

**Study Title: Endoscopic clot lavage as an adjunct to subgaleal shunt for the treatment of neonatal post-haemorrhagic hydrocephalus**

**Protocol Number: 15HI26**

**Protocol Version: *Version 5.0***

**ENLIVEN**

**Endoscopic Lavage after Intraventricular haemorrhage in Neonates**

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**Sponsor**

**Great Ormond Street Hospital for Children NHS Foundation Trust**

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**Signatures**

The Chief Investigator, Principal Investigators and Sponsor have discussed this protocol. All have agreed to perform the investigation as written and to abide by this protocol except in case of medical emergency or where departures from it are mutually agreed in writing.

**Chief Investigator**

Signature

Date:

**Participating Sites and Local Principal Investigators (PI)**

# Amendment History

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| **Amendment No.** | **Protocol Version No.** | **Date issued** | **Author(s) of changes** | **Details of Changes made** |
| 2 | 4 | 27/04/2017 | Aquilina / Dawes | (1) Additional MRI scanning time to obtain advanced sequences  (2) Additional CSF collection at the time of ventricular peritoneal shunt insertion if required by the neonate |
| 3 | 5 | 18/08/2017 | Aquilina / Dawes | Additional behavioural assessments:   * Stage 1: Early infancy (16-24 weeks) * Stage 2: Middle infancy (10-14 months) * Stage 3: Late infancy/"toddler-hood" (18-36 months) |

1. **ABBREVIATIONS**

|  |  |
| --- | --- |
| CI | Chief Investigator |
| CSF | Cerebrospinal fluid |
| DRIFT | Drainage irrigation and fibrinolysis trial |
| GCP | Good Clinical Practice |
| GOSH | Great Ormond Street Hospital |
| GP | General Practitioner |
| ICF | Informed Consent Form |
| IVH | Intraventricular haemorrhage |
| LP | Lumbar puncture |
| NICU | Neonatal Intensive Care Unit |
| NHS | National Health Service |
| NRES | National Research Ethics Service |
| PHH | Post haemorrhagic hydrocephalus |
| PHVD | Post haemorrhagic ventricular dilatation |
| PI | Principal Investigator |
| PIL | Participant/ Patient Information Leaflet |
| R&D | NHS Trust R&D Department |
| REC | Research Ethics Committee |
| SAE | Serious Adverse Event |
| SOP | Standard Operating Procedure |
| tPA | Tissue plasminogen activator |
| UCL | University College London |
| VI | Ventricular index |
| VPS | Ventricular peritoneal shunt |
| VSG | Ventricular subgaleal shunt |

# Study Synopsis

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| Title | Endoscopic clot lavage as an adjunct to subgaleal shunt for the treatment of neonatal post-haemorrhagic hydrocephalus |
| Sponsor name | GOSH |
| Primary objective | The **primary aim** of this research project is to determine whether neuroendoscopic clot lavage at the time of Ventricular Subgaleal Shunt (VSG) insertion reduces the rate of progressive Post Haemorrhagic Hydrocephalus (PHH) following neonatal intraventricular haemorrhage (IVH). |
| Secondary objective (s) | The **principle secondary aim** of this project are:  (1) To determine if neuroendoscopic clot lavage improves neurodevelopmental outcome following neonatal intraventricular haemorrhage (IVH), assessed in collaboration with Professor Vargha-Khadem through assessments undertaken at three time points:   * Stage 1: Early infancy (16-24 weeks) * Stage 2: Middle infancy (10-14 months) * Stage 3: Late infancy/"toddler-hood" (18-36 months)   (2) To determine if neuroendoscopic clot lavage improves neuroradiological outcome following neonatal intraventricular haemorrhage (IVH). In collaboration with Professor Chris Clark, participants will undergo advanced multi-shell diffusion MRI (measuring brain maturation and structural connectivity) and resting state functional MRI (measuring functional connectivity of the brain) at term equivalent and at six months of age.  (3) To analyse how intraventricular haemorrhage impacts on CSF characteristics. CSF collected at the time of subgaleal shunt insertion and definitive ventriculoperitoneal shunting (if required) will stored for around ten years and will used in future research including analysis for:   * Micro RNA expression * Lipid analysis * Neurofilament light protein * Nitric oxide * RNA expression within specific cell lineages |
| Study Design | Prospective randomised control study – comparing two study groups: Standard treatment with subgaleal shunt (control arm) vs Endoscopic ventricular washout with clot retrieval followed by placement of subgaleal shunt (intervention arm). |
| Study Endpoints | Other than randomisation to endoscopic lavage all neonates will undergo identical treatment with further management including: monitoring by twice weekly cranial ultrasound, and progression to implantation of a permanent VP shunt or removal of the VSG shunt.  All trial patients will undergo an MRI at term equivalent and at around six months of age, MRI at these time points is clinically indicated under standard clinical care. Neonates enrolled in the ENLIVEN study will have extra sequences added which will prolong the acquisition time by approximately 20 minutes.  All trial patients will also undergo three detailed behavioural assessments at three separate time points:   * Stage 1: Early infancy (16-24 weeks) * Stage 2: Middle infancy (10-14 months) * Stage 3: Late infancy/"toddler-hood" (18-36 months)   The endpoint of the trial will be reached when the 50th neonate enrolled in the ENLIVEN trial has undergone their final cognitive / behavioural assessement. |
| Sample Size | We aim to recruit 50 patients to this research project - 25 patients in the control arm and 25 patients in the intervention arm. |
| Summary of eligibility criteria | Neonatal Post Haemorrhagic Ventricular Dilatation requiring CSF diversion. Ventricular index on cranial ultrasound >97th Centile + 4mm after failure of at least one lumbar puncture to control further progression of ventriculomegaly. |
| Intervention | Endoscopic lavage of the blood clot within the ventricle containing the largest blood load will be undertaken. If required a septostomy through the septum pellucidum will be performed with exploration and lavage of the contralateral ventricle. A flexible endoscope, connected to a standard endoscopy stack will be used. This procedure is expected to last approximately 30 minutes longer than a standard Ventricular Subgaleal (VSG) shunt implantation. Artificial CSF will be used as the irrigating fluid to minimise the potential for electrolyte disturbance. |

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| Procedures: | |
| Screening & enrolment | Existing referral pathways will be used. In general patients who require treatment with a subgaleal shunt are adequately matched in terms of weight, gestation, extent of ventricular dilatation and extent of Intraventricular Haemorrhage (IVH) as such randomization will be undertaken using a sealed envelope system. |
| Baseline | Neonates requiring neurosurgical intervention for the treatment of post-haemorrhagic hydrocephalus (head circumference >97th Centile +4mm), referred from the GOSH referral catchment area, will be randomly allocated to either control / standard treatment or intervention / endoscopic lavage + standard treatment. |
| Treatment period | Endoscopic clot lavage represents a single intervention at the time of presentation. Other than this intervention all neonates will undergo identical care with length of inpatient treatment and subsequent intervention based purely on clinical need. As part of standard clinical care in neonates following IVH, all patients will undergo an MRI at term equivalent and at around six months of age. In addition to the routine scans acquired as part of standard clinical care, infants enrolled on the ENLIVEN trial will have additional sequences added, we anticipate that these extra sequences will take approximately 20 minutes and will pose no extra threat to the neonate. All trial patients will also undergo three detailed behavioural assessments at three separate time points:  Stage 1: Early infancy (16-24 weeks)  Stage 2: Middle infancy (10-14 months)  Stage 3: Late infancy/"toddler-hood" (18-36 months) |
| End of Study | From historical referral patterns we anticipate that around 12 patients will be randomised per year as such approximately 4 years of enrolment / randomisation will be required. The final cognitive / behavioural assessment will be made at around two years following randomisation as such we anticipate that data collection will take around 6 years in total. |

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# Introduction

## Background and Rationale

Despite advances in perinatal care, germinal matrix haemorrhage (GMH) remains a common complication after premature birth and occurs in up to 45% of premature babies weighing 500-750g (1) Up to 50% of neonates with large GMH extending into the ventricles develop symptomatic post-haemorrhagic ventricular dilatation (PHVD) (2) with many requiring permanent CSF diversion.

Progressive ventricular dilatation distorts periventricular white matter tracts and if left untreated is life threatening and carries a poor neurological prognosis (3). Prior to committing to ventricular-peritoneal shunt placement, management of PHVD requires insertion of a temporising device, usually a ventricular-subgaleal (VSG) shunt. This allows neonatal maturation (>2kg), defines the subgroup with progressive hydrocephalus and reduces the risk of shunt blockage associated with high protein and Hb within the CSF.

In addition to the impact of ventricular dilatation on the developing brain, intraventricular haemorrhage also elicits an inflammatory response in the wall of the lateral ventricle with attendant injury to the developing periventricular white matter(4) for example IVH has been shown to cause the release of transforming growth factor beta which promotes scarring in the subarachnoid space and physical obstruction of CSF flow and absorption (5).

IVH may also impact on neurogenesis and gliagenesis within the germinal matrix, an important source of pluripotential neurogenic stem cells (6). In vivo animal studies of GMH (7 8) and in vitro analysis of the effect of blood products on cell culture (9) suggest that blood products have an adverse impact on these stem cells.

In an attempt to negate the deleterious impact of intraventricular clot, the DRIFT (drainage, irrigation and fibrinolysis) study was set up to establish if continuous ventricular irrigation over 72 hours, to wash out the cytokines from the CSF and breakdown residual clot, could reduce the rate of progressive hydrocephalus and improve neurological outcome(10). Irrigation was achieved using 2 implanted ventricular catheters (right frontal & left occipital) and required intensive monitoring within a neonatal intensive care unit, with precise assessment of fluid inflow and outflow and continuous measurement of intracranial pressure.

The DRIFT study (Whitelaw et al 2010) was discontinued due to concerns related to the safety of prolonged ventricular irrigation and the incidence of re-bleeding related to the use of t-PA. Although the DRIFT study did not demonstrate a reduction in the requirement for a permanent VP shunt, cognitive and motor follow up at two years did demonstrate a significant reduction in the rate of death and severe disability in the DRIFT group compared to the group that received standard treatment(11) and further longitudinal studies have demonstrated that this improvement is long standing at least to school age equivalent (Whitelaw personal communication).

We would expect that endoscopic lavage carries the advantages of DRIFT at washing out the clot and intraventricular inflammatory mediators. However this procedure reduces the risk associated with 72 hours of irrigation to a single operative procedure and removes the need for prolonged drainage on the neonatal intensive care unit. The mechanical effect of direct endoscopic lavage also obviates the need for a fibrinolytic drug, which in the DRIFT study was associated with a significant rebleeding rate.

Intraventricular endoscopy is a safe procedure and a large number of neonatal procedures are carried out annually in our unit. In addition, endoscopic ventricular lavage for neonatal IVH has recently been described as safe in a small group of non-randomised neonates (12).

* 1. **Rationale for including advanced behavioural and neuroimaging assessments.**

In addition to routine clinical evaluation and the requirement for permanent cerebrospinal fluid diversion, sensitive, objective and blinded tests are essential to prove the validity of the endoscopic approach. To this end we propose to use advanced magnetic resonance (MR) imaging, in collaboration with Professor Chris Clark: Professor of Imaging and Biophysics.

* + 1. *Impacts of IVH on early cortical development detectable with MRI*

Histologically, premature birth has been shown to result in alterations in cortical architecture(13); specifically premature birth is associated with reduced dendritic arborisation(14), altered cortical synchronisation(15) and reduced cerebellar growth(16).  MRI is clinically indicated at around term equivalent and at 6 months of age as part of gold standard treatment. We propose to add additional imaging in order to acquire new data sets and assess more advanced parameters. In brief, all patients will undergo diffusion weighted imaging (DWI), resting state MRI and Arterial Spin sequences. We anticipate that these extra sequences will extend the routine scanning time by around 20 minutes and will pose no extra threat to the neonate.

In correlation with the behavioural analysis this advanced imaging will allow us not only to understand how IVH impacts on early cortical development but will also determine if endoscopic lavage mitigates some of the deleterious effects of NIVH on the developing brain microstructure.

In summary, we hypothesise that endoscopic clot ablation will:

1. Aid in the immediate management of PHH: By washing away clot and debris in the CSF, we would expect VSG shunts to work better and more consistently until it is time to make a decision, usually around term time (2kg body weight), as to whether a permanent VP shunt is required.

2. Reduce the incidence of PHVD: Early ventricular lavage reduces the concentration of inflammatory mediators arising from clot lysis. It is hoped that this will reduce the extent of arachnoid scarring, thereby reducing the physical obstruction to CSF flow and the reduction in CSF absorptive capacity.

3. Reduce prolonged exposure of the neural stem progenitor cells and the unmyelinated white matter in the periventricular regions to toxic metabolites, resulting in:

* A better neurological outcome, as has been demonstrated in the DRIFT study.
* Improvements in cortical architecture detectable with MRI

### Impact of IVH on behaviour

Severe haemorrhage with porencephalic-cyst formation is associated with a high risk of neurodevelopmental sequela(6) ; in these cases the mechanism of injury is thought to be related to the primary destructive impact at the time of haemorrhage (13). Outcome in infants without parenchymal damage is more variable with differing reports published in the literature(17-20). This may be due to the intrinsic variability in the secondary developmental impact of NIVH on the developing brain (6) a process which may potentially be amenable to intervention(21).

By using advanced assessments to analyse key domains of behaviour and cognition we will be in a position to determine both the nature of the deficit caused and the time course over which this becomes apparent.

In brief, participants will attend for visits at 3 stages:

* Stage 1: Early infancy (16-24 weeks)
* Stage 2: Middle infancy (10-14 months)
* Stage 3: Late infancy/"toddler-hood" (18-36 months)

At each of these time points the following assessments will be undertaken:

* **A Standardized Neuropsychological Assessment:** providing measures of cognition (Bayley Scales of Infant Development), language, and motor function, and a neurological screen, as well as specific tests aimed at evaluating memory function.
* **Event related potentials (ERPs)** – involving recording neural activity with encephaloencephalography (EEG).
* **Kinematic evaluation** - recording the joint movements and muscular activity (electromyography (EMG)) of infants as they perform spontaneous exploratory movements.

This study offers a unique opportunity to decipher the developmental impact of NIVH on the neonatal brain.

**References for Study Proposal included in Section 20**

# Objective and purpose

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| **Objectives** | **Outcome Measures/Endpoints** |
| **Primary Objective** | The principle aim of this study is to determine whether washing the blood clot out of the ventricle following neonatal intraventricular haemorrhage reduces the incidence of progressive ventricular enlargement i.e. hydrocephalus. We propose to break down and remove the blood clot from the ventricular system by directly delivering wash to the inside of the ventricle via an endoscope which is passed through the brain parenchyma immediately prior to subgaleal shunt placement.  The primary outcome measure for this study will therefore be the number of patients in each arm of the study that undergo ventricular peritoneal shunting i.e. does Neuroendoscopic lavage reduce the incidence of VP shunting? |
| **Secondary Objectives** | **Short term objectives**  A review of Neuroendoscopic cases undertaken in the Neurosurgical department of GOSH revealed that more than 100 procedures have been undertaken in patients less than one year with 8 procedures performed in neonates under one month of age, with no evidence of increased risk. As such whilst safety and efficacy of neuroendoscopy has been demonstrated, a secondary objective of this study will be to determine surgical parameters to determine best practice and assist in the design of a larger multicentre trial:  1. Length of additional surgical time required for neuroendoscopy  2. Amount of wash required for ventricular washout  3. Any adverse incidents encountered, specifically looking at the incidence of:  a. Rebleeding  b. Wound breakdown / infection  c. Electrolyte disturbance  **Medium term objectives**  In addition to investigating whether neuroendoscopy reduces the incidence of ventricular peritoneal shunting, a secondary objective of the study is to determine whether endoscopic lavage reduces the incidence of subgaleal shunt blockage. Subgaleal shunt blockage, defined as 'increasing ventricular size (monitored via transfontanelle ultrasound) with no evidence of subgaleal pocket change', exposes the neonate to the potentially deleterious impact of increased intraventricular pressure and may also necessitate shunt revision. By comparing the rate of subgaleal shunt blockage in the control and intervention arms we aim to determine if endoscopic clot lavage reduces the incidence of subgaleal shunt blockage.  **Long term objectives**  The DRIFT study (drainage, irrigation and fibrinolysis) demonstrated that ventricular washout was associated with a statistically significant reduction in severe disability and death. We anticipate that endoscopic lavage may also improve long term outcome through a similar mechanism however without the potential risks associated with prolonged washout. To assess long term outcome all neonates enrolled in the ENLIVEN trial will undergo cognitive and behavioural assessment at three time points; early infancy (16-24 weeks) middle infancy (10-14 months) and late infancy / “toddler-hood” (18-36 months).  Premature birth and in particular intraventricular haemorrhage are associated with alterations in cortical development and synchronisation. Using advanced MRI imaging we aim to determine how endoscopic lavage impacts on neuroradiological outcome. |

# Study Design

## Description of study design

*Background and introduction*

Babies born prematurely are prone to bleeding within the brain; because of this all premature neonates have regular ultrasound scans of their brain to check whether there is any evidence of bleeding. If bleeding has occurred, in most cases this will resolve spontaneously and will not require any further treatment however in some babies blood within the ventricles causes an obstruction in the flow of the cerebrospinal fluid (CSF) and if this progresses it can cause damage to the brain and is potentially life threatening.

*Transfer to Neurosurgery and Consent*

The group of neonates who develop hydrocephalus following an intraventricular bleed are referred to the Paediatric Neurosurgeons for CSF diversion; as such the research participants first interaction with the Neurosurgical team will be due to the fact that they have developed hydrocephalus secondary to haemorrhage. At this point the parents will be given the ‘Letter of Invitation’, which gives a brief introduction to the study.

If the hydrocephalus progresses beyond an accepted limit, despite performing 2 lumbar punctures, then the neonate is transferred to the Neurosurgical service at GOSH. On arrival to GOSH the neonate will be assessed by the on call Neurosurgical registrar and the parents will be asked if they wish to be given more information about the ENLIVEN study. If the parents express an interest in the study then they will be given the ‘Parent Information Leaflets’ which contains more detailed information regarding regarding the endoscopic lavage project. Either the same day or the following morning a suitably qualified member of the Neurosurgical team will discuss the project further with the family in order to ascertain whether they are willing to participate in the study.

If the family do not wish to participate in the study then the neonate will undergo a subgaleal shunt insertion as is current best practice at GOSH. If the family are willing to be enrolled in the study then they will be randomised into either the treatment arm i.e. endoscopic clot lavage followed by insertion of a subgaleal shunt, or the control arm i.e. insertion of a subgalael shunt in isolation.

*Technical details of the endoscopic lavage*

Endoscopic clot lavage involves passing an endoscope (essentially a small camera) through the brain and into the ventricular cavity, the clot can then be gently washed away under direct vision from the inside of the ventricle. If bleeding has occurred in both ventricles then a small hole is made in the thin wall which separates the ventricles (the septum pellucidum) and the endoscope is passed into the contralateral ventricle. We are testing how successful endoscopic lavage is as there is data to suggest that washing the clot out of the ventricle can improve the prognosis of neonates following haemorrhage both by reducing the need for permanent ventricular peritoneal shunting (VPS)(Schultz 2014) and also improving neurological outcome at 2 years (Whitelaw 2010).

At the time of surgical intervention, a sample of Cerbrospinal Fluid (CSF) is routinely sent to the microbiology lab for analysis in addition to this we propose to take a second sample of CSF for research purposes. This CSF would routinely be discarded and taking the sample in this way will pose no extra threat to the patient. Samples of CSF will be stored for around ten years and will be used in future research projects including: Micro RNA expression, lipid analysis, neurofilament light protein, nitric oxide, RNA expression within specific cell lineages.

When both ventricles are clear of blood clot the camera is removed and a subgaleal catheter is passed into the tract down which the camera was placed. We envisage that the ventricular washout will take around 30 minutes as such the anaesthetic time will be increased however we do not anticipate that the procedure will be painful as such the depth of anaesthesia and amount of analgesia should not need to be increased.

*Post operative care*

Following the operative intervention all subsequent treatment will be identical for all groups i.e. patients who did not participate in the study, treatment arm and control arm. The average length of stay in the Neurosurgical unit is around 48 hours, during this time close observation of the operative site is undertaken as well as monitoring for any evidence of biochemical disturbance or signs of infection this will require blood to be taken and analysed, this is standard practice and no additional bloods test are envisaged in addition to those which would ordinarily be taken. A CT scan or USS of the head to check the placement of the subgaleal shunt may also be performed prior to transfer.

When the neonate is deemed stable for transfer they will be referred back to their local unit for on-going care. Again this will be identical for all groups. All patients will have bi-weekly cranial ultrasound scans with measurements taken of the ventricular index, in addition to daily examination of the operative site, the size of the subgaleal pocket and the head circumference. Current standard practice is for weekly updates to be given to the neurosurgical team via telephone. For patients participating in the study this information will be recorded on a secure database on NHS computers and the data will be kept and protected for no around ten years.

*Decision for Ventricular Peritoneal Shunt*

At around term and/or when the neonate weighs more than 2kg the neonate will be transferred back to the Neurosurgical Team at GOSH, an MRI scan will be performed and a decision will be made regarding the need for permanent ventriculoperitoneal shunting. This decision will be made in a multidisciplinary team setting and will include Paediatric Neurosurgeons not directly involved in the care of the neonate. If VPS is deemed necessary this will be undertaken on the same admission. If not the neonate will be referred back to their local hospital for on-going care.

If a VPS is deemed necessary then an intraoperative sample of CSF will be taken for research. It is standard practice to send a sample of CSF for microbiology and taking a second sample of CSF for research purposes will pose no extra threat to the neonate. Following VPS insertion the neonate will be referred back to their local hospital for on-going care.

*Out patient reviews*

The first out patient review to check wound sites and clinical progress will be undertaken at 6-8 weeks following discharge. In brief, further out patient reviews will then be undertaken at GOSH at around 6,12,18 and 24 months.

Prior to the 6 month follow up an MRI scan of the head will be undertaken. An MRI scan at six months of age represents standard clinical practice, patients enrolled on the ENLIVEN trial will undergo extra acquisition sequences as detailed above which we anticipate will extend the acquisition time by around twenty minutes. In addition to this at around 6 months the neonates will undergo the first stage of the behavioural assessment.

At around 12 months, neonates will be reviewed in the Neurosurgical OPC and will also undergo the second stage of the behavioural assessment. At 18 months neonates will be reviewed in the Neurosurgical OPC and finally at around 24 months the neonates will again be reviewed in the Neurosurgical OPC and also undergo the final stage of the behavioural assessment.

It is also envisaged that long term follow up at five and ten years of age will be performed, again within the out patient department at GOSH.

Clinical review and behavioural assessment at around 24 months will conclude the data acquisition period of the ENLVEN study, however given that patients with VP shunt require long term follow up in the OPC, it is envisaged that further progress reviews will be undertaken at five and ten years to determine the long term impact of IVH and endoscopic lavage.

From statistical analysis based on the best evidence available we predict that 50 neonates (25 in the treatment arm and 25 in the control arm) will need to be randomised in this study to definitively answer the questions that we aim to address, i.e. does endoscopic clot lavage reduce the rate of permanent VPS and does endoscopic clot lavage improve outcome at two years. Based on historical referral patterns we anticipate that 4 years of data collection will be required to complete enrolment. A data monitoring group consisting of Neurosurgeons, Neonatologists and Neonatal Anaesthetists will meet every six months to undertake interim analysis and on an as required basis in the event of a complication deemed to be as a result of endoscopic lavage.

REFERENCES

Schulz M, Buhrer C, Pohl-Schickinger A, et al. Neuroendoscopic lavage for the treatment of intraventricular hemorrhage and hydrocephalus in neonates. J Neurosurg Pediatr 2014;13(6):626-35.

Whitelaw A, Jary S, Kmita G, et al. Randomized trial of drainage, irrigation and fibrinolytic therapy for premature infants with posthemorrhagic ventricular dilatation: developmental outcome at 2 years. Pediatrics 2010;125(4):e852-e58.

# Population

The study population for this study are premature neonates with symptoms and signs of progressive hydrocephalus (secondary to germinal matrix haemorrhage) requiring intervention (ventricular index over 97th centile + 4mm) with progressive ventricular enlargement despite at least 2 lumbar punctures).

## Inclusion Criteria

All premature neonates with progressive post haemorrhagic hydrocephalus will be included for randomisation. A standard treatment algorithm is already in use to guide referring neonatal units in the management of posthaemorrhagic ventricular dilatation (PHVD) following neonatal intraventricular haemorrhage (IVH). In brief, twice weekly transfontanelle ultrasound is used to monitor ventricular size, if the ventricular index increases past the 97th centile + 4mm then up to two lumbar punctures are performed, if this fails to prevent the progression of ventriculomegaly then the patient is referred to the Neurosurgical team at GOSH for insertion of subgaleal shunt.

We are not aware of any concurrent treatments that would be incompatible with endoscopic lavage nor do we anticipate involvement in other research precluding randomisation.

## Exclusion Criteria

Patients with coagulopathy or platelet disorders persisting on attempted correction will be excluded from randomisation.

# Study Procedures

## Recruitment

Existing referral pathways will be used: Neonates requiring neurosurgical intervention for the treatment of post-haemorrhagic hydrocephalus (head circumference >97th Centile +4mm), referred from the GOSH referral catchment area, will be randomly allocated to either: control / standard treatment or intervention / endoscopic lavage + standard treatment.

Neonates requiring neurosurgical intervention will ordinarily be discussed with the 'on-call' Neurosurgical registrar at GOSH. Arrangements are then made for transfer and admission of the neonate under the Neurosurgical team at GOSH. Following admission consent will be taken by a suitably trained member of the Neurosurgical team with surgical intervention planned on the next available elective operating list.

## Informed Consent

Informed consent will be taken by a suitably trained member of the Neurosurgical team.

## Screening and Eligibility Assessment

On referral to the Neurosurgical service at GOSH (i.e. when still at the local hospital), the family will be given the ‘Letter of Invitation’ which gives a brief introduction to the ENLIVEN study. On transfer to the Neurosurgical Team at GOSH the parents will be reviewed by the on call Neurosurgical registrar and, if the parents would like further information about the ENLIVEN study, they will then be given the ‘Parent Information Leaflets’ which contains more detailed information regarding the study.

On admission to the Neurosurgical ward, the neonate will be reviewed by a Junior Doctor specialising in General Paediatric Medicine and will also be seen by the Specialist Nurse Practitioners specialising in Neurosurgery. Parents will have the opportunity to discuss any aspects of the study requiring clarification during these reviews.

If parents are agreeable to participation then consent for the study will be taken at the same time as the standard consent for surgical intervention, this will normally be within 24 to 48 hours following admission.

Consent for the ENLIVEN trial will therefore be in taken in a staged process:

(1) Receipt of the ‘Letter of Invitation’ – approx. 5-7 days prior to intervention

(2) Receipt of the ‘Parent Information Leaflet’ – 24-48 hours prior to intervention

(3) Consent form signing done prior to surgical intervention – usually within 24 hours of surgical intervention

In some instances due to clinical necessity less than 24 hours may elapse between admission and surgical intervention. It is anticipated that following randomisation patients will undergo intervention expediently as such limited time between screening, randomisation and intervention is envisaged.

# Baseline Assessments

Baseline assessments undertaken on admission of the patient will include: Weight, head circumference, ventricular index (defined as the absolute distance between the falx and the lateral wall of the anterior horn in the coronal plane at the level of the third ventricle), examination of sutures, record of any apnoeas and bradycardias. Before considering surgical intervention all neonates require baseline bloods including FBC, U&E, clotting and group and save, this is a requirement of both the control and intervention arm and does not constitute an ‘extra’ assessment.

## Subsequent Visits

*Perioperative management*

Following subgaleal shunt insertion all neonates will have routine examination of the wound site and subgaleal pocket with post op bloods taken and either a CT head or ultrasound scan may also be performed to determine ventricular calibre and position of the intraventricular catheter .

*Inpatient monitoring*

After a short period of inpatient monitoring at GOSH (following subgaleal shunt insertion) dictated on a patient-to-patient basis by clinical need, neonates will be referred back to their local hospital for on going care.

During the inpatient stay at the local hospital, in addition to the local team alerting GOSH if there is clinical concern, progress will also be actively monitored by members of the research team via regular telephone conversations, with a record kept of ventricular index and head circumference and monitoring for any evidence of wound problems or recurrent haemorrhage.

Twice weekly ultrasound scans monitoring the ventricular index will continue to be performed, if the VI increases beyond the 97th centile +4mm and the subgaleal pocket is pronounced then this can be aspirated using a butterfly needle. If the VI continues to increase and the subgaleal pocket is not pronounced this implies that the shunt may be blocked and the neonate may need transfer back to GOSH for subgaleal shunt revision. Neonates will be reviewed in the Neurosurgical out patient clinic at GOSH at 6-8 weeks post op.

*Decision at term equivalent or weight approaching 2kg*

The aim of the subgaleal shunt is to facilitate temporary CSF drainage. This approach selects out the group of neonates who will require permanent CSF diversion whilst also facilitating neonatal maturation and normalisation of CSF characteristics, thus reducing the risk of shunt blockage. The decision as to whether permanent CSF diversion is required is made as the neonate approaches term equivalent age or acquires a weight of 2kg.

When the neonate reaches this decision point (i.e. term equivalent / >2kg weight) they will be transferred back to the Neurosurgical team at GOSH for evaluation. To aid in this decision making process an MRI is performed.

If formal CSF diversion is deemed necessary this will be undertaken on the same admission with a repeat sample of CSF taken at the time of surgical intervention. If VPS is not felt to be necessary then the neonate will be referred back to their local hospital and followed up in the outpatient clinic.

Other than the initial randomisation all interventions as detailed above will be identical for both treatment and control arms.

*Out patient monitoring*

Routine follow up in outpatient clinic will be performed:

|  |  |  |
| --- | --- | --- |
|  | * + - * 1. **Time Post Discharge** | * + - * 1. **Out patient intervention** |
| 1 | 6-8 Weeks | Neurosurgical OPC |
| 2 | 6 months | Neurosurgical OPC |
| MRI Scan |
| 3 | 12 months | Neurosurgical OPC |
| 4 | 18 months | Neurosurgical OPC |
| 5 | 24 months | Neurosurgical OPC |
| Bayley Outcome Assessment |

## Study Duration

Patients will be enrolled in the ENLIVEN study for 2 years. Based on historical referral patterns we anticipate that approx. 12 patients will be enrolled per year as such we envisage completing recruitment after approx. 4 years with the end of data acquisition at 6 years.

## Discontinuation/Withdrawal of Participants from Study

We are proposing to perform a single intervention at the time of subgaleal shunt placement, following this randomisation all subsequent treatment is identical in both patient arms. No additional procedures or interventions will be performed. Due to nature of this study withdrawal is not possible. All patients will require on going monitoring as a normal standard of care however if consent for participation is withdrawn then no further data pertaining to that patient will be collected for further analysis, but any data collected up to that point will be used.

## Definition of End of Study

The end of the trial is defined as the day on which the 50th patient enrolled in the study undergoes their Bayley developmental assessment at 2 years of age.

# Intervention

Endoscopic ventricular lavage is performed through a single burr hole. The side of the entry is dictated preoperatively to target the ventricle that is deemed to have the largest blood load. A high speed drill with diamond burr is used to position the burr hole anterior to the coronal suture approximately over Kochers point, this position facilitates access of the endoscope into the anterior horn of the lateral ventricle.

To facilitate optimal exploration of the ventricular system, a flexible endoscope, which has a diameter of 4 to 6 mm, will be used. The scope is passed through the burr hole and into the ventricle that contains the blood clot, artificial CSF is then used to break down and remove the clot. If required a septostomy through the septum pellucidum will be performed to allow exploration of the contralateral ventricle.

The procedure is expected to last approximately 30 minutes longer than standard VSG implantation and artificial CSF will be used to minimise the risk of electrolyte disturbance.

# Randomisation, Blinding and Code-breaking

Screening, randomisation and intervention will all be undertaken at GOSH. Randomisation will be undertaken using a sealed envelope system, these will be drawn up at the start of the study and kept in the possession of Mr Aquilina. Randomisation will be undertaken immediately prior to surgical planning.

## 11.2 Subject Withdrawal Criteria

All patients enrolled in the study i.e. both control and intervention arms will require a period of on going inpatient management followed by a decision to treat at term equivalent / 2kg weight acquisition as discussed above. This information is clinically vital and will need to be performed regardless of the withdrawal status of the patient, as such we anticipate that all data up to this decision point will be collected for all patients and will be entered into the analysis.

# Assessment of Safety

Potential risks associated with Neuroendoscopy:

1. Direct damage to the brain secondary to neuroendoscopy: the use of endoscopy is associated with a risk of inadvertent damage to the brain tissue due to direct trauma from the endoscope. This risk is mitigated by
   1. Employing an experienced endoscopist- the Neurosurgical department at GOSH represents a world authority in the use of Paediatric Neuroendoscopy with more than 100 procedures performed in infants under one year of age between 2005 & 2014.
   2. Using the smallest diameter flexible endoscope available
   3. Performing a single pass through the parenchyma with septostomy employed to access the contralateral ventricle if required.
2. Prolonged surgical time / increased use of resources at the detriment to other patients: we are committed to achieving the shortest possible effective theatre time, we anticipate an increased surgical time of around 30 -45 minutes and we do not feel that this extra surgical time will adversely affect the neonate. All procedures will be performed on elective lists as such emergency cover will not be affected and there is sufficient space on the elective lists to accommodate the increased surgical time required to undertake neuroendoscopic ventricular lavage.
3. Increased pain: we do not anticipate that neuroendoscopy will be a pain generating procedure as such depth of anaesthesia and analgesia should not need to be deepened.
4. Electrolyte disturbance: the minimum amount of wash will be used to achieve successful washout of the ventricular system however there is a potential risk that ventricular lavage could causes electrolyte imbalance. Close pre-op, intra-op and post-op monitoring of electrolyte levels in association with the Neonatology team will be used to mitigate this risk and artificial CSF will be used as the irrigant for lavage as this is perceived to impact less on electrolyte levels.Risk of rebleeding: the DRIFT study was terminated early due to the increased risk of rebleeding, whilst it is generally accepted that this complication was likely to be due to the use fibrinolysis in this trial and we do not anticipate encountering similar difficulties following endoscopic lavage, there is a theoretical risk that rebleeding may be exacerbated by lavage. Close post op monitoring using transfontanelle USS will be used to assess the rate of rebleeding with the potential to terminate the study early if rebleeding rate is seen to increase following endoscopic lavage.
5. Potential unanticipated adverse impact of intervention: in addition to the ‘known’ potential complications which will be closely monitored and controlled for, it remains plausible that neuroendoscopy may have an unanticapted impact on the developing brain. International experience would suggest that neuroendoscopy in this patient group is safe however regular independent oversight and an open approach to data collection and evaluation will be used to determine any other potential adverse impacts of neuroendoscopy.

Potential risks associated with extended MRI scanning

As alluded to above, as part of the gold standard management of IVH in prem neonates, an MRI scan is indicated at term equivalent / >2kg weight, when the decision regarding the need for ventricular peritoneal shunting is made, and at around 6 months. At term equivalent the scan can be undertaken using a ‘feed and wrap’ strategy and as such the extra scan time needed to acquire research images is not anticipated to impact adversely on the neonate. At six months the neonate will likely require intubation for MRI as such the extra MRI scanning time will require an increase in anaesthetic time, this is likely to be in the region of twenty minutes and does not pose any significant increase in risk for the neonate.

## Reporting Procedures for Serious Adverse Events

The data monitoring group will consist of: 3 Neurosurgeons: Mr Kristian Aquilina, Mr Greg Hall + 1 further Surgeon independent of the trial; 1 Neonatologist and 1 Paediatric Anaesthetist. The group will meet routinely every four months to discuss all cases involved in the trial and on an as required basis in the event of an adverse event perceived to be influenced by the use of neuroendoscopy. With the help of 'Bliss' the Neonatal Charity we have been in contact with a number of families who have first hand experience of Neonatal IVH, they have proved invaluable in designing the parent information leaflets and we hope to recruit a parent to sit as a lay member on the data monitoring group.

Key criteria for which we envisage stopping the research prematurely include:

(a) Recurrent haemorrhage

(b) Significant haemodynamic or electrolyte disturbance at the time of surgery - (for example persistent sodium imbalance beyond the normal range)

(c) Parenchymal damage deemed to be as a result of neuroendoscopy

# Statistics

## Statistical methods to be employed (plan of analysis)

Sample size and power calculations have been undertaken in collaboration with Ms Deborah Ridout Senior Research Fellow and Statistician at the Institute of Child Health.

A preliminary study by Schulz et al 2014 demonstrated a significant (p\*<0.05) reduction in the rate of ventricular peritoneal shunting following neuroendoscopic ventricular lavage; Control group 100% shunt rate (10 out of 10 neonates): Neuroendoscopy group 57.9% shunt rate (11 out of 19 neonates): 42.1% reduction in the rate of VP shunting.

Based on a rate of shunting in the control group of 100% (Schulz et al 2014) and a rate of shunting in the intervention group of 60% (Schulz et al 2014) a group size of 20 will be required for 80% power and a group size of 24 will be required for 90% power.

A review of the rate of shunting following subgaleal shunt insertion at GOSH has revealed a shunt rate of 90% (unpublished data) therefore if we predict a 40% reduction in the rate of shunting i.e. rate of shunting in the control group 90% and a rate of shunting in the intervention group 50%, a group size of 25 will be required for 80% power and a group size of 31 will be required for 90% power.

A secondary objective of this research project is to determine if Neuroendoscopy improves long-term developmental outcome (Bayley outcome score at two years). By extrapolating the data published in the DRIFT study (Whitelaw et al 2010) we anticipate that a group size of 25 will detect a difference between the control and intervention arms with 80% power.

In summary based on the best available evidence and in collaboration with Ms Deborah Ridout (Senior Research Fellow and Statistician at the Institute of Child Health), we predict that a group size of 25 neonates (i.e. 25 neonates in the control arm & 25 neonates in the intervention arm) will detect a 40% reduction in the rate of shunting (as published by Schultz et al 2014) with 80 to 90% power. It will also be sufficiently powered to detect changes in the Bayley outcome scores at two years (on the basis of the data published in the DRIFT trial (Whitelaw et al 2010)).

The primary objective of this research project is to determine if endoscopic ventricular lavage reduces the rate of ventricular peritoneal shunting. To assess this we will use descriptive statistics and Fisher’s exact test to compare outcome in the two sample groups.

To assess the secondary objectives we will utilise tests including Fisher’s exact test, unpaired Student’s T test, and Kaplan-Meier estimation, as appropriate.

As a secondary analysis we will use multivariate logistic regression to detect and adjust for the impact of any significant baseline covariates unbalanced in randomization.

# Data Management

## Source Documents

All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

## Direct Access to source data / documents

Only members of the study research team and authorised representatives from the sponsor will have direct access to the source data and study documentation. All source data and study documentation will also be available to external auditors if and when required, and inspectors in the event of regulatory inspection. Access to the final data set will remain with the chief investigator

## Data Recording and Record Keeping

All data will be recorded solely on GOSH computers within the hospital and stored on secure NHS servers in compliance with all data management protocols and stored for approximately ten years.

### **Archiving**

Archiving will be authorised by the Sponsor following submission of the end of study report.

Essential documents will be retained for approximately 5 years after completion of the study. These documents will be retained for longer if required by the applicable regulatory requirements.

# Patient Confidentiality & Data Protection

Patient identifiable data, including initials, date of birth and NHS number will be required for the registration process. The study staff will ensure that the participants’ anonymity is maintained. The participants will be identified only by initials and a participants ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

Data will be stored in a secure manner and in accordance with the Data Protection Act 1998.

# Sample Collection, Storage, Transfer and Analysis

**ANALYSIS OF CSF**

Samples of CSF will be taken by the operating Neurosurgeon on initial cannulation of the ventricle at the time of primary intervention for post haemorrhagic hydrocephalus and further at the time of ventricular peritoneal shunt insertion (if VPS is deemed necessary). Samples will be stored for around ten years and used in future basic science research projects.

A sample of CSF is routinely taken at both of the above time points with the remainder of the CSF that is expressed discarded. As such what we propose is that rather than discarding this sample we will take it for analysis.

Samples of CSF will be collected in theatre and stored on ice, they will then be sent expediently to the histopathology lab where they will be spun down to separate the supernatant and cellular component. The cellular component will then be re-suspended in 2ml of CSF and the serum will be aliquoted into 300ul Eppendorf tubes for future analysis. All samples once prepared will be stored at -80oC in freezer space allocated by Professor Thomas Jacques until further analysis. Once 10 samples have been obtained the first round of analysis will be undertaken.

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|  |
| Samples of CSF taken from neonates undergoing treatment for post-haemorrhagic hydrocephalus, Following collection samples are taken on ice to the lab for centrifugation. The supernatant is separated off, aliquoted into 300μl Eppendorf tubes, snap frozen in liquid nitrogen and stored at -80oC awaiting further analysis. The cellular component is re-suspended in 2ml of supernatant and similarly snap frozen and stored at -80 awaiting further analysis. |

*Analysis of Micro RNA and cfDNA -* **Undertaken in collaboration with Dr Ping Yip - Senior Lecturer – Queen Mary's University**

MicroRNA analysis of CSF will be carried out similarly to as previously described (22). Briefly, total RNA containing microRNAs will be extracted from the cell-free CSF using the MirVana PARIS isolation kit. Thereafter, with a candidate approach and quantification will be carried out using TaqMan microRNA assay, which involve reverse transcription polymerase chain reaction. The expression levels of candidate microRNAs will be compared to clinical data.

Cell free DNA analysis of CSF will be carried out similarly to previously described (23 24). Briefly, total DNA within the cell-free CSF will be extracted using the QIAamp circulating nucleic acid kit. Thereafter, real-time qPCR assays for candidate genomic targets will be compared to clinical data.

*Analysis of Lipidome –* **Undertaken in collaboration with Ms Vicky Jones – PhD Student – Imperial College London**

LC-MS (liquid chromatography mass spectrometry) will be used to analyse CSF samples taken from patients. Lipid extraction will be achieved with an isopropanol/hexane extraction method followed by the Bligh and Dyer extraction method (25). Separation will be achieved with mobile phase A (water based) and mobile phase B (isopropyl alcohol based) and run with a timed separation regimen. Lipid indentification will be performed with Lipidfinder and Lipidmaps (LIPID MAPS ® Lipidomics Gateway).

*Analysis of the Cellular component* – **Undertaken in collaboration with Dr Axel Heep – Senior Clinical Lecturer – University of Bristol**

Magnetic (MACS) or Fluorescence activated cell sorting (FACS) will be employed to isolate specific cell populations from the CSF, for example the transmembrane protein CD133 which has been shown to be expressed with high specificity within the proximal domain of the lateral ventricle(26 27)

RNA will then be extracted from thecell pellet using the RNeasy® kit supplied by Quiagen™. If necessary, amplification of the extracted RNA will be performed using the QuantiTect Whole Transcriptome Kit and analysis of the amplified cDNA product will be undertaken.

**ANALYSIS OF BLOOD SAMPLES**

Preoperative blood samples will be taken by a trained phlebotomist as part of the standard preoperative work up for theatre. In the first instance blood will be sent for Haptoglobin phenotyping to determine if there is correlation between haptoglobin phenotype and outcome.

# Financial Information and Insurance

The costs of the study will be met in house by the Neurosurgery department at GOSH. Cover for negligent harm will be provided by the Great Ormond Street Hospital for Children NHS Foundation Trust through the Clinical Negligent Scheme for Trusts (CNST).

# Publications Policy

Results of the study will be disseminated via social media portals through our collaboration with Bliss - the Neonatal Charity. Parents of children enrolled in the study will also be given the opportunity to receive updates regarding the progress of the study. The results of the study will be published in peer review journals and presented at relevant national and international conferences.

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**Appendix: Schedule of Procedures**

Screening at local Hospital Twice weekly USS

LP if VI >97% centile +4mm

If progressive VI despite LP then referral to Neurosurgery

Baseline Laboratory tests including – FBC, U&E, Clotting & G&S

Randomisation Sealed envelope system – two arms:

* Control = Ventricular Subgaleal Shunt (VSG)
* Intervention = Endoscopic clot lavage + VSG

Operative intervention Up to a maximum of 2mls of blood taken and stored for analysis

Up to a maximum of 10mls of CSF taken and stored for analysis

Inpatient monitoring @ GOSH

Twice weekly USS

Daily ward / wound review

+/- Cranial USS / CT Head

Inpatient monitoring @ Local Hospital

Twice weekly USS:

* If VI stable no intervention
* If VI increasing and subgaleal pocket palpable, for aspiration
* If VI increasing and subgaleal pocket not palpable, for referral to GOSH +/- shunt revision

Telephone monitoring every week up to term

Decision at term equivalent or weight approaching 2kg

Admission to GOSH for clinical evaluation and MRI scanning

If VI continuing to increase or if subgaleal pocket prominent

may need formal VP shunt

Neonate discussed in multidisciplinary team meeting including Neurosurgeons not directly involved in the care of the patient

Outpatient monitoring

|  |  |  |
| --- | --- | --- |
|  | **Time Post Discharge** | **Out patient intervention** |
| 1 | 6-8 Weeks | Neurosurgical OPC |
| 2 | 6 months | Neurosurgical OPC |
| MRI Scan |
| 3 | 12 months | Neurosurgical OPC |
| 4 | 18 months | Neurosurgical OPC |
| 5 | 24 months | Neurosurgical OPC |
| Bayley Outcome Assessment |

Community Paediatrician blinded to treatment arm – *in contrary to the routine follow up appointments detailed above Developmental assessment at 24 months will constitute an additional clinic appointment.*