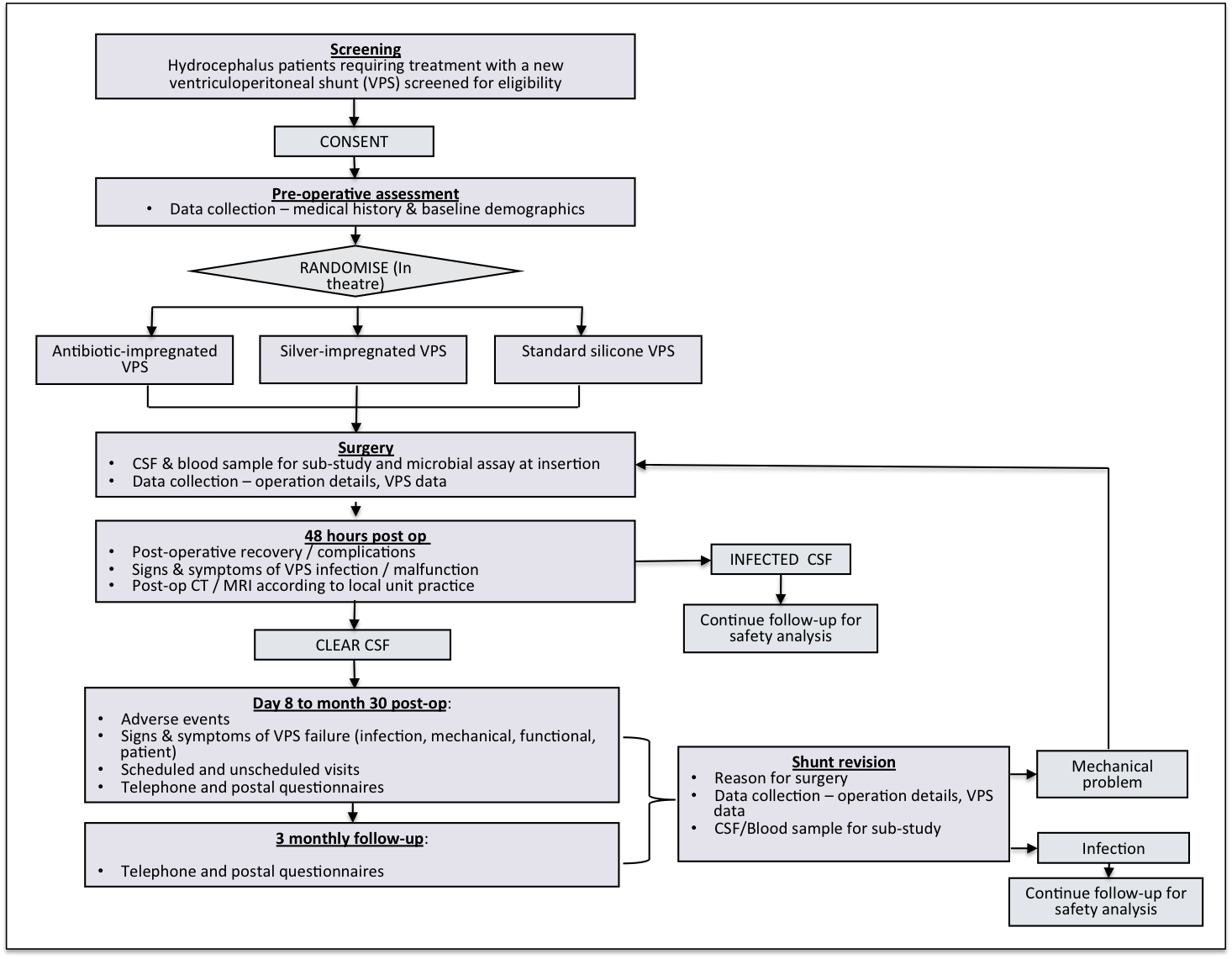
The writing group members are listed in the main author byline. The first two authors are joint first authors and along with EJC, DH, TS and CG wrote the first draft of the manuscript, which was revised and approved by all the authors, who also assume responsibility for the accuracy and completeness of its content. The decision to submit the manuscript for publication lies with the joint first authors. Statistical analysis was performed by EJC, MB and CG according to the statistical analysis plan.

Table S 1: Participating Sites and investigators and recruitment by center

| **Site name (number randomised)** | **Principle Investigator** | **Investigators** |
| --- | --- | --- |
| Alder Hey Children's Hospital Liverpool (119) | Conor Mallucci | Benedetta Pettorini  Christopher Parks  Ajay SInha  Libby van Tonder  Mitchel T Foster |
| Birmingham Children's Hospital (30) | Guirish Solanki | Desiderio Rodrigues |
| Bristol Frenchay Hospital (188) | Richard Edwards | Adam Williams (Co-PI) |
| Cambridge Addenbrooke's Hospital (85) | Matthew Garnett  Angelos Kolias (co-PI) | Karen Caldwell  Silvia Tarantino |
| Cardiff University Hospital of Wales (129) | Paul Leach | Malik Zaben  Gulam Zilani  Dmitri Shastin  Joseph Merola  Rahim Hussain  Ravindra Vemaraju  Liudmila Selezneva  Georgina Radford  Nadine Lloyd |
| Dublin Temple Street Children's University Hospital (69) | Darach Crimmins | John Caird (co-PI)  Maria Nunez Sayar  Noelle O’Mahoney |
| Great Ormond Street Hospital (71) | Dominic Thompson | Kristian Aquilina  Gregory James |
| James Cook Hospital (22) | Roger Strachan | Nitin Mukerji  Jonathan Pesic- Smith |
| King's College Hospital (36) | Bassel Zebian | Bhaskar Thakur (Co-PI)  Holly Dickson  Eniola Nsirim  Adedamola Adebayo |
| Leeds General Infirmary (92) | John Goodden | Kenan Deniz  Janet Clarke  Mary Kambafwile  Ian Anderson  Rebecca Chave-Cox  Asim Sheik  Ryan Mathew  Oliver Richards  Soumya Mukherjee  Paul Chumas  Atul Tyagi  Gnanamurthy Sivakumar |
| National Hospital Queens Square (73) | Ahmed Toma | Linda D’Antona  Laurence Watkins  Lewis Thorne  Claudia Carven  Vanessa Bassen |
| Newcastle General Hospital (14) | Damian Holliman | Ian Coulter (co-PI) |
| Nottingham Queen's Medical Centre (141) | Donald Macarthur | Maria Cartmill  Simon Howarth  Stuart Smith  Shazia Javed |
| Royal Children's Hospital Manchester (48) | Ian Kamaly | Roberto Ramirez |
| Salford Royal Hospital (82) | Andrew King | Ardash Nadig (Co-PI)  John Thorne |
| Sheffield Children's Hospital (41) & Sheffield Adults Sheffield Teaching Hospital (22) | Shungu Ushewokunze | Saurabh Sinha (co-PI)  Hesham Zaki  John McMullan |
| Southampton General Hospital (175) | Diederik Bulters | Ryan Waters (Co-PI)  George Zilidis  Joy Roach  Ahmed Sadek  Patrick Holton  Ardalan Zolnourian  Aabir Chakraborty |
| The Walton Centre Liverpool (155) | Michael D Jenkinson | Catherine McMahon  Neil Buxton  Emmanuel Chavredakis  Andrew R Brodbelt  David DA Lawson  Paul Eldridge  Jibril Farah  Rasheed Zakaria  Geraint Sunderland |
| Western General Hospital, Edinburgh (5) & Edinburgh Hospital (8) | Jothy Kandasamy | Mark Hughes (Co-PI)  Paul Brennan |

## 2. Trial flowchart

Figure S : Schematic of study design



VPS: ventriculoperitoneal shunt

CSF: cerebrospinal fluid

CT: computed tomography

MRI: magnetic resonance imaging

## 3. Screening data

Table S 2: Reasons consent not sought

|  |  |  |
| --- | --- | --- |
| Number of patients where consent not sought | **N** | 435 |
| **Reason consent not sought** | **n** | **n/N%** |
| Missed by research nurse/doctor | 177 | 40.7 |
| Not approached because of patient’s lack of understanding | 59 | 13.6 |
| Not approached because of consultant preference | 74 | 17.0 |
| Consultant preference. | 9 | 2.1 |
| Deteriation of patient condition. | 2 | 0.5 |
| No date for surgery. | 1 | 0.2 |
| Not appropriate. | 43 | 9.9 |
| Palliative patient. | 1 | 0.2 |
| Reason not known. | 2 | 0.5 |
| Requires different device | 11 | 2.5 |
| No reason provided. | 5 | 1.1 |
| Not approached because of other reason | 131 | 30.1 |
| Awaiting transfer of patient. | 1 | 0.2 |
| Do not speak English. | 8 | 1.8 |
| Insufficient time to consent. | 28 | 6.4 |
| No reason provided. | 14 | 3.2 |
| No shunt required. | 3 | 0.7 |
| No time to get consent. | 2 | 0.5 |
| Not appropriate. | 17 | 3.9 |
| Patient discharged. | 4 | 0.9 |
| Patient emigrating. | 1 | 0.2 |
| Patient transfer. | 1 | 0.2 |
| Relatives not available. | 41 | 9.4 |
| Requires different device | 4 | 0.9 |
| Site temporarily closed to recruitment. | 4 | 0.9 |
| Surgery cancelled. | 3 | 0.7 |
| No reason provided. | 14 | 3.2 |
| No longer eligible. | 5 | 1.1 |

Table S 3: Reasons consenting patient not randomised

|  |  |  |
| --- | --- | --- |
| Number of consenting patients not randomised | **N** | 67 |
| **Reason not randomised** | **n** | **n/N%** |
| Trial shunt not available | 7 | 10.4 |
| Trial trained staff not available | 10 | 14.9 |
| Unable to locate randomisation envelope | 1 | 1.5 |
| Other reason | 49 | 73.1 |
| Alternative procedure. | 3 | 4.5 |
| Consultant preference. | 3 | 4.5 |
| Family uncontactable. | 1 | 1.5 |
| No longer eligible. | 16 | 23.9 |
| No reason provided. | 2 | 3.0 |
| Patient emigrating. | 1 | 1.5 |
| Patient missed. | 5 | 7.5 |
| Surgeon forgot envelope. | 1 | 1.5 |
| Surgery cancelled. | 14 | 20.9 |
| Trial closed to recruitment. | 3 | 4.5 |

## 4. Baseline measurements and clinical effectiveness outcomes

Table S 4: Additional baseline patient characteristics and physical examination

| **Baseline Characteristic** | **Standard shunt** | **Antibiotic shunt** | **Silver shunt** | **Total** |
| --- | --- | --- | --- | --- |
| Patients randomised | 536 | 538 | 531 | 1605 |
| Weight (kg) |  |  |  |  |
| N | 523 | 523 | 515 | 1561 |
| Med (LQ - UQ) | 64.0 (8.8 – 82.7) | 63.0 (9.6 – 82.0) | 63.0 (7.3 – 80.0) | 63.1 (8.7 – 81.5) |
| (Min, Max) | (1.1, 161.0) | (0.8, 163.0) | (1.3, 145.0) | (0.8, 163.0) |
| Missing | 13 | 15 | 16 | 44 |
| Heart rate (BPM) |  |  |  |  |
| N | 530 | 532 | 521 | 1583 |
| Med (LQ - UQ) | 84 (72 – 120) | 85 (70 – 116.5) | 84 (70 – 124) | 84 (70 – 121) |
| (Min, Max) | (48, 190) | (44, 185) | (43, 185) | (43, 190) |
| Missing | 6 | 6 | 10 | 22 |
| Overall neurological assessment (GCS) |  |  |  |  |
| N | 499 | 509 | 503 | 1511 |
| Med (LQ - UQ) | 15 (14 – 15) | 15 (14 – 15) | 15 (15 – 15) | 15 (14 – 15) |
| (Min, Max) | (5, 15) | (3, 15) | (4, 15) | (3, 15) |
| Missing | 37 | 29 | 28 | 94 |
| Neurological assessment (GCS) eye score |  |  |  |  |
| N | 507 | 514 | 510 | 1531 |
| Med (LQ - UQ) | 4 (4 – 4) | 4 (4 – 4) | 4 (4 – 4) | 4 (4 – 4 ) |
| (Min, Max) | (1, 4) | (1, 4) | (1, 4) | (1, 4) |
| Missing | 29 | 24 | 21 | 74 |
| Neurological assessment (GCS) verbal score |  |  |  |  |
| N | 501 | 510 | 504 | 1515 |
| Med (LQ - UQ) | 5 (5 – 5) | 5 (5 – 5) | 5 (5 – 5) | 5 (5 – 5) |
| (Min, Max) | (1, 5) | (1, 5) | (0, 5) | (0, 5) |
| Missing | 35 | 28 | 27 | 90 |
| Neurological assessment (GCS) motor score |  |  |  |  |
| N | 506 | 513 | 510 | 1529 |
| Med (LQ - UQ) | 6 (6 – 6) | 6 (6 – 6) | 6 (6 – 6) | 6 (6 – 6) |
| (Min, Max) | (1, 6) | (1, 6) | (1, 6) | (1, 6) |
| Missing | 30 | 25 | 21 | 76 |

**Note:** Med: Median; LQ: Lower Quartile; UQ: Upper Quartile; Min: Minimum; Max: Maximum

Table S 5: Baseline risk assessment

| **Risk of assessment** | **Standard shunt** | **Antibiotic shunt** | **Silver shunt** | **Total** |
| --- | --- | --- | --- | --- |
| Patients randomised | 536 | 538 | 531 | 1605 |
| Previous staph aureus infection (requiring treatment last six months), n(%) |  |  |  |  |
| Yes | 18 (3.4) | 15 (2.8) | 16 (3.0) | 49 (3.1) |
| No | 516 (96.6) | 523 (97.2) | 515 (97.0) | 1554 (96.9) |
| Missing | 2 | 0 | 0 | 2 |
| Active skin/wound infection, n (%) |  |  |  |  |
| Yes | 7 (1.3) | 8 (1.5) | 5 (0.9) | 20 (1.2) |
| No | 527 (98.7) | 530 (98.5) | 525 (99.1) | 1582 (98.8) |
| Missing | 2 | 0 | 1 | 3 |
| MRSA infection in the last six months, n (%) |  |  |  |  |
| Yes | 6 (1.1) | 4 (0.7) | 5 (0.9) | 15 (0.9) |
| No | 529 (98.9) | 533 (99.3) | 524 (99.1) | 1586 (99.1) |
| Missing | 1 | 1 | 2 | 4 |
| Pre-term at birth, n (%) |  |  |  |  |
| Yes | 78 (15.2) | 82 (15.7) | 76 (15.0) | 236 (15.3) |
| No | 435 (84.8) | 440 (84.3) | 429 (85.0) | 1304 (84.7) |
| Missing | 23 | 16 | 26 | 65 |
| Abdominal surgery in the last month, n (%) |  |  |  |  |
| Yes | 3 (0.6) | 3 (0.6) | 8 (1.5) | 14 (0.9) |
| No | 530 (99.4) | 535 (99.4) | 523 (98.5) | 1588 (99.1) |
| Missing | 3 | 0 | 0 | 3 |
| Tracheotomy, n (%) |  |  |  |  |
| Yes | 32 (6.0) | 13 (2.4) | 21 (4.0) | 66 (4.1) |
| No | 502 (94.0) | 525 (97.6) | 510 (96.0) | 1537 (95.9) |
| Missing | 2 | 0 | 0 | 2 |
| Percutaneous endscopitc gastromy, n (%) |  |  |  |  |
| Yes | 14 (2.6) | 7 (1.3) | 15 (2.8) | 36 (2.2) |
| No | 520 (97.4) | 531 (98.7) | 516 (97.2) | 1567 (97.8) |
| Missing | 2 | 0 | 0 | 2 |
| Previous cerebrospinal fluid (CSF) leak within the last month, n (%) |  |  |  |  |
| Yes | 57 (10.7) | 51 (9.5) | 35 (6.6) | 143 (8.9) |
| No | 477 (89.3) | 487 (90.5) | 496 (93.4) | 1460 (91.1) |
| Missing | 2 | 0 | 0 | 2 |
| Previous EVD in last three months, n (%) |  |  |  |  |
| Yes | 105 (19.7) | 95 (17.7) | 90 (16.9) | 290 (18.1) |
| No | 427 (80.3) | 443 (82.3) | 441 (83.1) | 1311 (81.9) |
| Missing | 4 | 0 | 0 | 4 |

#### **Table S 6: Comparison of infection classifications between assessment by central review (primary outcome) and treating surgeon (secondary outcome 1)**

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | Reason for revision (treating surgeon) | |
|  |  | Infection | Not infection |
| Reason for revision (central review) | Infection | 68 (17.1%) | 7 (1.8%) |
| Not infection | 10 (2.5%) | 313 (78.6%) |

#### **Figure S 2: Kaplan Meier curve showing all cause failure of shunt by type**

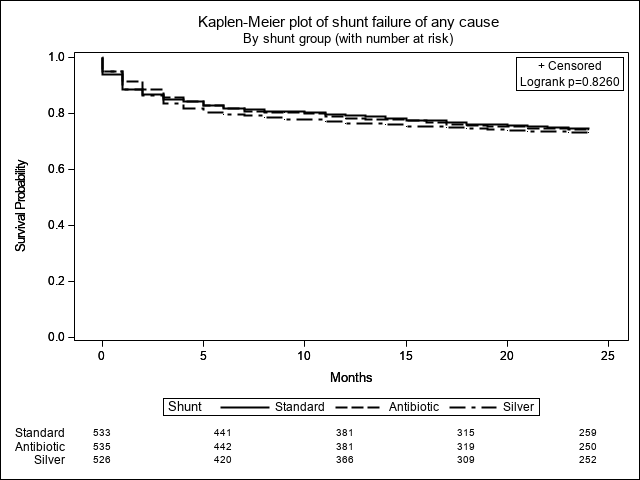


Table S 7: Summary of reasons for shunt failure, classified by treating surgeon, according to catheter type

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Comparators** | **Reason for shunt failure**  Observed (Row %, Col %) | | | |  |  |  | |  |
| **Suspected infection** | **Mechanical shunt failure** | **Functional shunt failure** | **Failure due to patient** | **Total** |  | **Chi-square test results** | | |
|  |  |  |  |  |  |  |  |  | |
| *Antibiotic vs. Standard* | |  |  |  |  |  |  |  | |
| 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 | 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 | 48 | 121 | 84 | 9 | 262 |  | *P*-value | 0.02 | |
|  |  |  |  |  |  |  |  |  | |
| *Silver vs. Standard* | |  |  |  |  |  |  |  | |
| 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 | 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 | 63 | 116 | 77 | 10 | 266 |  | *P*-value | 0.71 | |
|  |  |  |  |  |  |  |  |  | |
|  |  |  |  |  |  |  |  |  | |

Table S 8: Organisms cultured from CSF and peritonealinfections, split by shunt type

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Shunt type** | **Standard shunt** | | **Antibiotic shunt** | | **Silver shunt** | | **Total** | |
| **Number of infections (N)** (1) | 23 (2) | | 6 | | 27 (3) | | 56 | |
|  |  | |  | |  | |  | |
| **Gram stain** |  |  |  |  |  |  |  |  |
| *Broad group* |  |  |  |  |  |  |  |  |
| **Species** (4) | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** |
|  |  |  |  |  |  |  |  |  |
| ***Gram positive*** |  |  |  |  |  |  |  |  |
| *Staphylococcus aureus* |  |  |  |  |  |  |  |  |
| Staphylococcus aureus | 6 | 26.1 | 0 | 0.0 | 11 | 40.7 | 17 | 30.4 |
| *Coagulase negative staphylococci* |  |  |  |  |  |  |  |  |
| Coagulase negative staphylococcus, 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 |
| Staphylococcus species mixed | 1 | 4.3 | 0 | 0.0 | 0 | 0.0 | 1 | 1.8 |
| *Other gram positives* |  |  |  |  |  |  |  |  |
| 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 |
|  |  |  |  |  |  |  |  |  |
| ***Gram negative*** |  |  |  |  |  |  |  |  |
| *Enterobacteriacea* |  |  |  |  |  |  |  |  |
| Enterobacter cloacae | 0 | 0.0 | 1 | 16.7 | 2 | 7.4 | 3 | 5.4 |
| Escherichia coli (E. Coli) | 0 | 0.0 | 1 | 16.7 | 2 | 7.4 | 3 | 5.4 |
| Klebsiella pneumonia | 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* |  |  |  |  |  |  |  |  |
| Pseudomonas aeruginosa | 1 | 4.3 | 1 | 16.7 | 0 | 0.0 | 2 | 3.6 |

1 Organisms cultured reported for infections centrally classified as *Definite – Culture positive* and *Probable – Culture uncertain* only, see Table 3.

2 22 *Definite – culture positive* and one *Probable – Culture uncertain* infections.

3 25 *Definite – culture positive* and two *Probable – Culture uncertain* infections.

4 Where more than one organism was grown from one infection episode, except for mixed coagulase negative staphylococci, each organism has been listed.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Standard shunt** | | **Antibiotic shunt** | | **Silver shunt** | | **Total** | |
|  | **N** | **%** | **N** | **%** | **N** | **%** | **N** | **%** |
| **Summary of revisions** |  |  |  |  |  |  |  |  |
| First clean revision (1) | 98 | . | 120 | . | 105 | . | 323 | . |
| No shunt removal/revision | 61 | 62.2 | 69 | 57.5 | 65 | 61.9 | 195 | 60.4 |
| shunt removal/revision (for any cause) | 37 | 37.8 | 51 | 42.5 | 40 | 38.1 | 128 | 39.6 |
|  |  |  |  |  |  |  |  |  |
| **Reason for revision as classified by central review** | | | | |  |  |  |  |
| ***Reason for revision*** |  |  |  |  |  |  |  |  |
| 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 |
|  |  |  |  |  |  |  |  |  |
| ***Type of infection*** | | | |  |  |  |  |  |
| *shunt 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 (2) | 0 | 0.0 | 1 | 2.0 | 0 | 0.0 | 1 | 0.8 |
| *shunt deep incisional infection* |  |  |  |  |  |  |  |  |
| shunt deep incisional infection | 0 | 0.0 | 0 | 0.0 | 1 | 2.5 | 1 | 0.8 |
| 1 Randomised participants that had de novo shunt removed for reason other than infection, as assessed by central review, eligible for outcome set (n=323), see Table 3.  2 Where the committee is unable to classify an infection, an infection is identified as reported on the case report forms. There was four cases where the committee were unable to classify and one of these were clinically classified as an infection. | | | | | | | | |

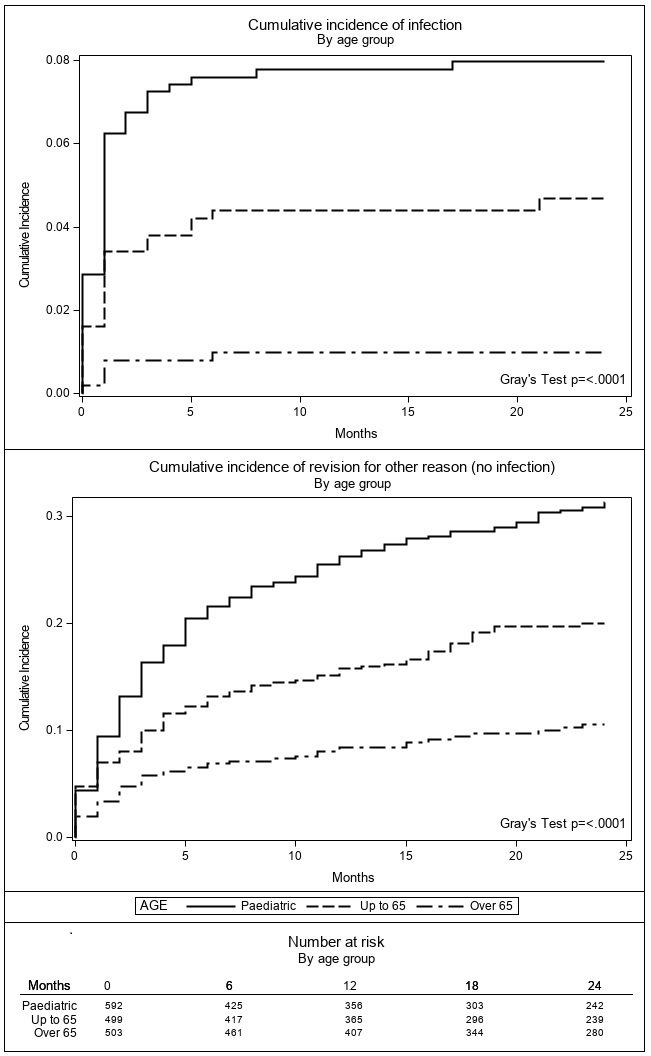
Table S 9: Summary of revisions following clean insertion (no infection of de novo shunt), and reasons for this revision assessed by central review

Table S 10: Summary of revisions, and reasons for revision as classified central review, of first shunt according to age group

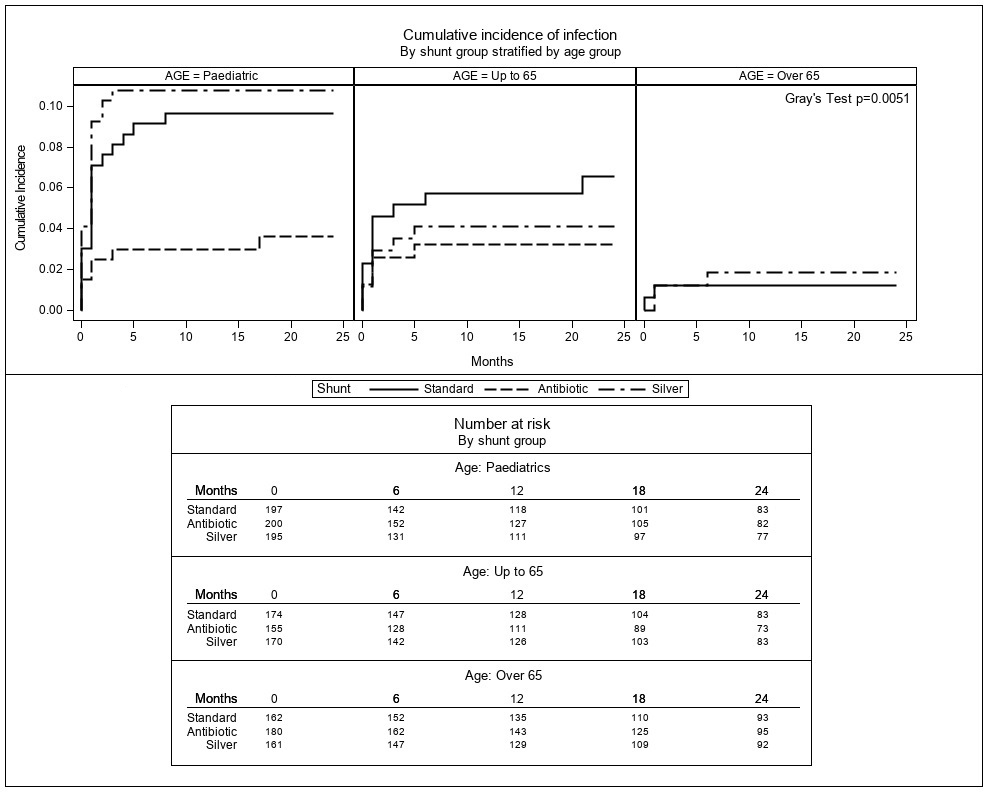
|  | Age group | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Paediatric | | Up to 65 years | | Over 65 years | | Total | |
|  | N | % | N | % | N | % | N | % |
| Eligible for primary outcome (1) | 592 | . | 499 | . | 503 | . | 1594 | . |
| No shunt removal/revision | 367 | 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 |

1 Randomised participants that did not receive a shunt (n=4) and had infection at time of insertion (n=7) were excluded from the primary outcome set, see Figure 2.

Figure S 3 Cumulative incidence plots of infection (top) and competing risk (bottom) by age group



#### **Figure S 4: Cumulative incidence of infection by shunt type stratified by age group**



#### **Table S 11: Adverse events related to the shunt and summary of most common** types

|  | **Standard shunt** | | | **Antibiotic shunt** | | | **Silver shunt** | | | **Other shunt 1** | | | **Total** | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | N=531 | | | N=545 | | | N=525 | | | N=136 | | | N=1601 | | |
|  | **Events** | **Patients** | | **Events** | **Patients** | | **Events** | **Patients** | | **Events** | **Patients** | | **Events** | **Patients** | |
| **Adverse event** 2 | N | N | N/N% | N | N | N/N% | N | N | N/N% | N | N | N/N% | N | N | N/N% |
| *Total* | *201* | *135* | *25.4* | *210* | *127* | *23.3* | *191* | *134* | *36.4* | *52* | *18* | *13.2* | *654* | *413* | *25.8* |
| Ventricular catheter obstruction | 21 | 20 | 3.8 | 39 | 31 | 5.7 | 29 | 26 | 5.0 | 7 | 7 | 5.1 | 96 | 79 | 4.9 |
| Shunt infection(3) | 40 | 39 | 7.3 | 17 | 16 | 2.9 | 24 | 24 | 4.6 | 9 | 9 | 6.6 | 90 | 88 | 5.5 |
| Shunt valve obstruction | 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 |
| Cerebrospinal fluid (CSF) leak | 16 | 16 | 3.0 | 17 | 14 | 2.6 | 16 | 12 | 2.3 | 4 | 3 | 2.2 | 53 | 45 | 2.8 |
| Wound infection(3,4) | 13 | 10 | 1.9 | 11 | 11 | 2.0 | 16 | 14 | 2.7 | 3 | 2 | 1.5 | 43 | 37 | 2.3 |
| Distal 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 op, 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 |

1 Patients who experience an event after shunt revision, where shunt was not replaced like for like, are reported as part of ‘Other shunt’ group.

2 Adverse event are presented for types when experienced by greater than 1% of patients in the safety set. All presented adverse events were expected.

3 Shunt and wound infections include all revisions, infections as an outcome in the efficacy analyses are a subset of these.

4 Wound infections as adverse events include shunt superficial incisional infections (without cerebrospinal fluid (CSF) or tubing involvement) and deep incisional infection, only shunt deep incisional infections are considered infections as an outcome in the efficacy analyses and therefore are a subset of these.

## 5. Economic analysis

Methods

The economic analysis adopted the perspective of the National Health Service (NHS) and Personal Social Service providers in the United Kingdom (UK). The primary analysis was a cost-effectiveness analysis, based on the incremental cost per first shunt failure averted for impregnated and standard shunts due to any cause. This differed from the primary clinical outcome because of the potential consequences (e.g. related to surgery) on patients’ health, of clean shunt failures. However, given that infected shunts are more impactful on health outcomes, the incremental cost per shunt infection averted was included as an important secondary economic endpoint, together with a cost utility analysis which estimated the incremental cost per Quality-Adjusted Life Year (QALY) gained in a restricted sample of trial participants.

*Resource use and costs*

Costs were estimated by measuring the healthcare resource use associated with each shunt during the study period. These included: (i) hospital inpatient stays and procedures; (ii) hospital outpatient and Accident and Emergency (A&E) visits; (iii) concomitant medicines; and (iv) contact with other healthcare professionals, including General Practitioners (GPs) and school nurses.

This was achieved by considering data collected as part of the trial and as part of routine care: (i) Patient Level Information and Costing System (PLICS) data contains details of admission and discharges, Healthcare Resource Group (HRG) codes relating to the type of care patients received, and the point of delivery (inpatient, outpatient, A&E). PLICS data were requested for all patients from 3-months prior to randomisation to the final follow-up of the last patient (April 2018). (ii) Resource use questionnaires completed by trial participants, their guardian or their parents were designed to collect information on trial participants’ use of primary care services, personal social services and non-scheduled clinic attendances.1,2 Questionnaires were administered early post-operatively, and then posted to patients by research nurses every 12 weeks until the end of trial. Patients completed these and returned them to the study sites. (iii) Dedicated sections within the case report form were used to record trial participants’ use of concomitant medicines 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. (iv) The cost of the initial shunt catheter; 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 2016-17. Adjustments were made for inflation using the pay cost index and the health service cost index if cost were from an earlier period.3

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

Health resource groups (HRGs) were used as the main currency of the economic analysis4 for inpatient stays (Table S 12) and outpatient contacts (Table S 13) with cost codes allocated based on the latest available National Schedule of Reference Costs5 or, when not available, based on the National Tariff.6 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 reason for admission and condition, extracted from the patient resource use questionnaires.

Unit costs of all items of primary health care resource use and outpatient contacts were taken from the Compendium of Unit Costs of Health and Social Care3 (Table S 14). 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 Formulary7 and the Prescription Costs Analysis for NHS England.8 The cost of each medicine was calculated by multiplying the unit price by the daily quantity of prescribed medication and by the number of days of treatment.

Table S 12: Unit costs of elective and day cases inpatient hospital attendances for the most frequent HRG codes (top 15 out of 281)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **HRG code** | **HRG name** | **Attendance** | **Unit cost** | **Reference** |
| AA13A | Intermediate Intracranial Procedures Except Trauma with Cerebral Degenerations or Miscellaneous Disorders of Nervous System with CC | Elective/Day case | £4888 | 6 |
| PA42Z | Brain Tumours with length of stay 1 day or more | Elective/Day case | £3052 | 6 |
| AA19A | Minor Intracranial Procedures Except Trauma with Cerebral Degenerations or Miscellaneous Disorders of Nervous System, with CC | Elective/Day case | £2041 | 6 |
| AA52G | Very Major Intracranial Procedures, 18 years and under, with CC Score 0-3 | Elective/Day case | £6210 | 5 |
| PA44Z | Neoplasm Diagnoses with length of stay 0 days | Elective/Day case | £533 | 6 |
| AA25A | Cerebral Degenerations or Miscellaneous Disorders of Nervous System, with CC | Elective/Day case | £1269 | 6 |
| AA52C | Very Major Intracranial Procedures, 18 years and under, with CC Score 0-3 | Elective/Day case | £6210 | 5 |
| PM44Z | Paediatric Neoplasm Diagnoses with length of stay 0 days | Elective/Day case | 1373 | 5 |
| AA13B | Intermediate Intracranial Procedures Except Trauma with Cerebral Degenerations or Miscellaneous Disorders of Nervous System without CC | Elective/Day case | £4409 | 6 |
| PA01A | Nervous System Disorders with CC | Elective/Day case | £1056 | 6 |
| AA21A | Minor Intracranial Procedures Except Trauma with Other Diagnoses with CC | Elective/Day case | £1489 | 6 |
| AA52D | Very Major Intracranial Procedures, 19 years and over, with CC Score 0-3 | Elective/Day case | 7907 | 5 |
| PR01C | Paediatric Nervous System Disorders with CC Score 2-4 | Elective/Day case | £2417 | 5 |
| PA28A | Feeding Difficulties and Vomiting without CC | Elective/Day case | £2,190 | 6 |
| AA54A | Intermediate Intracranial Procedures, 19 years and over, with CC Score 4+ | Elective/Day case | £5,787 | 5 |

CC – complication or comorbidity

Table S 13: Unit costs of hospital outpatient attendances ordered by the most frequent HRG codes (top 15 out of 122 HRG and 162 treatment function codes).

|  |  |  |  |
| --- | --- | --- | --- |
| **HRG** | **Treatment function code** | **HRG name** | **Unit cost** |
| WF01A | 150 | Neurosurgery | £188 |
| WF01A | 218 | Paediatric Neurosurgery | £179 |
| WF01A | 300 | General Medicine | £164 |
| WF01A | 400 | Neurology | £161 |
| WF01A | 216 | Paediatric Ophthalmology | £115 |
| WF01A | 420 | Paediatrics | £180 |
| WF01A | 252 | Paediatric Endocrinology | £229 |
| WF01A | 260 | Paediatric Medical Oncology | £243 |
| WF01A | 218 | Paediatric Neurosurgery | £179 |
| WF01A | 251 | Paediatric Gastroenterology | £195 |
| WF01A | 100 | General Surgery | £123 |
| WF01A | 258 | Paediatric Respiratory Medicine | £204 |
| WF01A | 290 | Community Paediatrics | £265 |
| WF01B | 150 | Neurosurgery | £236 |
| WF01B | 400 | Neurology | £217 |
| WF01B | 290 | Community Paediatrics | £376 |
| WF01B | 216 | Paediatric Ophthalmology | £119 |
| WF01B | 320 | Cardiology | £156 |
| WF01B | 252 | Paediatric Endocrinology | £330 |
| WF01B | 218 | Paediatric Neurosurgery | £255 |
| WF01B | 303 | Clinical Haematology | £223 |
| WF01B | 214 | Paediatric Trauma and Orthopaedics | £136 |
| WF01B | 314 | Rehabilitation Service | £248 |
| WF01B | 130 | Ophthalmology | £110 |
| WF01B | 171 | Paediatric Surgery | £185 |
| WF01B | 180 | Accident & Emergency | £157 |
| WF01B | 713 | Psychotherapy | £158 |
| WF01B | 191 | Pain Management | £177 |
| WF02A | 216 | Paediatric Ophthalmology | £102 |
| WF02A | 214 | Paediatric Trauma and Orthopaedics | £142 |
| WF02A | 260 | Paediatric Medical Oncology | £258 |
| WF02A | 421 | Paediatric Neurology | £375 |
| WF02A | 218 | Paediatric Neurosurgery | £170 |
| WF02A | 258 | Paediatric Respiratory Medicine | £176 |
| WF02A | 251 | Paediatric Gastroenterology | £251 |
| WF02A | 256 | Paediatric Infectious Diseases | £269 |
| WF02A | 252 | Paediatric Endocrinology | £230 |
| WF02A | 253 | Paediatric Clinical Haematology | £328 |
| WF02A | 219 | Paediatric Plastic Surgery | £145 |

Unit costs from reference 5

Table S 14: Unit costs of consultations with healthcare professionals

|  |  |  |
| --- | --- | --- |
| **Profession** | **Unit cost** | **Reference** |
| GP surgery visit (per 9.22 minutes consultation) | £38.00 | 3 |
| Nurse at surgery (per 9 minutes consultation | £5.40 | 3 |
| Telephone triage - GP led (per call) | £14.75 | 3 |
| Telephone triage - nurse led (per call) | £7.90 | 3 |
| Prescription | £29.20 | 3 |
| Paediatric consult (per consultation) | £196.00 | 3 |
| Physiotherapy (per consultation) | £86.00 | 3 |
| Continence nurse (per consultation) | £80.00 | 5 |
| Specialist nurse adult face to face (per consultation) | £77.00 | 5 |
| District Nurse | £38.00 | 5 |
| Doctor home visit (per visit) | £87.46 | 3 |
| Consultant psychiatric (per consultation) | £108.00 | 3 |
| Health visitor (per consultation) | £53.00 | 5 |
| School nurse (per consultation) | £54.00 | 5 |
| Occupational therapist (per consultation) | £79.00 | 5 |
| Speech therapist adult (per consultation) | £88.00 | 5 |
| Dietician (per consultation) | £81.00 | 5 |
| Speech therapist child (per consultation) | £94.00 | 5 |
| Clinical Psychology (per consultation) | £144.70 | 5 |
| Care work and social care (per intervention) | £54.00 | 3 |
| Social worker (per intervention) | £54.00 | 3 |
| Community nurse (per consultation) | £89.00 | 5 |
| Shunt Nurse Specialist (per consultation) | £77.00 | 5 |

*Health outcomes*

The primary health outcome for the economic analysis was first shunt failure (due to any cause) averted. A sensitivity analysis considered first shunt 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-dimension (EQ-5D) questionnaires. The EQ-5D-3L-Proxy (parent or guardian) was used for participants aged 5 to under 18 years old; and for participants aged over 18 years old who lacked capacity to consent for themselves. The EQ-5D-3L-Y (youth) was administered to participants aged 8 to under 18 years old. Adults were asked to complete the EQ-5D-3L questionnaire, and all participants aged 8 and over were administered the EQ visual analogue scale (EQ-VAS).

The EQ-5D-3L descriptive system includes five dimensions (mobility, self-care, usual activities, pain and anxiety) with each dimension having three levels of morbidity (no problems, some problems and extreme problems), which are scored 1, 2 and 3 respectively. UK tariff scores9 for EQ-5D-3L were applied to responses to the EQ-5D-3L, EQ-5D-3L-Y and EQ-5D-3L-Proxy, as no separate scoring systems are yet available for the youth and proxy versions.

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

Additionally, the child version of the Hydrocephalus Outcome Questionnaire (HOQ) was administered to participants aged 8 to 18 years old, and the parent proxy version for participants aged 5 to under 8 years old. The HOQ is a Canadian 51-item outcome questionnaire designed specifically for use in paediatric hydrocephalus.10,11 Responses to each item are given a score from 0 (worse health status) to 4 (better health status). Set combination of items make up three health dimensions: Physical, socio-emotional 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) and 1 (best health state).

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

*Analyses*

Analyses included all randomised participants, consistent with the ‘intention to treat’ principle. All statistical tests were two-sided and the statistical significance level was set at 2.5% and confidence intervals calculated at 97.5% to adjust for multiplicity for the observed and imputed data.

Data were examined for missingness. The appropriate method for dealing with missing cost data was dependent on the share of missing data and likely mechanism of missingness.12 Costs relating to hospitalisations were primarily sourced from PLICS data. Where PLICS data were not available or missing, the use of hospital services was based on entries in case report forms, or otherwise from participants’ resource use questionnaires.13 In the base-case analysis, any remaining missing data were multiply imputed using the method of chained equations.14 The number of imputed datasets 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 datasets were generated using predictive mean matching, from a set of imputation models constructed from all potential prognostic factors: sex, age (paediatrics from 0 up to 16 years, adults from 16 up to 65 years of age, and adults ≥65 years of age), site, time spent in the trial, whether a first treatment failure had occurred, and by 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 National Institute for Health and Care Excellence.15

*Cost analysis*

Hospitalisations were costed from baseline to 24 months. Adjustments were made to apportion any costs of hospital stays which crossed baseline or which continued after the 24 month time horizon. Similarly, adjustments were made to courses of drug treatment which spanned the period preceding baseline or beyond the 24 month time horizon, to apportion costs to only those administered during the 0-24 month time horizon.

Participants’ use of health care and personal social services between randomised groups were described and tabulated, reporting mean resource use items for each intervention and differences between the intervention groups. The 97.5% confidence intervals 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 shunt failure. Due to the large sample, the near-normality of sample means was assumed and Ordinary Least Squares regression applied in the base-case.16 The regression was specified with total (discounted), per-patient costs as the dependent variable, and the stratifying variables, site (discrete) and age (3 categories), and time in study (continuous, in days), and treatment failure, as predictors:

Cost = β0 + β1rand\_group + β2treat\_fail + β3age + β4time\_in\_trial + β5site + e

Similarly, mean outcome by intervention group was also by Ordinary Least Squares regression, specified with treatment failure (discounted) as the dependent variable, total cost (discounted), site (discreet), age (3 categories), time in study (continuous) and intervention group as predictors:

Effect = β0 + β1rand\_group + β2total­\_costs + β3age + β4time\_in\_trial + β5site + e

*Cost effectiveness analysis*

In the base-case cost-effectiveness analysis, the outcome of interest was the incremental cost per (first) shunt 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) calculated for the remaining 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: (i) applying different discount rates (0%, 1.5% and 6% per annum for both costs and outcomes); (ii) using observed data for costs (no multiple imputation); and (iii) using a different analytic approach for analysing costs (generalised linear models (GLM), 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 Akaike information criterion (AIC) and Bayesian information criterion (BIC) and the Modified Park test to determine the distribution family.17

Additionally, a stratified cost-effectiveness analysis was undertaken for the three age categories of paediatrics, adults up to 65, and ≥65 years of age.

*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: (i) confirmed infection; (ii) mechanical cause, (iii) functional reason and; (iv) patient factors. A cost-utility analysis was performed to estimate the incremental cost per QALY gained. This latter analysis was restricted to participants aged ≥5 years, as no utility data were collected for children under 5 years of age. Uncertainty in the incremental cost utility ratio was considered using non-parametric bootstrap analysis, using 1,000 replicates, and depicted in cost-effectiveness acceptability curves, which present the probability of each shunt being cost-effective for given ceiling thresholds of costs per QALY.18 The cost utility analysis considered the reference threshold range of between £20,000 and £30,000 per QALY.15

All analyses were conducted using Stata version 13 (StataCorp LLC, Texas, USA) and reported according to the Consolidated Health Economic Evaluation Reporting Standards.19

Results

*Data completeness*

The level of missing hospital cost data, resource use diaries and concomitant medication was balanced across the three intervention groups (Table S 15).

PLICS data were made available by 10 out of the 19 neurosurgical units. Some level of missingness was also noted within the hospital data supplied. PLICS data were reported for 199/536 participants allocated to standard shunts, 208/538 participants allocated to antibiotic shunts, and 210/531 participants allocated to silver. Resource uses questionnaires were completed by 423 (27%) participants: 145 participants allocated to standard, 146 allocated to antibiotic, and 132 allocated to silver shunts. The costs of concomitant medications were available for 88% of trial participants; 466, 463 and 467 allocated to standard, antibiotic and silver shunts, respectively.

For the multiple imputation, and based on the variable with the highest fraction of missing information value (FMI 0.580), 50 datasets were imputed.20

*Resource use and cost analysis*

Table S 16 presents observed, mean disaggregated healthcare resource use from randomisation and up to 24 months, by intervention group. There were no discernible differences between intervention groups with respect to patients’ use of primary or secondary healthcare.

Based on the incomplete, observed data, the mean, total 2-year costs were £5,124, £6,012 and £5,520 in the antibiotic-impregnated, silver-impregnated and standard shunt groups, respectively (Table S 17). The majority of costs related to hospital inpatient procedures, followed by outpatient clinic visits and contacts with healthcare professionals in primary care. With the exception of GP costs, there were no significant differences in costs between either of the impregnated and standard shunts.

Table S 15: Summary of data completeness by type, and intervention group.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | | **Participants aged ≥5 years (N=1098)** | | | **All trial participants (N=1594)** | | |
| **Group** | **Variable** | **Complete** | | **Incomplete (imputed)** | **Total** | **Complete** | **Incomplete (imputed)** | **Total** |
| Standard | Utility at baseline | 240 | | 129 | 369 |  |  |  |
| Utility early post-operative | 233 | | 136 | 369 |  |  |  |
| Utility at 12-weeks | 190 | | 179 | 369 |  |  |  |
| Utility at End of Study | 189 | | 180 | 369 |  |  |  |
| 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 | Utility at baseline | 244 | | 125 | 369 |  |  |  |
| Utility early post-operative | 231 | | 138 | 369 |  |  |  |
| Utility at 12-weeks | 174 | | 195 | 369 |  |  |  |
| Utility at End of Study | 179 | | 190 | 369 |  |  |  |
| 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 | Utility at baseline | 224 | | 136 | 360 |  |  |  |
| Utility early post-operative | 220 | | 140 | 360 |  |  |  |
| Utility at 12-weeks | 177 | | 183 | 360 |  |  |  |
| Utility at End of Study | 191 | | 169 | 360 |  |  |  |
| 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 |  |  |  |
| Utility early post-operative | 684 | | 414 | 1098 |  |  |  |
| Utility at 12-weeks | 541 | | 557 | 1098 |  |  |  |
| Utility at End of Study | 559 | | 539 | 1098 |  |  |  |
| 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 |

Table S 16: Disaggregated healthcare resource from randomisation and up to 24 months, by intervention group. Listed are the most frequent items of resource use, including the top 16 HRGs (out of 463). Values are mean counts (range) [number of patients].

|  |  |  |  |
| --- | --- | --- | --- |
| **Item of resource use** | **Standard shunts** | **Antibiotic-impregnated shunts** | **Silver-impregnated shunts** |
| 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] |
| IP HRG - AA13A | 1.0 (0-1) [27] | 1.0 (0-1) [36] | 1.0 (0-2) [439] |
| IP HRG - AA19A | 1.4 (0-3) [7] | 1.5 (0-4) [8] | 1.5 (0-3) [10] |
| IP HRG - AA25A | 0.6 (0-3) [12] | 0.72 (0-3) [11] | 0.85 (0-2) [7] |
| IP HRG - AA52C | 1 (0-1) [12] | 1 (0-1) [9] | 0.83 (0-2) [12] |
| IP HRG - PA44Z | 2.3 (0-4) [3] | 3.0 (0-5) [4] | 4.0 (0-7) [3] |
| IP HRG - PA42Z | 6.7 (0-19) [4] | 6.7 (0-15) [4] | 3.0 (0-6) [4] |
| IP HRG - AA52G | 1.5 (0-3) [6] | 1.0 (0-1) [8] | 1.2 (0-3) [10] |
| IP HRG - PM44Z | 0.4 (0-4) [10] | 1 (0-1) [5] | 0.46 (0-6) [13] |
| OP HRG - WF01A | 5.7 (0-36) [63] | 5.7 (0-72) [67] | 5.5 (0-28) [60] |
| OP HRG - WF01B | 2.4 (0-16) [38] | 2.0 (0-9) [38] | 1.7 (0-5) [38] |
| OP HRG - VB05Z | 0.44 (0-5) [18] | 0.28 (0-11) [25] | 0.25 (0-22) [35] |
| OP HRG - VB02Z | 1.3 (0-3) [7] | 1.8 (0-4) [4] | 2.0 (0-3) [3] |
| OP HRG - VB03Z | 1.0 (0-1) [2] | 1.5 (0-4) [6] | 1.7 (0-2) [3] |
| OP HRG - VB09Z | 6.0 (0-6) [1] | 1.0 (0-1) [3] | 1.0 (0-1) [3] |
| OP HRG - WF01C | 1 (0-1) [5] | 0.77 (0-2) [9] | 0.62 (0-4) [8] |
| OP HRG – BZ | 1 (0-1) [8] | 0.5 (0-4) [6] | 1 (0-1) [1] |

OP outpatient; IP inpatient; GP general practitioner

Table S 17: Disaggregated and total costs 0 to up to 24 month from randomisation, by intervention group. Values are means (£) (97.5% CI) [number of participants].

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Costs relating to** | **Standard** | **Antibiotic-impregnated** | **Silver-impregnated** | **Difference**  **antibiotic-standard** | **Difference**  **silver-standard** |
| Inpatient visits | 14302 (10850, 20074) [120] | 11738 (9717, 14306)  [135] | 14481 (11802, 17573)  [163] | -2564 (-8700, 1794) | 179 (-6330, 4987) |
| Outpatient visits | 2328 (1533, 3572) [161] | 2117 (1488, 2958)  [170] | 2220 (1522, 3607)  [177] | -211 (-1563, 995) | -109 (-1553, 1245) |
| GP visits | 188 (108, 374)  [91] | 91 (71, 121)  [82] | 91 (66, 129)  [74] | -97 (-282, -10) | -97 (-282, -8) |
| Nurse visits | 133 (58, 309)  [54] | 97 (50, 169)  [51] | 60 (29,119)  [44] | -36 (-216, 66) | -73 (-247, 22) |
| Health Visitor | 303 (75, 821)  [18] | 131 (75, 201)  [19] | 272 (157, 378)  [15] | -172 (-685, 66) | -31 (-493, 228) |
| Physiotherapy | 500 (242, 1082)  [31] | 190 (122, 284)  [25] | 633 (344, 1029),  [18] | -310 (-889, -34) | 133 (-501, 605) |
| Occupational therapist | 81 (18, 183)  [20] | 139 (60, 242)  [22] | 69 (15, 175)  [15] | 58 (-68, 177) | -12 (-128, 105) |
| Other healthcare professionals | 245 (185, 356)  [74] | 286 (178, 558)  [66] | 212 (169, 267)  [66] | 40 (-118, 311) | -34 (-151, 50) |
| Concomitant medications | 211 (134, 356)  [469] | 127 (81, 191)  [466] | 271 (137, 512)  [470] | -84 (-234, 13) | 60 (-119, 306) |
| Total cost\* | 5520 (4239, 7554)  [532] | 5124 (4174, 6285)  [535] | 6012 (4874, 7308)  [484] | -394 (-2544, 1372) | 492 (-1688, 2398) |

\*Calculated as the mean cost for observed data per patient

The adjusted, base-case analysis yielded a total cost of £18,707 (97.5% CI £13,888, £26,966) in the standard group, £14,192 (97.5% CI £12,450, £17,786) in the antibiotic-impregnated group, and £17,385 (97.5% CI £14,649, £22,355) in the silver-impregnated group. Based on incremental analysis, the difference in 2-year costs between the silver-impregnated and standard shunts was -£1,322 (97.5% CI -£9,295, £5,592); and between antibiotic- and silver-impregnated shunts of -£3,192 (97.5% CI -£8,382, £1,227) (Table S 18).

Overall, the cost of shunt failures was £8,604 (97.5% CI £4,696, £12,511) due to any cause; £10,844 (97.5% CI £4,267, £17,436) due to confirmed infection; £5,479 (97.5% CI £882, £10,076) due to mechanical failure; £5,149 (97.5% CI -£542, £10,840) due to functional failure; and £7,028 (97.5% CI -£5,803, £19,859) due to patient influences.

Table S 18. Adjusted total (24 month, discounted) costs: results of the OLS regression based on imputed data

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Coefficient (£)** | ***p*-value** | **97.5% CI (£)** |
| Intercept | 28796.83 | 0.000 | 10845.34, 46748.32 |
| Antibiotic-impregnated shunts | -4514.66 | 0.030 | -9169.53, 140.19 |
| Silver-impregnated shunts | -1322.33 | 0.557 | -6456.95, 3812.27 |
| Treatment failure | 8603.91 | 0.000 | 4696.00, 12511.82 |
| Age - up to 65 | -3670.40 | 0.113 | -8886.24, 1545.44 |
| Age - ≥65 | -2872.09 | 0.227 | -8233.51, 2489.33 |
| Time in trial (days) | -7.09 | 0.129 | -17.61, 3.43 |
| Centre A | 33.59 | 0.997 | -23137.15, 23204.33 |
| Centre B | -901.01 | 0.906 | -18118.44, 16316.41 |
| Centre C | 732.23 | 0.922 | -16116.42, 17580.88 |
| Centre D | -8262.26 | 0.289 | -25868.11, 9343.59 |
| Centre E | -1615.54 | 0.856 | -21698.98, 18467.90 |
| Centre F | -8657.07 | 0.282 | -26785.97, 9471.82 |
| Centre G | -11152.65 | 0.147 | -28493.21, 6187.91 |
| Centre H | -5695.04 | 0.477 | -23805.53, 12415.46 |
| Centre I | 638.42 | 0.943 | -19533.70, 20810.55 |
| Centre J | -1701.73 | 0.825 | -19070.15, 15666.69 |
| Centre K | -4921.65 | 0.543 | -23203.33, 13360.04 |
| Centre L | -4898.48 | 0.561 | -23919.14, 14122.18 |
| Centre M | -6878.41 | 0.374 | -24346.42, 10589.60 |
| Centre N | -7992.50 | 0.295 | -25226.53, 9241.53 |
| Centre O | 1158.21 | 0.940 | -33654.62, 35971.04 |
| Centre P | -2290.29 | 0.846 | -28875.46, 24294.88 |
| Centre Q | -5408.04 | 0.485 | -22913.22, 12097.13 |
| Centre R | -7347.52 | 0.336 | -24590.30, 9895.26 |
| Centre S | -1171.56 | 0.878 | -18447.40, 16104.27 |
| Centre T | -5911.51 | 0.460 | -23978.95, 12155.93 |

*Economic health outcomes*

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

The distribution of participants (or their parents’ or guardians’) responses to the EQ-5D questionnaires are presented in Table S 19. There was a low return rate of the EQ-5D questionnaire, with combined (EQ-5D-3L-Y, EQ-5D-3L-Proxy, and EQ-5D-3L) data available for only about half of participants. Their responses suggest a general improvement across all dimensions from baseline to the end of the study, with no clear differences between intervention groups for any given dimension. Similarly, the response rates of participants, their parents or guardians to the EQ-VAS, which are presented in Table S 20, were also low, but indicate a general trend for improvement from baseline to the end of study.

The relationship between mean utility scores, by failure type, and across each study time point is presented in Table S 21. There is no consistent direction of effect in the data. Utility may be somewhat reduced in patients who experience shunt failures, than those who do not; however, this is inconclusive (and may indeed counter-intuitive e.g. in relation to failures due to patient-factors).

Table S 19: 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 are reported by intervention group.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Intervention group** | **Level 1** | **Level 2** | **Level 3** | **Total** |
| **Mobility** | | | | | |
| Baseline | Standard | 109 | 37 | 8 | 154 |
| Antibiotic | 103 | 46 | 10 | 159 |
| Silver | 104 | 44 | 5 | 153 |
| Early post-operative | Standard | 56 | 138 | 52 | 246 |
| Antibiotic | 62 | 141 | 38 | 241 |
| Silver | 59 | 130 | 39 | 228 |
| 3-months | Standard | 75 | 111 | 12 | 198 |
| Antibiotic | 75 | 99 | 14 | 188 |
| Silver | 11 | 91 | 11 | 113 |
| End of study | Standard | 86 | 102 | 10 | 198 |
| Antibiotic | 86 | 95 | 10 | 191 |
| Silver | 82 | 107 | 11 | 200 |
| **Self-care** | | | | | |
| Baseline | Standard | 120 | 80 | 49 | 249 |
| Antibiotic | 116 | 88 | 46 | 250 |
| Silver | 107 | 81 | 41 | 229 |
| Early post-operative | Standard | 99 | 94 | 56 | 249 |
| Antibiotic | 98 | 95 | 46 | 239 |
| Silver | 90 | 92 | 45 | 227 |
| 3-months | Standard | 38 | 25 | 15 | 78 |
| Antibiotic | 35 | 24 | 15 | 74 |
| Silver | 34 | 28 | 10 | 72 |
| End of study | Standard | 128 | 57 | 12 | 197 |
| Antibiotic | 120 | 55 | 15 | 190 |
| Silver | 135 | 52 | 13 | 200 |
| **Usual activities** | | | | | |
| Baseline | Standard | 46 | 126 | 77 | 249 |
| Antibiotic | 43 | 118 | 90 | 251 |
| Silver | 46 | 114 | 68 | 228 |
| Early post-operative | Standard | 44 | 128 | 73 | 245 |
| Antibiotic | 48 | 110 | 76 | 234 |
| Silver | 45 | 115 | 66 | 226 |
| 3-months | Standard | 65 | 100 | 33 | 198 |
| Antibiotic | 61 | 98 | 25 | 184 |
| Silver | 77 | 81 | 26 | 184 |
| End of study | Standard | 87 | 85 | 26 | 198 |
| Antibiotic | 81 | 76 | 30 | 187 |
| Silver | 89 | 76 | 35 | 200 |
| **Pain or discomfort** | | | | | |
| Baseline | Standard | 95 | 123 | 28 | 246 |
| Antibiotic | 127 | 98 | 22 | 247 |
| Silver | 104 | 98 | 24 | 226 |
| Early post-operative | Standard | 86 | 136 | 22 | 244 |
| Antibiotic | 88 | 143 | 11 | 242 |
| Silver | 73 | 136 | 19 | 228 |
| 3-months | Standard | 105 | 77 | 12 | 194 |
| Antibiotic | 112 | 60 | 13 | 185 |
| Silver | 98 | 79 | 7 | 184 |
| End of study | Standard | 130 | 55 | 11 | 196 |
| Antibiotic | 116 | 65 | 9 | 190 |
| Silver | 129 | 62 | 8 | 199 |
| **Anxiety or depression** | | | | | |
| Baseline | Standard | 112 | 110 | 23 | 245 |
| Antibiotic | 107 | 117 | 24 | 248 |
| Silver | 122 | 79 | 25 | 226 |
| Early post-operative | Standard | 144 | 85 | 14 | 243 |
| Antibiotic | 150 | 78 | 13 | 241 |
| Silver | 150 | 62 | 15 | 227 |
| 3-months | Standard | 124 | 58 | 12 | 194 |
| Antibiotic | 109 | 64 | 8 | 181 |
| Silver | 125 | 50 | 8 | 183 |
| End of study | Standard | 126 | 52 | 15 | 193 |
| Antibiotic | 121 | 55 | 10 | 186 |
| Silver | 128 | 60 | 6 | 194 |

Table S 20: Responses to the EQ-VAS thermometer, by version and intervention group.

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

Table S 21: Mean utility scores by failure type, across each study time point. Values in parentheses are the number of reported observations.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Baseline** | **Early post operation** | **12 weeks** | **End of study** |
| **No failure** | 0.451 (575) | 0.479 (550) | 0.641 (430) | 0.677 (466) |
| **Failure due to patient** | 0.637 (5) | 0.550 (6) | 0.794 (4) | 0.469 (4) |
| **Mechanical failure** | 0.337 (65) | 0.396 (68) | 0.594 (61) | 0.640 (50) |
| **Functional failure** | 0.615 (41) | 0.386 (40) | 0.574 (40) | 0.588 (28) |
| **Failure due to infection** | 0.380 (23) | 0.332 (22) | 0.562 (7) | 0.678 (11) |
| **All cause failure** | 0.438 (133) | 0.393 (134) | 0.596 (111) | 0.616 (93) |

*Incremental analysis – base case*

In the base-case analysis, both antibiotic- and silver-impregnated shunts were located in the south-west quadrant of the cost-effectiveness plane, in relation to standard shunts, being less effective (associated with higher rates of first shunt 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 shunts save £62,358 for each additional failure compared with standard; and antibiotic-impregnated shunts save £638,600 per additional failure in comparison to silver-impregnated shunts.

*Sensitivity analyses*

The ICERs were stable to changes in discount rate (ranging from undiscounted to 6% per annum) and choice of regression modelling (Table S 22). However, there were differences in cost-effectiveness when limiting the analysis to observed data, without multiple imputation. In this analysis, antibiotic-impregnated shunts dominated silver-impregnated shunts, and save £56,771 for each additional failure compared with standard.

Based on the GLM model, where 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 shunt failure (any cause) with antibiotic-impregnated catheters (versus silver); and £85,802 with silver-impregnated catheters (versus standard).

Table S 22: Results of sensitivity analyses. Negative ICERs relate to incremental cost and outcome coordinates in the south-west quadrant of the cost-effectiveness plane. Values are means (97.5% CI).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Total cost (£)** | **Proportion failure** | **Incremental cost** | **Incremental failure** | **ICER** |
| **Base-case** | | | | | |
| Antibiotic | 14192 (12450, 17786) | 0.259 (0.218, 0.303) | -3192 (-8382, 12272) | 0.005 (-0.046, 0.063) | -638,600 |
| Silver | 17385 (14649, 22355) | 0.254 (0.209, 0.296) | -1322 (-9295, 5592) | 0.021 (-0.035, 0.078) | -62,358 |
| Standard | 18707 (13888, 26966) | 0.233 (0.191, 0.273) | - | - | - |
| **0% Discount rate** | | | | | |
| Antibiotic | 14331 (12621, 18064) | 0.260 (0.219, 0.302) | -3212 (-8619, 1534) | -0.006 (-0.048, 0.061) | -535,333 |
| Silver | 17542 (14768, 22523) | 0.254 (0.209, 0.298) | -1340 (-9454, 5782) | -0.021 (-0.036, 0.078) | -63,810 |
| Standard | 18882 (14015, 27224) | 0.234 (0.192, 0.275) | - | - | - |
| **1.5% Discount rate** | | | | | |
| Antibiotic | 14269 (12515, 17989) | 0.260 (0.219, 0.301) | -3023 (-8575, 1527) | -0.006 (-0.048, 0.060) | -539,821 |
| Silver | 17473 (14570, 22449) | 0.254 (0.209, 0.297) | -1332 (-9386, 5764) | -0.021 (-0.035, 0.078) | -63,429 |
| Standard | 18805 (13959, 27070) | 0.233 (0.191, 0.273) | - | - | - |
| **6% Discount rate** | | | | | |
| Antibiotic | 14099 (12378, 17776) | 0.258 (0.217, 0.301) | -3179 (-8364, 1224) | -0.005 (-0.046, 0.062) | -635,800 |
| Silver | 17278 (14551, 22242) | 0.253 (0.208, 0.295) | -1310 (-9184, 5715) | -0.021 (-0.035, 0.078) | -62,381 |
| Standard | 18589 (13802, 26721) | 0.231 (0.190, 0.271) | - | - | - |
| **Observed data (without imputation)** | | | | | |
| Silver | 6186 (5842, 6530) | 0.255 (0.247, 0.258) | - | - | Dominated |
| Antibiotic | 5296 (4952, 5640) | 0.250 (0.243, 0.258) | -545 (-1128, 2215) | 0.010 (-0.046, 0.065) | -56,771 |
| Standard | 5841 (5497, 6185) | 0.241 (0.233, 0.248) | - | - | - |
| **Generalised Linear Modelling for costs** | | | | | |
| Antibiotic | 15012 (12893, 18955) | 0.259 (0.218, 0.303) | -1680 (-8333, 3033) | -0.005 (-0.046, 0.063) | -336,000 |
| Silver | 16693 (14397, 20888) | 0.254 (0.209, 0.296) | -1819 (-12813, 4506) | -0.021 (-0.035, 0.078) | -85,802 |
| Standard | 18512 (13766, 26178) | 0.233 (0.191, 0.273) | - | - | - |

*Sub-group analyses*

A stratified cost-effectiveness analysis indicated that cost-effectiveness was dependent on age (Table S 23). In paediatrics, antibiotic shunts were dominant (south-east quadrant of the cost-effectiveness plane) with mean savings of £5,312 and additional benefits of 0.004 shunt failures (due to any reason) averted. Put another way, for every 250 patients first receiving an antibiotic-impregnated instead of a standard shunt, there would be 1 fewer case of shunt failure (due to any reason), and a cost saving of £1,328,000.

For adults below 65 years of age, silver-impregnated shunts were most cost-effective, with antibiotic shunts being extendedly dominated. In older adults, aged ≥65 years, silver-impregnated shunts save £29,375 for each additional failure compared with standard; and antibiotic-impregnated shunts save £786,375 per additional failure in comparison to silver-impregnated shunts.

*Alternative cost-effectiveness and cost-utility analyses*

A cost-effectiveness analysis based on the incremental cost per confirmed infection averted, indicated that silver-impregnated shunts were dominated by standard, whereas antibiotic-impregnated shunts were dominant, saving £4,059 per 0.030 fewer infection-related shunt failures. Compared with standard, antibiotic-impregnated shunts save £135,753 per shunt infection avoided (Table S 24).

For the cost-effectiveness measure of incremental cost per mechanical failure averted, both silver- and antibiotic-impregnated shunts were dominated by standard, as they were associated with higher rates of mechanical failures, and higher costs than standard shunts. With regards to functional failures, antibiotic shunts are both less effective, and less expensive than standard, while silver-impregnated catheters cost an additional £387,667 per additional functional failure averted. The opposite was observed when considering the incremental cost per shunt 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 shunts cost an additional £7.4m per failure averted, while silver-impregnated shunts save £3.9m per additional failure, each in comparison with standard.

*Hydrocephalus Outcome Questionnaire*

Responses to the Hydrocephalus Outcome Questionnaire were analysed using mixed models for repeated measures. The model included the Hydrocephalus Outcome Questionnaire score as the dependent variable; treatment group, time and the corresponding interaction as fixed effects; and patient as a random effect. However, due to the small number of returned forms, the patient model did not converge and the parent model output contained warnings that final hessian not positive definite. For this reason this outcome is presented descriptively only (Tables S 25, S 26).

*Cost utility analysis*

In the cost utility analysis of trial participants aged ≥5 years, and based on multiple imputation to account for missing data, antibiotic shunts were dominated by silver. Compared with standard, silver shunts are £183 more costly, and yield 0.096 additional QALYs overall, resulting in an incremental cost of £1,904 per QALY gained. The cost-effectiveness acceptability curve showing the probability of each shunt being cost-effective, by a range of cost per QALY thresholds, is depicted in Figure S 5.

Table S 23: Results of sub-group analyses, defined by age categories. Negative ICERs relate to incremental cost and outcome coordinates in the south-west quadrant of the cost-effectiveness plane. Values are means (97.5% CI).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Total cost (£)** | **Proportion failure** | **Incremental Cost** | **Incremental Failure** | **ICER** |
| **Base-case** | | | | | |
| Antibiotic | 14192 (12450, 17786) | 0.259 (0.218, 0.303) | -3192 (-8382, 1227) | 0.005 (-0.046, 0.063) | -638,600 |
| Silver | 17385 (14649, 22355) | 0.254 (0.209, 0.296) | -1322 (-9295, 5592) | 0.021 (-0.035, 0.078) | -62,358 |
| Standard | 18707 (13888, 26966) | 0.233 (0.191, 0.273) | - | - | - |
| **Paediatrics aged <16 years** | | | | | |
| Antibiotic | 14859 (11650, 22381) | 0.362 (0.248, 0.469) | -5312 (-16289, 2271) | 0.004 (-0.107, 0.102) | Dominant |
| Standard | 20171 (14632, 33160) | 0.365 (0.242, 0.484) | - | - | - |
| Silver | 19518 (15338, 28372) | 0.384 (0.256, 0.493) | - | - | Dominated |
| **Adults aged <65 years** | | | | | |
| Antibiotic | 13940 (9748, 18489) | 0.306 (0.173, 0.453) | -2651 (-8841, 2058) | 0.039 (-0.063, 0.149) | Extendedly dominated |
| Silver | 16591 (11992, 22565) | 0.266 (0.131, 0.420) | -2845 (-10188, 4751) | 0.027 (-0.076, 0.140) | -105,370 |
| Standard | 19437 (13109, 28306) | 0.239 (0.113, 0.384) | - | - | - |
| **Adults aged ≥65 years** | | | | | |
| Antibiotic | 14730 (11676, 21353) | 0.123 (0.069, 0.179) | -1881 (-8011, 4666) | 0.024 (-0.052, 0.106) | -78,375 |
| Silver | 16611 (12693, 23830) | 0.099 (0.043, 0.157) | -329 (-9205, 6657) | 0.011 (-0.059, 0.089) | -29,375 |
| Standard | 16941 (12374, 27346) | 0.088 (0.036, 0.138) | - | - | - |

Table S 24: Results of alternative cost-effectiveness and cost-utility analyses. Negative ICERs relate to incremental cost and outcome coordinates in the south-west quadrant of the cost-effectiveness plane. Values are means (97.5% CI).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Total cost (£)** | **Outcome** | **Incremental Cost** | **Incremental Outcome** | **ICER** |
| **Confirmed infections** | | | | | |
| Antibiotic | 14446 (12660, 18054) | 0.027 (0.013, 0.043) | -4059 (-12567, 1422) | -0.030 (-0.058, -0.002) | Dominant |
| Standard | 18505 (13872, 27274) | 0.057 (0.035, 0.083) | - | - | - |
| Silver | 17331 (14584, 22136) | 0.057 (0.038, 0.080) | - | - | Dominated |
| **Mechanical failures** | | | | | |
| Standard | 14110 (14021, 27648) | 0.092 (0.066, 0.120) | - | - | - |
| Silver | 17426 (14682, 22445) | 0.119 (0.088, 0.154) | - | - | Dominated |
| Antibiotic | 18749 (12303, 17564) | 0.134 (0.103, 0.167) | - | - | Dominated |
| **Functional failures** | | | | | |
| Silver | 17483 (14767, 22396) | 0.069 (0.047, 0.092) | -1163 (-9349, 5815) | -0.003 (-0.040, 0.030) | 387,667 |
| Standard | 18646 (13837, 27066) | 0.072 (0.048, 0.101) | - | - | - |
| Antibiotic | 14157 (12397, 17576) | 0.084 (0.057, 0.108) | -4488 (-12919, 960) | 0.011 (-0.027, 0.049) | -374,000 |
| **Patient factors** | | | | | |
| Antibiotic | 14196 (12438, 17648) | 0.008 (0.001, 0.018) | -4441 (-12825, 987) | -0.001 (-0.015, 0.012) | 7,401,667 |
| Standard | 18638 (13983, 27464) | 0.009 (0.001, 0.018) | - | - | - |
| Silver | 17451 (14712, 22543) | 0.009 (0.001, 0.019) | 1186 (-9255, 5694) | -0.000 (-0.011, 0.010) | -3,953,333 |
| **Cost utility analysis based on imputed data** | | | | | |
| Silver | 9115 (7596, 12682) | 1.319 (1.207, 1.365) | 183 (-3035, 3854) | 0.096 (-0.488, 0.188) | 1,904 |
| Standard | 8932 (7301, 11980) | 1.223 (1.136, 1.298) | - | - | - |
| Antibiotic | 9643 (7545, 11736) | 1.250 (1.163, 1.336) | - | - | Dominated |

Table S 25: Hydrocephalus Outcome Questionnaire - Patient

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Standard VPS** | | | | **Antibiotic impregnated VPS** | | | | **Silver impregnated VPS** | | | | **Total** | | | |
| **Scale** | **BL** | **EARLY** | **12W** | **END** | **BL** | **EARLY** | **12W** | **END** | **BL** | **EARLY** | **12W** | **END** | **BL** | **EARLY** | **12W** | **END** |
| ***Physical health*** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Completed item | 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 |
| ***Socio-emotional health*** | |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Completed item | 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 | 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 | 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 |

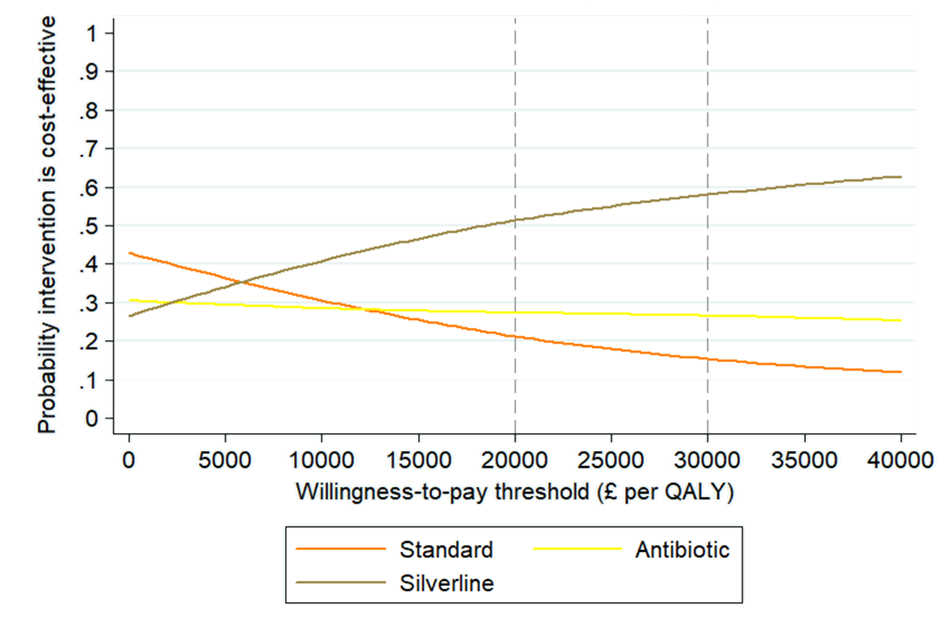
**Note:** *Questionnaire key*: HOQ – Hydrocephalus outcome questionnaire. *Time point key*: BL – Baseline; EARLY – Early post op; 12W – 12 week follow up; END – End of study.

Table S 26: Hydrocephalus Outcome Questionnaire - Parent

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Standard VPS** | | | | **Antibiotic impregnated VPS** | | | | **Silver impregnated VPS** | | | | **Total** | | | |
| **Scale** | **BL** | **EARLY** | **12W** | **END** | **BL** | **EARLY** | **12W** | **END** | **BL** | **EARLY** | **12W** | **END** | **BL** | **EARLY** | **12W** | **END** |
| ***Physical health*** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Completed item | 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 |
| ***Socio-emotional health*** | |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Completed item | 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 | 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 | 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 |

**Note:** *Questionnaire key*: HOQ – Hydrocephalus outcome questionnaire. *Time point key*: BL – Baseline; EARLY – Early post op; 12W – 12 week follow up; END – End of study.

Figure S 5: Cost-effectiveness acceptability curves indicating the probability of each shunt being cost-effective (based on incremental cost per QALY gained) for a range of threshold (willingness to pay) values.



Vertical lines indicate the NICE threshold range of £20,000 to £30,000 per QALY.23

References for economic analysis

1. Database of Instruments for Resource Use Measurement. BASICS Health Service Diary. 2019. http://www.dirum.org/instruments/details/112 [Accessed 15 March 2019]
2. Ridyard CH, Hughes DA. Methods for the collection of resource use data within clinical trials: a systematic review of studies funded by the UK Health Technology Assessment program. Value Health. 2010 Dec;13(8):867-72.
3. Curtis L, Burns A. Unit Costs of Health and Social Care 2017, Personal Social Services Research Unit, University of Kent, Canterbury. 2017 https://doi.org/10.22024/UniKent/01.02/65559 [Accessed 10 March 2019]
4. Geue C, Lewsey J, Lorgelly P, Govan L, Hart C, Briggs A. Spoilt for choice: implications of using alternative methods of costing hospital episode statistics. Health Econ 2012;21:1201–16.
5. Department of Health and Social Care. NHS reference costs 2015 to 2016. https://www.gov.uk/government/publications/nhs-reference-costs-2015-to-2016 [Accessed 10 March 2019]
6. NHS England. NHS National Tariff Payment System 2016/17. https://www.gov.uk/government/publications/nhs-national-tariff-payment-system-201617 [Accessed 10 March 2019]
7. Joint Formulary Committee. British National Formulary. London: BMJ Group and Pharmaceutical Press; 2017.
8. NHS Business Services Authority (NHS BSA). Prescription Cost Analysis Data. Newcastle upon Tyne: NHS BSA; URL: www.nhsbsa.nhs.uk/prescription-data/dispensing-data/prescription-cost-analysispca-data [Accessed 10 March 2019]
9. Dolan P. Modeling valuations for EuroQol health states. Med Care. 1997 Nov;35(11):1095-108.
10. Kulkarni AV, Rabin D, Drake JM. An instrument to measure the health status in children with hydrocephalus: the Hydrocephalus Outcome Questionnaire. J Neurosurg. 2004 Nov;101(2 Suppl):134-40.
11. Kulkarni AV, Drake JM, Rabin D, Dirks PB, Humphreys RP, Rutka JT. Measuring the health status of children with hydrocephalus by using a new outcome measure. J Neurosurg. 2004 Nov;101(2 Suppl):141-6.
12. Gabrio A, Mason AJ, Baio G. Handling Missing Data in Within-Trial Cost-Effectiveness Analysis: A Review with Future Recommendations. Pharmacoecon Open. 2017 Jun;1(2):79-97.
13. Franklin M, Lomas J, Walker S, Young T. An Educational Review About Using Cost Data for the Purpose of Cost-Effectiveness Analysis. Pharmacoeconomics. 2019 Feb 12. doi: 10.1007/s40273-019-00771-y.
14. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med. 2011 Feb 20;30(4):377-99.
15. National Institute for Health and Care Excellence (NICE). Guide to the Methods Of Technology Appraisal 2013. Process and Methods [PMG9]. London: NICE; 2013. URL: www.nice.org.uk/process/pmg9/ [Accessed 10 March 2019].
16. Mihaylova B, Briggs A, O'Hagan A, Thompson SG. Review of statistical methods for analysing healthcare resources and costs. Health Econ. 2011 Aug;20(8):897-916.
17. Polsky D, Glick H. Costing and cost analysis in randomized controlled trials: caveat emptor. Pharmacoeconomics. 2009;27(3):179-88.
18. Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. Health Econ. 2001 Dec;10(8):779-87.
19. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, Augustovski F, Briggs AH, Mauskopf J, Loder E; CHEERS Task Force. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. BMJ. 2013 Mar 25;346:f1049.
20. Graham JW, Olchowski AE, Gilreath TD. How many imputations are really needed? Some practical clarifications of multiple imputation theory. Prev Sci. 2007 Sep;8(3):206-13.

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## 6. List of substantial protocol amendments

| **Protocol Version** | **Key amendments** |
| --- | --- |
| 2.0  (21/11/12) | * Protocol- ‘Allergy to antibiotics associated with the antibiotic shunt’ added to the   exclusion criteria. |
| 3.0  (22/03/13) | * 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 endpoint 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  (25/07/13) | * Section 5.1 Inclusion Criteria and Exclusion criteria updated to :   b. Indwelling ventricular access device (e.g. Ommaya or Rickham reservoir or –  ventriculo-subgaleal shunt or similar) are allowed  c. Indwelling EVD allowed |
| 5.0  (20/12/13) | * Section 4: Trial design   + Primary Endpoint changed to read ‘Time to failure of the first VPS due to infection‘ * Section 5.2 Exclusion Criteria changed to:   1. Previous indwelling ventricular or lumbar peritoneal or atrial shunt.  2. Allergy to silver |
| 6.0  (01/04/14) | * Section 11.3.5 Nominated Consent added |
| 8.0  (10/08/15) | * Protocol Summary Section, Study Duration: Maximum Follow up changed from 2.5 years to 2 years |
| 9.0  (10/08/16) | * Change of study end date to 31st 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 United Kingdom & Ireland   Study Duration-amended the duration to ‘utilising a recruitment period of 4 years, 2 months |
| 1. 10.0 2. (11/08/17) | * 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  (05/04/18) | Section added to the protocol in order to access HES Data for patients with a Welsh Postcode |
| 13.0  (25/09/18) | * Study end date change to 31/01/2019 |