ENLIVEN-UK

Endoscopic Lavage after Intraventricular Haemorrhage in Neonates in the UK: A national randomised controlled trial on the efficacy of neuro-endoscopic lavage

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Sponsor	University College London (UCL)
Comprehensive Clinical Trials Unit Trial Adoption Group #	CTU/2021/374
Sponsor R&D ID #	146650
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REC #	23/SW/0137
IRAS #	322127

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General information

This document was constructed using the Comprehensive Clinical Trials Unit (CCTU) at UCL Protocol template Version 7. It describes the ENLIVEN-UK trial, sponsored by UCL and co-ordinated by CCTU.

It provides information about procedures for entering participants into the trial, and provides sufficient detail to enable: an understanding of the background, rationale, objectives, trial population, intervention, methods, statistical analyses, cost-effectiveness analyses, ethical considerations, dissemination plans and administration of the trial; replication of key aspects of trial methods and conduct; and appraisal of the trial's scientific and ethical rigour from the time of ethics approval through to dissemination of the results. The protocol should not be used as an aide-memoire or guide for the treatment of other patients. Every care has been taken in drafting this protocol, but corrections or amendments may be necessary. These will be circulated to registered investigators in the trial. Sites entering participants for the first time should confirm they have the correct version through a member of the trial team at CCTU.

CCTU supports the commitment that its trials adhere to the SPIRIT guidelines. As such, the protocol template is based on an adaptation of the Medical Research Council CTU protocol template and the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Statement for protocols of clinical trials (1). The SPIRIT Statement Explanation and Elaboration document (2) can be referred to, or a member of CCTU Protocol Review Committee can be contacted for further detail about specific items.

Sponsor

University College London (UCL) is the trial sponsor and has delegated responsibility for the overall management of the ENLIVEN-UK trial to CCTU. Queries relating to UCL sponsorship of this trial should be addressed to the CCTU Director, CCTU at UCL, Institute of Clinical Trials & Methodology, 90 High Holborn 2nd Floor, London, WC1V 6LJ or via the Trial Team.

Funding

Funding for this research has been provided by the National Institute for Health and Care Research (NIHR HTA) (grant reference: NIHR151288). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Trial Registration

This trial has been registered with the ISRCTN Clinical Trials Register, where it is identified as ISRCTN14018410.

Trial Administration

Please direct all queries to the Clinical Trial Manager at UCL CCTU in the first instance; clinical queries will be passed to the Chief Investigator by the Trial Manager.

Coordinating Unit:

Comprehensive Clincal Trials Unit at UCL (UCL CCTU)
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Structured trial summary

Acronym or short title	ENLIVEN-UK
Scientific Title	Endoscopic Lavage after Intraventricular Haemorrhage in Neonates in the UK: A national randomised controlled trial on the efficacy of neuro-endoscopic lavage.
CCTU Trial Adoption Group #	CTU/2021/374
Sponsor R&D ID #	146650
REC #	23/SW/0137
IRAS #	322127
Primary Registry and Trial Identifying Number	ISRCTN14018410
Date of Registration in Primary Registry	21/12/2023
Source of Monetary or Material Support	NIHR HTA
Sponsor	University College London with sponsor responsibilities delegated to CCTU.
Contact for Public Queries	ctu.enquiries@ucl.ac.uk
Contact for Scientific Queries	Mr Kristian Aquilina Consultant Paediatric Neurosurgeon Great Ormond Street Hospital for Children NHS Foundation Trust Kristian.Aquilina@gosh.nhs.uk
Countries of Recruitment	United Kingdom
Health Condition(s) or Problem(s) Studied	Post-haemorrhagic hydrocephalus
Intervention(s)	**Intervention**: Neuroendoscopic lavage (NEL) with temporising device **Control**: Temporising device alone
Key Inclusion and Exclusion Criteria	**Inclusion Criteria:** 1. Preterm infants: Born at <37 weeks' gestational age. 2. Intraventricular Haemorrhage (IVH): Papile Grades II-IV on cranial ultrasound scan. 3. PHVD: Ventricular index at or beyond the threshold point of the 97th centile for gestational age plus 4 mm on the Levene chart despite 2 attempted lumbar or ventricular punctures. **Exclusion Criteria:** 1. Infants with coagulopathy (INR >1.6) or platelet disorders (platelet count under 80,000/mL) that persist on attempted correction. Clinical judgement will be made by the Investigator. 2. Infant too unstable for neurosurgical intervention. (This is a clinical judgement made

	by the responsible neurosurgeon, neonatologist and anaesthetic team). 3. Parents or carers unwilling to provide informed consent.
Study Type	Phase III, multi-centre, assessor-blinded, randomised controlled interventional trial of NEL with temporising device (Intervention- Arm A) vs temporising device alone (control - Arm B) in preterm infants with PHVD, including an internal pilot study. The primary outcome assessor will be blinded to the treatment allocation, as will the Trial Statistician and the Clinical Project Manager. Treatment allocation will be in a 1:1 ratio using minimisation via www.sealedenvelope.com.
Study setting	Paediatric neurosurgical units
Date of First Enrolment	May 2024
Target Sample Size	100
Trial Duration	72 months
Primary Objective	To establish the efficacy and safety of the addition of NEL to standard of care during temporising device insertion. It is hypothesised that the addition of NEL will be safe and will improve neurodevelopmental outcomes at 2 years in children with severe IVH and PHVD.
Primary Outcome(s)	To detect a 20-point (clinically significant) difference in the Cognitive Quotient (CQ) measured by the Bayley Scales of Infant and Toddler Development Fourth Edition (Bayley IV) at 2 years' corrected age (+/- 2 months) following addition of NEL to the standard of care.
Key Secondary Outcomes	1. Developmental Measures: a. Motor quotient (MQ) b. Language quotient (LQ) 2. Other neurological and functional assessments conducted during the 2-year follow-up visit: a. Presence of seizures during the first 2 years and use of anticonvulsant medication at 2 years. b. Presence of cerebral palsy (+ accompanying Gross Motor Function Classification System (GMFCS) grade and deficit distribution map using the Classification of SCPE c. Assessment of hearing and vision (British Association of Perinatal Medicine classification) d. Parent report: i. Brief Infant Toddler Social Emotional Assessment (BITSEA) ii. Quantitative Checklist for Autism in Toddlers (Q-CHAT)

	3. Mortality up to 2 years corrected age. 4. NEL & VP shunt related outcomes: a. Safety of NEL b. Further surgical procedures, including revision of the temporising drainage device (VAD or VSG), addition of a second temporising device, surgery for loculated or isolated ventricles, and revisions of the VP shunt, if implanted, until two years' corrected age. c. Requirement for VP shunt insertion at 6 months' corrected age. 5. Quality of life and health economic assessments: a. Health-Related Quality of Life (HRQoL) in children: assessed at 12-months and 2 years' corrected age b. HRQoL in primary caregiver: EuroQoL EQ-5D-5L assessed at baseline, 6 months, 12 months and 2 years' corrected age. c. Healthcare resource use costs: assessed at 3 -6-,12-, 18- months and 2 years' corrected age. d. Subsequent cost-effectiveness analysis & cost-benefit analysis of impact on carers based on responses to the EQ-5D-5L
Transitional Research Collections	There will be 3 translational research collections: 1. Collation of imaging: Immediate pre- and post-operative ultrasound scans and MRI scans performed until the child reaches 2 years of age will be collated in a centralised repository for future radiological biomarker analysis 2. Collection of cerebrospinal fluid (CSF): CSF from the index surgery and, where applicable, permanent shunt insertion, and any unscheduled visits at the Neurosurgical Unit will be collected and stored for future biomarker analysis. 3. Collection of blood: Blood from the index surgery and, where applicable, permanent shunt insertion, and any unscheduled visits at the Neurosurgical Unit will be collected and stored for future biomarker analysis.
Pilot Trial	An internal pilot trial will be conducted over the first 12 months of recruitment, beginning when the first centre opens. This pilot trial will have specific aims of assessing recruitment feasibility, barriers to recruitment and protocol adherence with a clear 'traffic light' progression

	criteria. The progress of the trial will be reviewed by the TSC and Funder against the traffic light progression criteria The Independent Data Monitoring Committee will also meet prior to progression beyond the pilot to confirm there are no safety concerns.

Roles and responsibilities

These membership lists are correct at the time of writing; please see terms of reference documentation in the TMF for current lists.

Protocol contributors

Name	Affiliation	Role
Kristian Aquilina	GOSH	Chief Investigator (CI)
Conor Mallucci	Alder Hey Children's NHS Foundation Trust	Co-CI
Emilia Caverly	UCL CCTU	Clinical Project Manager
Amalia Ndoutoumou	UCL CCTU	Clinical Project Manager
Alyson MacNeil	UCL CCTU	Clinical Trial Manager
Victoria Pittordou	UCL CCTU	Clinical Trial Manager
Monica Panca	UCL CCTU	Health Economist
Andrew Embleton-Thirsk	UCL CCTU	Statistician

Saniya Mediratta	Department of Neurosurgery, Royal London Hospital	Co-applicant, North Thames Neurosurgical Training Rotation, Royal College of Surgeons.
Aswin Chari	UCL, GOSH, senior trainee in neurosurgery	Co-applicant, North Thames Neurosurgical Training Rotation, Royal College of Surgeons.
Patrick Bauserman	UCL, MRes student	UCL, Trial Management Group.

Role of trial sponsor and funders

Name	Affiliation	Role
University College London (UCL)	N/A	Regulatory sponsor
UCL Comprehensive Clinical Trials Unit (CCTU)	UCL	UCL as the trial sponsor has delegated all sponsor duties to UCL CCTU. A Clinical Project Manager (CPM) will oversee the Trial Manager (TM) who will be responsible for the day-to-day management of the trial, identifying and providing support to the trial teams at all participating sites and coordinating centres. Responsibilities include securing arrangements to initiate, manage and finance the trial. CCTU staff will be involved in site set up including trial protocol and participant information development, ethics submissions, case report form development and database construction, in collaboration with the ENLIVEN-UK Trial Management Group.
NIHR HTA	Part of the UK Government health research organisations, funded by the Department of Health and Social Care (DHSC)	Trial funder

Trial Team

Name	Affiliation	Role and responsibilities
Kristian Aquilina	GOSH	Chief Investigator, primarily responsible for the concept, design and the conduct of the trial.
Conor Mallucci	Alder Hey Children's NHS Foundation Trust	Co- CI, responsible for the design, supervision, and interpretation of the trial

Felicia Ikeji & James Blackstone	UCL CCTU	Head of Clinical Trials Operations, providing contracting and oversight of trial delivery
Hakim-Moulay Dehbi	UCL CCTU	Head of Statistics providing statistical advice and oversight of the study statistician
Andrew Embleton-Thirsk	UCL CCTU	Trial Statistician, providing statistical analysis at all stages of the trial; Case Report Form (CRF) development, writing of Statistical Analysis Plan (SAP), analyses for IDMC reports, data cleaning and final analysis.
Monica Panca	UCL CCTU	Senior Health Economist providing advice and oversight of the health economics component of the trial
Amalia Ndoutoumou	UCL CCTU	Clinical Project Manager, providing oversight of governance, trial conduct, Quality Management in line with CCTU SOPs and prevailing legislation and budget management.
Victoria Pittordou	UCL CCTU	Trial Manager, providing the day-to-day management of the trial including the development of trial protocol and supporting patient documents, ethics and regulatory submissions, sites set up and support to all participating sites.
Averick Bellows	UCL CCTU	Data Manager, responsible for the development of the CRF and Metadata design, database testing, Data Management Plan, data queries, preparation of reports, data cleaning.

Trial Management Group

Name	Affiliation	Role and responsibilities
Kristian Aquilina	GOSH	Chair, Consultant Paediatric Neurosurgeon, Chief Investigator. Overall responsibility for the conduct of the trial, ensuring deliverables and expectations of the oversight group are met.
Conor Mallucci	Alder Hey Children's NHS Foundation Trust	Deputy Chair, Consultant Neurosurgeon, co-CI. Assist the CI in the trial set-up and trial management, and lead on the mechanistic aspects of the trial.
Aswin Chari	GOSH & UCL	Senior academic neurosurgical trainee. Support clinical delivery of the trial, including data collection.
Saniya Mediratta	Department of Neurosurgery, Royal London Hospital	Neurosurgical trainee. Support clinical delivery of the trial, and liaison with PPI. North Thames Neurosurgical Training Rotation, Royal College of Surgeons.

Neil Marlow	UCL	Co-applicant. Expertise in academic neonatology, particularly in relation to long term outcome evaluations in neonatology trials
Andrew Whitelaw	University of Bristol	Co-applicant. Expertise in academic neonatology, particularly in relation to intraventricular haemorrhage and clinical trials related to it.
Cheryl Battersby	Imperial College; Chelsea and Westminster NHS Foundation Trust.	Co-applicant. Expertise in academic neonatology.
William Dawes	Department of Neurosurgery, Royal London Hospital	Co-applicant. Expertise in clinical and academic paediatric neurosurgery, particularly in intraventricular haemorrhage, clinical and research.
Laurence Galland	Lay member	Co-applicant. Patient group representative and mother of child with intraventricular haemorrhage secondary to prematurity.
Gregory James	GOSH	Co-applicant. Expertise in paediatric neurosurgery.
Sally Jary	University of Bristol	Co-applicant. Expertise in assessment of neonates and infants, and application of cognitive tests in clinical trials.
Cristine Sortica da Costa	GOSH	Co-applicant. Expertise in clinical and academic neonatology
Patrick Bauserman	UCL	MRes student, UCL.
Hakim-Moulay Dehbi	UCL CCTU	Senior oversight statistician. Oversight and supervision of trial statistician in designing the statistical analysis plan (SAP), statistical analyses and statistical reports.
Andrew Embleton-Thirsk	UCL CCTU	Trial Statistician. Produce statistical reports and provide statistical input on trial analyses.
Monica Panca	UCL CCTU	Senior Health Economist. Oversight and supervision the Trial Health Economist in designing the Health Economic Analysis Plan (HEAP), undertaking health economic analyses and provide review of the health economic content of the protocol and relevant reports.
Amalia Ndoutoumou	UCL CCTU	Clinical Project Manager. Oversight of the trial conduct as per protocol, regulations and trial budget.
Victoria Pittordou	UCL CCTU	Trial Manager & Trial Management Group Facilitator. Manage the day-to-day running of the trial according to the protocol and regulations.
Averick Bellows	UCL CCTU	Data Manager. Support the TM and manage data collection as per protocol across participating sites.

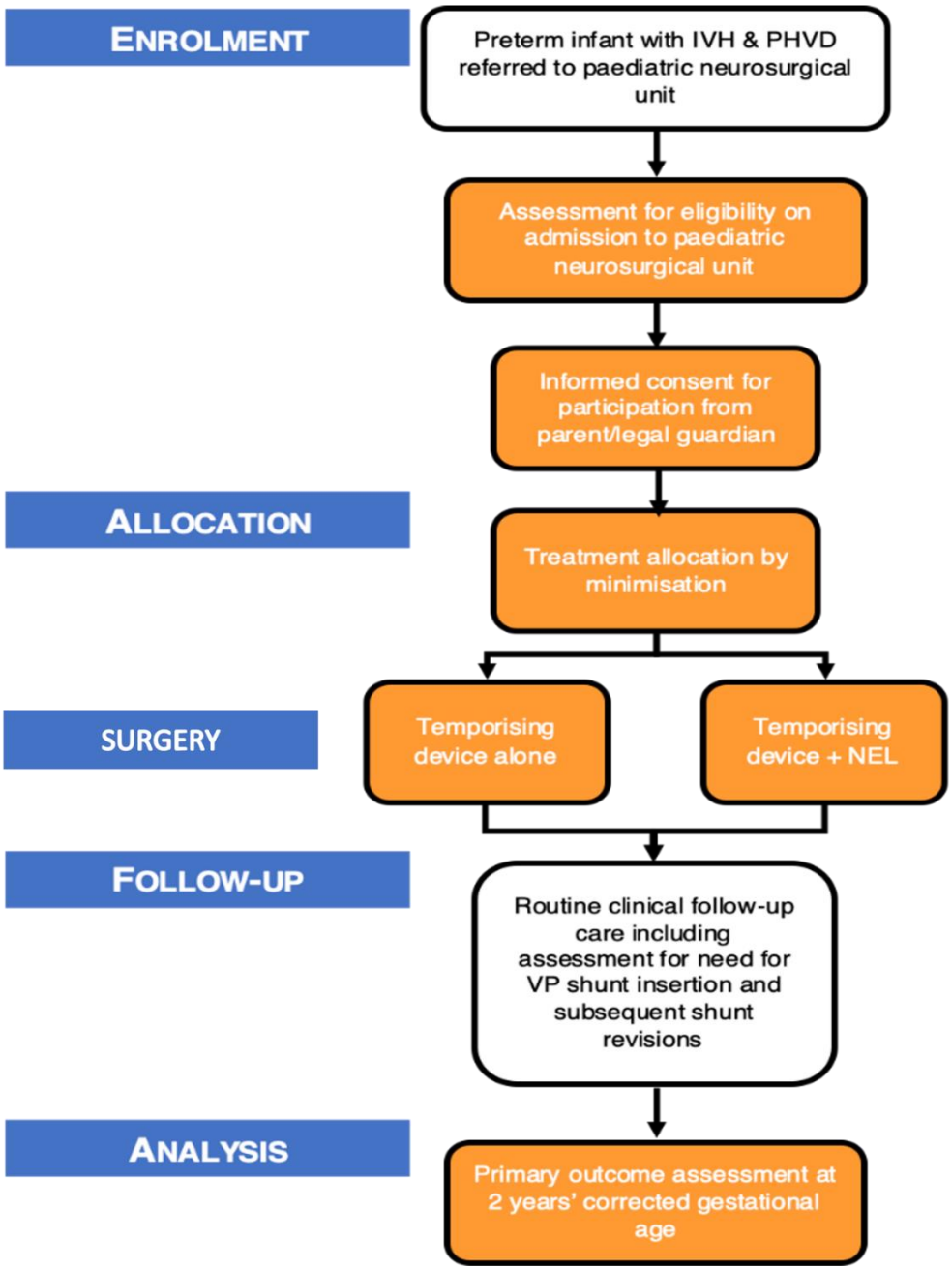
Trial Steering Committee

Name	Affiliation	Role
Dr Frances O'Brien	Oxford University Hospital	Independent Chair. Consultant Neonatologist
Victoria Homer	University of Birmingham	Independent statistician
Professor Ulrich Wilhelm Thomale	Charite Hospital, Berlin, Germany	Paediatric Neurosurgeon
Professor Peter Hutchinson	Addenbrooke's Hospital	Non-independent. Professor of Neurosurgery
Steve Walker-Cox	Lay Member	Public and Patient Involvement Representative
Ramon Luengo-Fernandez	Health Economics Research Centre, Nuffield Department of Population Health, University of Oxford	Health Economist; Associate Professor

Independent Data Monitoring Committee

Name	Affiliation	Role
Professor Michael Jenkinson	The Walton Centre, Liverpool, and University of Liverpool	Independent Chair Consultant Neurosurgeon, NIHR Professor of Neurosurgery
Professor John Kestle	Department of Neurosurgery, University of Utah	Senior academic neurosurgeon, Lead of the Hydrocephalus Clinical Research Network in the US.
Michaela Brown	The Walton Centre, Liverpool, and University of Liverpool	Independent Statistician Consultant Neurosurgeon, NIHR Professor of Neurosurgery

Trial Diagram



Key:
IVH – *Intraventricular Haemorrhage*
PHVD– *Post-haemorrhagic Ventricular Dilatation*
NEL – *Neuroendoscopic Lavage*
VP - *Ventriculoperitoneal*

Abbreviations

AE	Adverse Event
BANNFU	British Association for Neonatal Neurodevelopmental Follow-up
BAPM	British Association of Perinatal Medicine
BITSEA	Brief Infant Toddler Social Emotional Assessment
CA	Competent Authority
CCTU	Comprehensive Clinical Trials Unit at UCL
CI	Chief Investigator
CP	Cerebral Palsy
CQ	Cognitive Quotient
CRF	Case Report Form
CSF	Cerebrospinal Fluid
CTA	Clinical Trial Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
EC	Ethics Committee
EDC	Electronic Data Capture
EQ-5D-5L	EuroQoL EQ-5D-5L
EU	European Union
GMFCS	Gross Motor Function Classification System
GOSH	Great Ormond Street Hospital
GP	General Practitioner
HE	Health Economist
HEAP	Health Economics Analysis Plan
HRA	Health Research Authority
HRQoL	Health-Related Quality of Life
ICH	International Conference on Harmonisation
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
IVH	Intraventricular Haemorrhage
IRAS	Integrated Research Application System
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention to Treat
LQ	Language Quotient
MedDRA	Medical Dictionary for Regulatory Activities
MQ	Motor Quotient
NAE	Notifiable Adverse Event
NEL	Neuroendoscopic Lavage
NHS	National Health Service
NICU	Neonatal Intensive Care Unit
PAG	Patient Advisory Group
PHVD	Post-haemorrhagic Ventricular Dilatation
PI	Principal Investigator
PIN	Participant Identification Number
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
PSS	Personal Social Services
Q-CHAT	Quantitative Checklist for Autism in Toddlers
QA	Quality Assurance
QALY	Quality-Adjusted Life Year
QC	Quality Control
QMMP	Quality Management and Monitoring Plan
QP	Qualified Person
R&D	Research and Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCPE	Surveillance of Cerebral Palsy in Europe
SHINE	Bifida Hydrocephalus Information Networking
SOP	Standard Operating Procedure
TAPQOL	TNO-AZL Preschool Children's Quality of Life
TD	Temporising Device
TMF	Trial Master File
TMG	Trial Management Group
ToR	Terms of Reference
TSC	Trial Steering Committee
UCL	University College London
VAD	Ventricular Access Device
VSGS	Ventriculo-Subgaleal shunt
VP	Ventriculoperitoneal

Glossary

Term	Definition
Corrected age	Chronological age, minus the number of weeks the infant was born before the time of 40 weeks gestational age.
Foreseeable SAE	Any AE that: • results in death • is life threatening* • requires hospitalisation or prolongs existing hospitalisation** • results in persistent or significant disability or incapacity • is a congenital anomaly or birth defect • or is another important medical condition*** **AND** •is listed in section 6.1.2 (Foreseeable Adverse Events) These events must be reported **within 5 days** of site becoming aware if there is **no causal relationship** to trial intervention (NEL). **These events must be reported within 24 hours of site becoming aware if causally related to trial intervention (NEL).**
Intraventricular Haemorrhage	A bleed into the ventricles of the brain
Neuroendoscopic Lavage	Procedure to 'washout' blood and blood products from the ventricles
Notifiable Adverse Event	Any AE that is listed in section 6.2 (Notifiable Adverse Events)
Post-haemorrhagic hydrocephalus	Progressive ventricular enlargement and elevated intracranial pressure following Intraventricular haemorrhage
Temporising Device	Device used to affect CSF drainage when an infant develops PHVD. This will be either a VAD or VSGS.
Term equivalent Age	Age at which an infant would have been born if they had not been premature
Unforeseeable SAE	Any AE that: • results in death • is life threatening* • requires hospitalisation or prolongs existing hospitalisation** • results in persistent or significant disability or incapacity • is a congenital anomaly or birth defect • or is another important medical condition*** **AND** •is **not** listed in section 6.1.2 (Foreseeable Adverse Events) **These events must be reported within 24 hours of site becoming aware if causally related or unrelated to trial intervention (NEL).**
Ventricular Access Device (VAD)	Device used to affect CSF drainage by repeated aspiration when an infant develops PHVD.
Ventricular endoscopy	Procedure used to perform surgery within the ventricles of the brain.
Ventriculo-Subgaleal shunt (VSGS)	Device used to affect CSF drainage when an infant develops PHVD.

1 Background

1.1 Rationale

Around one in thirteen infants is born preterm in the United Kingdom. Despite major advances in survival, intraventricular haemorrhage (IVH) remains one of the most serious complications of preterm birth. In England, almost 500 children develop severe IVH annually (3). Over 50% of these progress to post-haemorrhagic ventricular dilatation (PHVD), where there is progressive enlargement of the ventricles, with distension of the periventricular white matter, raised intracranial pressure and injury to the developing brain. As well as pressure and distortion, the mechanisms of brain injury in PHVD include pro-inflammatory cytokines and free radicals from iron and hypoxanthine persisting in the ventricles for months (4). In childhood, PHVD is associated with a very high rate of cognitive disability and cerebral palsy (CP) (5). IVH and PHVD are the most common cause of neurological disability in preterm infants and have been shown to be the most significant predictors of cognitive disability (3,6,7). Optimising early and effective management in the neonatal period is therefore important to improving long-term cognitive and functional outcomes, both of which are extremely important to families of these children (8).

Current management involves drainage of cerebrospinal fluid (CSF) only (9). Although there is no established consensus on the management algorithm, most UK centres follow a stepwise approach which involves the insertion of an initial temporising device (a ventricular access device (VAD) or ventriculo-subgaleal shunt (VSGS)) when the infant develops PHVD. In up to 75% of these children, permanent CSF diversion via a ventriculoperitoneal (VP) shunt is required, which usually occurs around term-equivalent age. Despite this rational approach, there is still significant morbidity with high rates of shunt dysfunction requiring revision surgery (10).

Optimising long-term cognitive and functional outcomes is important in this patient group as it has been shown to be a priority for families of children with hydrocephalus (8,11). Despite timely intervention, the burden of poor neurodevelopmental outcomes is worse in PHVD compared to other forms of infant hydrocephalus (12). The increased risk of poor outcomes carries important economic implications, from increased time in intensive care through higher requirements for allied health professional support, to long-term special education needs in 60%. These increased needs may reduce family employment prospects (13).

This research is therefore important because severe cognitive disability deprives the child of education, independence and employment, and places unusually heavy demands on the rest of the family and society as well as healthcare resources.

1.1.1 Explanation for choice of comparators

Several interventions for PHVD have been tested in randomised trials and non-randomised studies at various stages of the treatment pathway. Although in the past, treatment was only started once the ventricles were large enough to raise intracranial pressure and cause symptoms with overt neurological deterioration, recent studies have suggested that earlier treatment, based on standardised ultrasound measurements of ventricular size, is beneficial (14,15). Across the UK, the majority of paediatric neurosurgical units have taken a ventricular size of 4mm above the 97th centile as the treatment threshold.

The use of acetazolamide and furosemide to reduce CSF production resulted in increased death, disability or impairment and probably increased requirement for a VP shunt (16). Repeated taps, lumbar punctures and intraventricular streptokinase to remove clot from CSF pathways also did not improve outcome (17,18).

The DRIFT (Drainage, Irrigation, Fibrinolysis Trial) study was the first trial to demonstrate a significant reduction in the proportion of children with severe cognitive disability or death at follow-up at two and ten years (13,19,20). The improved cognition at ten years was equivalent

to a two-year developmental improvement. This suggested that effective washout of blood from the CSF may limit the extent of brain injury. DRIFT involves the insertion of two catheters into the ventricles of a premature infants: irrigating fluid flows in through one and out through the other. The irrigation is continued for about five days, during which very close and specialist monitoring of fluid flow and intracranial pressure is required. DRIFT also requires the use of fibrinolytic agents, and a proportion of babies had secondary bleeds in the ventricles following treatment. The DRIFT technique requires specialist and dedicated expertise over a long period of time, and is difficult to implement, teach and disseminate. Development of techniques that enable easier lavage of intraventricular blood, ideally contained within a single brief surgical procedure, is required.

In the last five years, neuroendoscopic lavage (NEL) has been suggested as a promising treatment option. It is a 30-minute adjunct to the surgical procedure of inserting the temporising device into the enlarged ventricles. NEL washes out blood, clot and its breakdown products as well as debris from the CSF within the ventricles (Figure 1). Unlike DRIFT, NEL does not require injection of a fibrinolytic agent, reducing the risk of secondary haemorrhage. By washing out the blood, NEL may also reduce scarring within the CSF flow pathways, improve CSF circulation and reduce the risk of requiring permanent CSF drainage with a VP shunt. Retrospective evaluations from Europe have shown promising results with the procedure showing safety, reductions in permanent VP shunt insertion and revision rates and favourable neurodevelopmental outcome, although none were prospective comparative trials (21-25). Although not part of the standard of care in the UK, paediatric neurosurgeons carry out endoscopic procedures and NEL for other indications in babies, older children and adults, and are therefore comfortable and competent to perform the procedure.

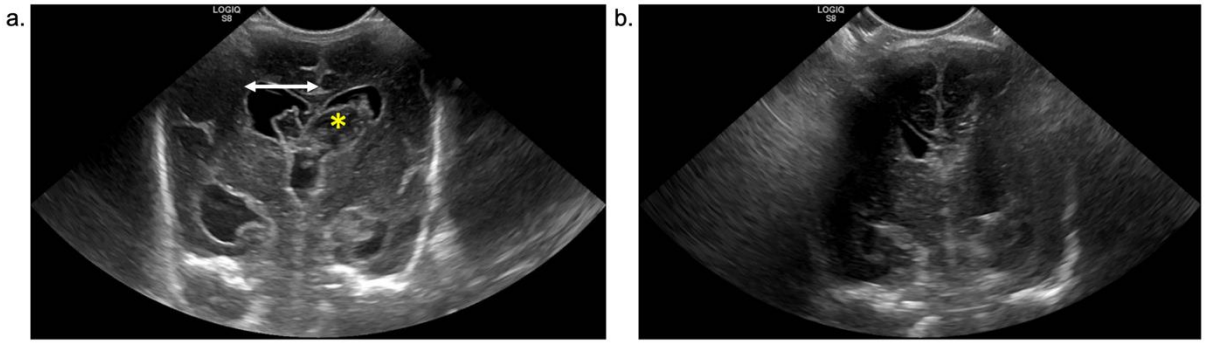


Figure 1 - Example of cranial ultrasound scan (a) before and (b) after NEL. (a) Ultrasound before NEL showing dilated lateral ventricle (white arrow showing left ventricular index measurement) and extensive clot (yellow asterisk) within them. (b) Ultrasound after NEL showing a decompressed ventricular system with reduced clot burden.

Over the last 3 years, the ENLIVEN (Endoscopic Lavage after Intraventricular Haemorrhage in Neonates) pilot study at Great Ormond Street Hospital (GOSH) has been randomly assigning preterm infants with PHVD to VSGS with NEL or VSGS alone (26). Between January 2018 and January 2022, 17 infants have been enrolled in this single centre pilot study. This represents two thirds of the admissions to the service for treatment of PHVD, establishing that recruitment is feasible and that parents are willing to enrol their child. NEL was carried out with an endoscope on the side of the greater blood load. The study was powered to detect a reduction in the need for VP shunt insertion at 6 months. To date we have seen no difference in the primary outcome in this small number of patients. Infants who underwent lavage were less likely to require tapping or revision of their VSG shunt, suggesting that the overall reduction in the amount of blood and debris in the CSF by the irrigation reduced the risk of VSG shunt blockage. The median body weight at NEL in this patient group was 886g; although this was lower than in the published studies described above, there have been no safety concerns.

The above evidence makes a compelling case to undertake a large multi-centre randomised controlled trial of NEL in the UK to assess efficacy and safety.

1.2 Objectives

The objective of this study is to establish the efficacy and safety of the addition of NEL to standard care during temporising device insertion. It is hypothesised that the addition of NEL will be safe and will improve neurodevelopmental outcomes at 2 years in children with severe IVH and PHVD.

1.3 Trial Design

This is a phase III, multi-centre, randomised, assessor-blinded, controlled trial of NEL with temporising device (intervention Arm A) vs temporising device alone (standard treatment/Control Arm B) in preterm infants with IVH and PHVD, with internal pilot trial. 100 infants will be recruited over a 3-year period in 12 or more neurosurgical units throughout the United Kingdom.

For a summary of the participant schedule of assessments, please refer to **section 5.2**.

The internal pilot study will be conducted over the first 12 months of recruitment, beginning when the first centre opens. This pilot study will have specific aims of assessing recruitment feasibility, barriers to recruitment and protocol adherence. Please refer to **section 8.3.4** for further detail.

1.4 Benefit Risk Assessment

Hydrocephalus secondary to intraventricular haemorrhage is the most important cause of neurological disability after premature birth. The DRIFT studies have demonstrated that early irrigation of blood and its breakdown products leads to an improvement in cognitive scores at two years, which is maintained at ten years (13,19). The DRIFT procedure requires approximately five days of irrigation of the brain through two indwelling catheters on the neonatal intensive care unit. It is difficult to carry out, and is associated with risks of infection, catheter blockage and raised intracranial pressure.

Ventricular endoscopy, in contrast, is a well-established procedure that is carried out routinely by paediatric neurosurgeons. Irrigation of the blood and its breakdown products within the ventricular system is carried out in a controlled procedure, within approximately 30 minutes, under direct vision. It is hypothesized that NEL is equivalent to DRIFT in conferring potential cognitive benefit whilst being a simpler and more deliverable technique.

NEL will be carried out within the same operative procedure as insertion of a clinically indicated temporising device and therefore does not mandate an additional anaesthetic episode. If NEL is successful at demonstrating the cognitive benefits of DRIFT, it will have the added advantage of being reproducible throughout the UK, rather than restricted to one or two dedicated centres in the country. It is not considered to represent a risk to the infant that is higher than standard medical care.

Standard therapy (Arm B- control) involves insertion of a temporising device, which, for a period of time, typically six to eight weeks, allows diversion of CSF from the ventricles. The device can be either a VAD or a VSG. Both are equivalent for this purpose, and different neurosurgical units and the neonatal units with whom they work will have their own preference. They are associated with the same operative and post-operative risk, namely infection, recurring haemorrhage inside the ventricles, new haemorrhage related to ventricular decompression, catheter blockage, failure of absorption of CSF from the subgaleal pocket of a ventricular-subgaleal shunt, seizures, external leakage of CSF, electrolyte disturbance and a very small risk of stroke. In our experience, all these are rare and occur in less than 5% of cases.

The intervention being evaluated in this randomised trial, NEL will be carried out in addition to insertion of a temporising device (Arm A - Intervention). In our experience and in published studies, the additional risks of endoscopic lavage are low, and occur in less than 5% of cases

(21-25). The risks relate to standard neuro-endoscopic surgery and are expected to be lower than the risks of DRIFT. These include infection, further haemorrhage within the ventricles, haemorrhage related to ventricular decompression, seizures, CSF leak, electrolyte disturbance and a <1% risk of brain injury (21-25). These risks are not expected to be significantly higher than insertion of a temporising device alone. In theory the risk of electrolyte disturbance and seizures, related to the presence of lavage fluid within the ventricles, is slightly higher than with insertion of a temporizing device. This will be mitigated by use of warm Ringer lactate solution or artificial CSF, and by monitoring of serum electrolytes post-lavage. These infants are routinely cared for within a neonatal intensive care unit environment and close care and supervision is routine.
Several published studies have suggested that the requirement for permanent CSF diversion through a ventricular peritoneal shunt is reduced after lavage compared to insertion of a temporising device alone (22,24,25). This is a potential additional advantage of NEL that will be evaluated as an exploratory outcome.
The risks associated with NEL will be mitigated by ensuring that patient recruitment will only take place in established paediatric neurosurgical units and will be undertaken by paediatric neurosurgeons who routinely perform a range of neuro-endoscopic procedures. Each paediatric neurosurgical unit is affiliated with a neonatal unit to ensure appropriate neonatal care. A number of meetings have taken place to discuss the technical details of the irrigation procedure, and a surgical consensus statement has been published (28). In addition, a meeting with world experts in endoscopic lavage in this population is planned before commencement of recruitment to enable a wider discussion and sharing of operative nuances, experience and knowledge.

2 Selection of Sites/Investigators

2.1 Site Selection

The trial sponsor has overall responsibility for site and investigator selection and has delegated this role to CCTU.

2.1.1 Study Setting

This trial will take place in 12 or more paediatric neurosurgical units based across the United Kingdom.
A list of participating sites can be obtained upon request from the ENLIVEN-UK Trial Manager at UCL CCTU.

2.1.2 Site/Investigator Eligibility Criteria

Once a site has been assessed as being suitable to participate in the trial, the trial team will provide them with a copy of this protocol.
To participate in the ENLIVEN-UK trial, investigators and trial sites must fulfil a set of criteria that have been agreed by the Sponsor and ENLIVEN-UK Trial Management Group (TMG) and that are defined below.
Eligibility criteria:

1. A named clinician is willing and appropriate to take Principal Investigator responsibility
2. Suitably trained staff are available to recruit participants, enter data and collect samples.
3. Paediatric neurosurgeons in the unit must be experienced in infant neuro-endoscopy and NEL and must attend a dedicated trial training session on the NEL procedure arranged by the sponsor.

2.1.2.1 Principal Investigator's (PI) Qualifications and Agreements

The Principal Investigators (PIs) must be willing to sign a PI Declaration (part of the Clinical Trial Site Agreement), to comply with the trial protocol (confirming their specific roles and responsibilities relating to the trial, and that their site is willing and able to comply with the requirements of the trial). This includes confirmation of appropriate qualifications (provide an up-to-date CV), familiarity with procedure and agreement to comply with the principles of GCP. The PI must agree to permit monitoring and audit as necessary at the site, and to maintain documented evidence of staff who have been delegated significant trial related duties.

2.1.2.2 Resourcing at site

- The investigator should demonstrate potential for recruiting the required number of suitable participants within the agreed recruitment period.
- The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.
- The investigator should have available an adequate number of qualified staff and suitable facilities for the anticipated duration of the trial in order to conduct the trial properly and safely.
- The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, intervention, and their trial-related duties and functions.
- The site should have sufficient data management resources to allow prompt data return to the CCTU (refer to the Data Management Plan for timelines).

2.2 Site approval and activation

Site training will be performed prior to the activation of each site and will include all processes for the trial including but not limited to protocol training, data management procedures, procedures for the intervention, adverse event reporting procedures, procedures for laboratory samples and frequency and expectations for monitoring visits. A log of Site Initiation Visit attendees will be kept in the Trial Master File (TMF) as a record of participants present. The Visit may occur in person or via Videoconference as outlined in the Quality Management and Monitoring Plan (QMMP).

The Trial Manager or delegate will notify the PI in writing of the plans for site activation. Sites will not be permitted to recruit any patients until a letter for activation has been issued. On receipt of the signed Clinical Trial Site Agreement (including the signed PI Declaration), completed delegation of responsibilities log and staff contact details, the Trial Manager or delegate will complete the green light process and issue written confirmation of site activation to the site PI.

The site must conduct the trial in compliance with the protocol as agreed by the Sponsor and, by the Ethics Committee (EC). The PI or delegate must document and explain any deviation from the approved protocol and communicate this to the trial team at CCTU.

A list of activated sites may be obtained from the Trial Manager.

3 Selection of Participants

There will be **NO EXCEPTIONS** (waivers) to eligibility requirements at the time of trial entry. Questions about eligibility criteria should be addressed PRIOR to attempting to randomise a participant.

The eligibility criteria for this trial have been carefully considered and are the standards used to ensure that only medically appropriate participants are entered. Participants not meeting the criteria should not be entered into the trial for their safety and to ensure that the trial results can be appropriately used to make future treatment decisions for other people with similar

diseases or conditions. It is therefore vital that exceptions are not made to these eligibility criteria.
Participants will be considered eligible for enrolment in this trial if they fulfil all the inclusion criteria and none of the exclusion criteria as defined below.

3.1 Participant Inclusion Criteria

The criteria below should be used to determine a patient's eligibility for the trial.
Inclusion Criteria:

1. Premature infants born before 37 weeks of gestational age
2. IVH: Papile Grades II-IV on cranial ultrasound scan
3. PHVD: Ventricular index at or beyond the threshold point of the 97th centile for gestational age plus 4 mm on the Levene chart despite 2 attempted lumbar or ventricular punctures.

3.2 Participant Exclusion Criteria

Exclusion Criteria:

1. Infants with coagulopathy (INR >1.6) or platelet disorders (platelet count under 80,000/mL) that persist on attempted correction. Clinical judgement will be made by the Investigator.
2. Infants deemed too unstable for neurosurgical intervention. This is a clinical judgement made by the responsible neurosurgeon, neonatologist and anaesthetic team.
3. Parents or carers unwilling to provide informed consent.

3.3 Recruitment

A target of 100 participants will be recruited to this trial: 50 in each arm over a 3-year recruitment period.
It is anticipated that there will be 12 or more recruitment sites across the UK, all of which will have expertise in treating IVH, PHVD and performing NEL in infants.
Recruitment will be monitored regularly using anonymised Pre-screening and Screening logs and engagement with participating sites to identify any barriers to recruitment, and strategies implemented where possible to overcome these barriers. In addition, an internal pilot study will be conducted over the first 12 months of recruitment. This pilot will have specific aims of assessing recruitment feasibility, barriers to recruitment and protocol adherence. Please see **section 8.3.4** for further details. The pilot study may identify additional barriers to recruitment; measures to overcome modifiable factors will be implemented prior to the substantive trial phase.
Awareness will be raised through the British Association of Perinatal Medicine, neonatal networks, conferences, and social media to ensure eligible patients are referred in a timely manner. The neurosurgical and neonatology co-applicants have broad access to the neurosurgical and neonatology communities and will ensure that all participating units open promptly and sustain recruitment throughout the trial.
To maximise recruitment, the study team have worked with the PAG (representatives from Spina Bifida Hydrocephalus Information Networking Equality (Shine) and the British Association for Neonatal Neurodevelopmental Follow-up (BANNFU) network) to optimise the Patient Information Sheet (PIS).
In addition, each neurosurgical unit PI will be supported by a neurosurgical trainee, who will participate in the NIHR Associate PI scheme. These trainees will be recruited by our neurosurgical trainee co-applicants and will be actively involved in site set-up and recruitment.
Reporting over the trial set-up and recruitment period will be conducted on a regular basis to the ENLIVEN-UK Trial Management Group (TMG), independent trial oversight committees and the trial funder. Remedial actions will be put in place if any concerns arise.

3.4 Co-enrolment Guidance

Co-enrolment of participants into other studies is permitted. Co-enrolment to a trial with a neurodevelopmental outcome must be discussed with the Sponsor and Chief Investigator prior to enrolment.

3.5 Screening Procedures and Informed Consent

In the NHS, preterm infants with IVH and PHVD are cared for in neonatal intensive care units (NICUs), not all of which have a neurosurgical service on-site. At the stage of developing PHVD and requiring neurosurgical intervention, preterm infants are referred to the regional specialist paediatric neurosurgical unit (of which there are 18 in total in the UK) and jointly cared for by neurosurgeons and neonatal specialists at the paediatric neurosurgical unit's NICU. Following treatment, infants are often transferred back to their local NICU for ongoing management until further neurosurgical assessment/treatment is warranted. All ENLIVEN-UK trial follow-up assessments will be performed at the paediatric neurosurgical unit.

Neonatologists at the neonatal units will be aware of the ENLIVEN-UK trial and will inform the parent/legal guardian(s) of the trial once the diagnosis of PHVD has been made and the treatment threshold is reached. The pathway for informing the parent/legal guardian(s) of the trial may vary depending on whether the infant is being treated in a hospital with a neurosurgical unit on-site or whether they need to be referred into the trial site's neurosurgical unit for treatment for PHVD.

Once the child is accepted for transfer for intervention or a parent / legal guardian arrives at the paediatric neurosurgical unit, they will be informed of the trial. The two possible pathways are outlined below:

For parent/guardian(s) of an infant invited to the trial at a neonatal unit with the neurosurgical unit on-site.

- Parent/guardian(s) will be informed of the trial by the neonatologist or other appropriately trained staff on the neonatal unit who will provide a full explanation of the trial and all relevant treatment options. During these discussions the current approved patient information sheet should be discussed.

- Parent/ legal guardian(s) will be given time to reflect on the information and the opportunity to ask questions. It is envisaged that there will be up to 48 hours for parents to make the decision to participate. Every effort will be made to ensure that access to the trial is optimised by having discussions about the trial (with the help of an in-person translator and a witness if required) as early as possible.

- Following a discussion with a medically qualified investigator or suitable trained and authorised delegate, any questions will be answered and if the parent/legal guardian(s) are willing for their infant to participate, written informed consent on the current approved version of the consent form will be obtained.

For parent/guardian(s) of an infant referred to the trial site neurosurgical unit for PHVD treatment from another hospital's NICU (NB: The NICU Units (based at other NHS Trusts) will not be set-up as Participant Information Centres).

- It is envisaged that the neonatologist will be aware of the ENLIVEN-UK trial and will explain to the parent/guardian(s) that the neurosurgical unit (which their infant is being referred for treatment for PHVD) is taking part in the ENLIVEN-UK trial.

- If the parent/legal guardian(s) wish to learn more about the trial, the neonatologists at NICU will inform them of the trial website where they can access a copy of the patient information sheet along with contact details of the neurosurgical team at the regional specialist paediatric neurosurgical unit.

- Sites will aim to arrange for one of the investigators or other appropriately trained staff in the neurosurgical unit to hold a video consultation with the parents prior to the neonate's transfer in order to explain the trial and its requirements.

- On arrival at the neurosurgical unit, one of the investigators or other appropriately trained staff will provide a full explanation of the trial and all relevant treatment options. During these discussions the current approved patient information sheet should be discussed

- Parent/legal guardian(s) will be given time to reflect on the information and the opportunity to ask questions. It is envisaged that there will be up to 48 hours for parents to make the decision to participate. Every effort will be made to ensure that access to the trial is optimised by having discussions about the trial (with the help of an in-person translator and a witness if required) as early as possible on arrival at the neurosurgical unit.

- Following a discussion with a medically qualified investigator or suitable trained and authorised delegate, any questions will be answered and if the parent/legal guardian(s) are willing for their infant to participate, written informed consent on the current approved version of the consent form will be obtained.

Only one parent/legal guardian will be required to sign the consent form. An eligible infant will not be enrolled in the trial if there is a clear disagreement between two or more parents/legal guardians about taking part in the trial.

For all patients, consent will be re-sought if new information becomes available that affects consent in any way. This will be documented in a revision to the appropriate format of the PIS and the parent/legal guardian(s) will be asked to sign an updated corresponding consent form. These will be approved by the REC prior to their use.
Written informed consent to enter and be randomised into the trial must be obtained from parents/guardians/person with legal responsibility (including legal authorities) for children, after explanation of the aims, methods, benefits, and potential hazards of the trial and **BEFORE** any trial-specific procedures are performed.
The only procedures that may be performed in advance of written informed consent being obtained are those that would be performed on all infants as usual standard of care, such as lumbar punctures and full blood count. These represent standard of care and are not specific to the trial.

It must be made completely and unambiguously clear that the parent/legal guardian(s) of the infant is free to refuse to participate in all or any aspect of the trial, at any time and for any reason, without incurring any penalty or affecting their treatment of their child. Consent must be sought again if a child's legal guardian changes.

Signed consent forms must be kept by the investigator and a copy given to the parent/legal guardian(s) of the participant. The consent process should be documented in the participant's medical records. With the consent obtained, a letter should be sent to the general practitioner (GP) informing him/her of the trial and the infant's involvement in it at the time of the first follow-up at term equivalent age.

Infant's parent/guardian(s) will be asked for their preferred method by which the trial team may be able to communicate with them throughout the trial. Sites will ensure that communication with the infant's parents/guardians(s) will be managed and maintained according to their local policies.

3.6 Trial Visits

Screening Visit
A preliminary evaluation of eligibility for the trial should be made by the site investigator before informed consent is obtained. Once written informed consent is obtained the patient will be allocated a Participant Identification Number (PIN) and the screening and baseline assessments will be completed, including details of the infant's clinical status, grade of IVH and ventricular indices. The screening and baseline visits can occur on the same day as long as the infant's parent/guardian(s) have been given time to reflect on the information in the PIS and following a discussion with a medically qualified investigator where they have and been given the opportunity to ask questions.

Baseline Visit
Infant's parent/guardian(s) must give written informed consent before any trial specific investigations may be carried out. The following assessments or procedures are required within 7 days prior to randomisation and are required to confirm eligibility.

- Papile grade
- Cranial Ultrasound - the ultrasound scan used to confirm eligibility will be stored by sites and a copy sent to Great Ormond Street Hospital where they will be uploaded and stored in the Data Safe Haven. Please see Imaging Transfer Guidelines for further details.
- Head circumference
- Birth weight
- Routine blood results for Haematology, Biochemistry & Coagulation/clotting
- Imaging history
-
- Clinical Assessment
- Signs of Raised ICP

<u>Questionnaires:</u>

- EuroQoL EQ-5D-5L

The infant's parent/guardian(s) should complete the EuroQoL EQ-5D-5L Quality of Life questionnaire. This is required to be completed within 28 days prior to randomisation as it is not required to confirm eligibility.

Questionnaires should be completed at the start of the visit before any other procedures are performed. The completed questionnaire responses to the EQ-5D-5L must be reviewed during the visit to check for self-reported 'severe' or 'extreme' anxiety and depression. Parents/guardians reporting these symptoms should be signposted to access support from their healthcare provider e.g., their GP.
In cases where the questionnaires have been returned to the research team by post, the EQ-5D-5L responses must be assessed by a member of the research team as soon as they are received to check for self-reported 'severe' or 'extreme' anxiety and depression. Parents/guardians reporting these symptoms should be contacted and signposted to access support from their healthcare provider e.g., their GP.

Surgery (t=0) / Randomisation

Investigators (or delegated individual) should review all results received from the baseline visit assessments to re-confirm eligibility, i.e., the participant **meets ALL the inclusion criteria and NONE of the exclusion criteria.** Randomisation should be carried out **within 7 days** of completion of the baseline assessments confirming eligibility.
The following activities will be undertaken:

- Randomisation – immediately prior to surgery
- Study procedure performed. Either: Arm A – NEL with temporising device (Intervention) OR Arm B – temporising device alone (Control).
- Review of Adverse Events
- Review of Concomitant medications for prophylactic antibiotics and anti-epileptic medications prescribed.
- Optional CSF Sample Collection (see Appendix 1 and Laboratory Sample Management Plan for further details)
- Optional Research Blood Sample Collection (see Appendix 1 and Laboratory Sample Management Plan for further details)

Following the trial procedure, inform the participant's parent/legal guardian(s) which trial treatment arm the participant was randomised to receive and provide them with the corresponding Trial Information Card.

Post-Operative Follow-Up (t=24-48 hours)

This visit should take place between 24 to 48 hours after 'surgery (t=0)' visit. The following assessments will be undertaken:

- Cranial Ultrasound
- Head circumference
- Routine blood results for Haematology, Biochemistry & Coagulation/clotting
- Clinical Assessment
- Review of Shunt/Temporising Device information
- Wound site check
- Discharge Information
- Review of Adverse Events
- Review of Concomitant medications for prophylactic antibiotics and anti-epileptic medications prescribed.

First Clinical Follow-Up (t=term equivalent +/- 1 month)

This visit should take place at term equivalent +/- 1 month. The following assessments will be undertaken:

- Head circumference
- Wound site check
- Clinical Assessment
- Review of Shunt/Temporising Device information
- Review of Adverse Events
- Review of Concomitant medications for prophylactic antibiotics and anti-epileptic medications prescribed.

- MRI scan – *if performed as standard of care assessment **only***

VP shunt insertion (if required)

The need for VP shunt insertion will be determined by the clinical team at term-equivalent age as required by standard care. The following assessments will be undertaken:

- Cranial Ultrasound
- Head Circumference
- Shunt Insertion Information
- Clinical Assessment
- Review of Adverse Events
- Optional CSF Sample Collection (see Appendix 1 and Laboratory Sample Management Plan for further details)
- Optional Research Blood Sample Collection (see Appendix 1 and Laboratory Sample Management Plan for further details)

3-6 Months Clinical Follow-Up Visit (+/-2 months)

This visit should take place at 3-6 months after surgery (t=0) visit (+/-2 months). The following assessments will be undertaken:

- Head circumference
- Clinical Assessment
- Review of Shunt/Temporising Device information
- Review of Adverse Events

Questionnaires & Telephone Interview:

- At 3-6 months: Adapted Client Service Receipt Inventory (CSRI children version)
- At 6 months: EuroQoL EQ-5D-5L – *Please ensure parent/guardian(s) are reminded to complete the EQ-5D-5L at 6-months. If the visit is scheduled earlier than 6 months, please ask parent/guardian(s) to take this questionnaire away for completion and return by post or at their next trial visit.*

Age 1 Year Clinical Follow-Up (+/- 2 months)

This visit should take place at age 1 year (+/-2 months). The following assessments will be undertaken:

- Head circumference
- Clinical Assessment
- Review of Shunt/Temporising Device information
- Review of Adverse Events

Questionnaires & Telephone Interview:

- EuroQoL EQ-5D-5L
- Adapted Client Service Receipt Inventory (CSRI children version)
- TNO-AZL TAPQOL

Questionnaires should be completed at the start of the visit before any other procedures are performed. The completed questionnaire responses to the EQ-5D-5L must be reviewed during the visit to check for self-reported 'severe' or 'extreme' anxiety and depression. Parents/guardians reporting these symptoms should be signposted to access support from their healthcare provider e.g., their GP.

In cases where the questionnaires have been returned to the research team by post, the EQ-5D-5L responses must be assessed by a member of the research team as soon as they are received to check for self-reported 'severe' or 'extreme' anxiety and depression. Parents/guardians reporting these symptoms should be contacted and signposted to access support from their healthcare provider e.g., their GP.

18 Months of Age Follow-Up (+/- 2 months) – (Telephone Follow-Up)

This visit should take place at 18 months of age (+/-2 months). The following assessments will be undertaken:

- Review of Adverse Events

Questionnaires (Telephone Interview):

- Adapted Client Service Receipt Inventory (CSRI children version)

2 Years corrected Age Follow-Up (+/- 2 months)

This visit should take place at 2 years corrected age (+/-2 months). The following assessments will be undertaken on two separate visits as follows:

The following assessments performed by a member of the research team at site:

- Weight
- Head circumference
- Incidence of seizures
- Wound site check
- Clinical Assessment
- Review of Shunt/Temporising Device information
- Review of Adverse Events
- Review of Concomitant medications for prophylactic antibiotics and anti-epileptic medications prescribed.

Questionnaires:

- EuroQoL EQ-5D-5L
- Adapted Client Service Receipt Inventory (CSRI children version)
- TNO-AZL TAPQOL
- Brief Infant Toddler Social Emotional Assessment (BITSEA)
- Quantitative Checklist for Autism in Toddlers (Q-CHAT)

Questionnaires should be completed at the start of the visit before any other procedures are performed. The completed questionnaire responses to the EQ-5D-5L must be reviewed during the visit to check for self-reported 'severe' or 'extreme' anxiety and depression. Parents/guardians reporting these symptoms should be signposted to access support from their healthcare provider e.g., their GP.

In cases where the questionnaires have been returned to the research team by post, the EQ-5D-5L responses must be assessed by a member of the research team as soon as they are received to check for self-reported 'severe' or 'extreme' anxiety and depression. Parents/guardians reporting these symptoms should be contacted and signposted to access support from their healthcare provider e.g., their GP.

The following assessments will be performed by a qualified and validated independent clinical development specialist **blinded to the treatment arm.** This specialist will be independent from the trial team and the visit may take place outside of the neurosurgical unit (e.g., in a clinic room at local hospital). The arrangements for this visit will be coordinated by UCL CCTU with the site research teams and independent clinical development specialist.

- Bayley Scales of Infant and Toddler Development (4th edition) (Bayley IV)
- Cerebral palsy assessment, CP subtype (SCPE) & Gross Motor Function Classification System (GMFCS) grade
- Vision and hearing assessment (BAPM classification)

Unscheduled Visits to Neurosurgical Unit

Additional visits (unscheduled visits) will be performed as deemed clinically necessary (i.e. all returns to the neurosurgical unit occurring in between scheduled visits until completion of 2-year follow-up). These unscheduled visits must be clearly documented in the participants medical notes. Sites are encouraged to undertake the following assessments:

- Clinical Assessment
- Physical examination

- Wound site check
- Head circumference
- Review of Shunt/Temporising Device information
- Review of Adverse Events. Note: All incidences of unexpected return to theatre for temporising device dysfunction, infection or CSF leak (CTCAE grade 3 and above) must be reported as a Notifiable Adverse Event (see section).
- MRI scan – *if performed as standard of care assessment* ***only***
- Optional CSF Sample Collection (see Appendix 1 and Laboratory Sample Management Plan for further details).
- Optional Research Blood Sample Collection (see Appendix 1 and Laboratory Sample Management Plan for further details).

4 Trial Intervention

4.1 Introduction

Randomisation will be carried out immediately prior to surgery (after the participating infant is taken to theatre). Eligible participants will be randomly assigned in a 1:1 ratio to:
Arm A - NEL with temporising device (Intervention)
OR
Arm B - temporising device alone (Control).
Parents and guardians will not be aware of the allocated arm prior to the surgery. They will be informed which procedure has been performed after the surgery.
Both the intervention (Arm A) and control arm (Arm B) procedures will be performed by paediatric neurosurgeons who have experience in infant neuro-endoscopy. Although novel in this context, NEL is not a new procedure to neurosurgeons, who will have experience in endoscopic procedures and lavage for a range of indications as part of standard of care treatment.

4.2 Arm A: NEL with Temporising Device - (Intervention)

NEL with Temporising Device
Infants allocated to the NEL with temporising device arm (Arm A) will undergo insertion of an endoscope into the lateral ventricle via a peel-away catheter on the side of higher blood load. Ultrasound guidance may be used at the surgeon's discretion for optimal placement of the endoscope. Following irrigation of the lateral ventricle with Ringer's Lactate or other appropriate lavage solution, the third ventricle and contralateral ventricle (via a septostomy) are also irrigated until the effluent is clear. Blood clots on the ependymal surface may be gently aspirated. The endpoint of the lavage will be at the surgeon's discretion and defined as a 'maximal safe lavage' when the effluent is clear and there has been an attempt to dislodge and wash out clots. This endpoint has been clearly defined by a consensus process of the involved surgeons (28). Once the procedure is completed, a temporising device (either a VAD or VSGS) is inserted, at the discretion of the treating surgeon in line with local practice. Please refer to Table 6 for details of mitigations of risks associated with NEL.

4.3 Arm B: Temporising Device Alone - (Control)

Temporising Device Alone
Infants allocated to the temporising device arm (Arm B) will undergo the standard surgical procedure to insert either a VAD or VSGS, at the discretion of the treating surgeon, in line with their standard current practice. Both VAD and VSGS are associated with the same operative and post-operative risk, namely infection, recurring haemorrhage inside the ventricles, new haemorrhage related to ventricular decompression, catheter blockage, failure of absorption of

CSF from the subgaleal pocket of a ventricular-subgaleal shunt, seizures, external leakage of CSF, electrolyte disturbance and a very small risk of stroke. In our experience, all these are rare and occur in less than 5% of cases. The management of these risks will remain at the discretion of the treating neurosurgical team.

4.4 Concomitant Care

Premature infants are at risk of multiple medical problems involving many organ systems. Therefore, any concomitant treatments needed by the infant during the study period are permitted. These infants are typically on multiple medications, and data on their administration is beyond the remit of this study. However, details of prescribed prophylactic antibiotics and anti-epileptic medications must be recorded as per section 3.6 (Trial Visits).

4.5 Unblinding

Due to the study design, only the primary outcome assessor and individuals making strategic decisions for the trial including the Trial Statistician and the Clinical Project Manager will be blinded to the treatment arm. Therefore, emergency unblinding is not necessary.

4.6 Protocol Treatment Discontinuation

In consenting to the trial, parent/legal guardian(s) of participants are consenting to the infant's trial procedure (either Arm A NEL with Temporising Device or Arm B Temporising Device alone), trial follow-up and data collection. However, an individual parent/legal guardian can request to stop trial follow-up and data collection early for any of the following reasons:

1. Any change in the participant's condition that in the clinician's opinion justifies the cancellation of planned trial surgery.
2. Withdrawal of consent for participation in the trial by the parent/legal guardian(s)
3. The participant never underwent standard of care insertion of a temporising device.
4. Any change in the participant's condition that in the clinician's opinion justifies the discontinuation of trial follow-up after the surgery has been completed.

Intra-operative discontinuation of the NEL (due to complications or technical difficulties as listed in the operative CRF) does not mandate removal of the participant from the trial. Any subsequent treatment following intra-operative discontinuation of the NEL will be at the treating clinician's discretion.

As participation in the trial is entirely voluntary, the parent/legal guardian(s) may choose to discontinue participation of their infant for trial follow-up and data collection at any time without penalty or loss of benefits to which they would otherwise be entitled. Although not obliged to give a reason for discontinuing participation, a reasonable effort should be made to establish this reason, whilst remaining fully respectful of their rights.

It should be clear to the parent/legal guardian(s) and recorded in the patient notes what aspect(s) of the trial the participant is discontinuing their participation. These could include:

- Early cessation **from sample collections**
- Early cessation **from questionnaires**
- Early cessation **from further trial follow-up**
- Early cessation **electronic health record use.**

Patients should remain in the trial for the purpose of follow-up and data analysis (unless the parent/legal guardian(s) withdraws their consent from all stages of the trial). If a patient ceases follow-up early, refer to Section 5.5.

Data on patients who stop follow-up early will be kept and included in analyses where possible. Infants that are withdrawn by their parent/guardian(s) after having had their baseline data collected, but prior to randomisation, will be recorded as withdrawals. As they will not have been randomised, they will not count towards the target sample size though their baseline data will still be summarised at the reporting stage. Infants who are withdrawn after they have

undergone surgery (either Arm A NEL with Temporising Device or Arm B Temporising Device alone), will not be able to withdraw from the surgical part of the trial, only from trial follow-up visits. Participant's parent/guardian(s) will be fully advised of this at the time of consent for the trial and the time of consent for the surgical procedure.

4.7 Compliance and Adherence

The PI at the participating site is responsible for compliance and adherence to the trial protocol.

4.7.1 Trial Intervention (NEL with Temporising Device)

The ENLIVEN-UK trial surgical intervention is performed once by a suitably qualified paediatric neurosurgeon who is a member of the site team. All paediatric neurosurgeons delegated to perform the surgical intervention in ENLIVEN-UK must be experienced in infant neuro-endoscopy and NEL and must attend a dedicated trial training session on the NEL procedure arranged by the Sponsor. Therefore, non-compliance with the intervention is not anticipated but trial data will be reviewed on a monthly basis and post-operative ultrasound scans, will be reviewed at least quarterly by the TMG to evaluate any variability in the surgical procedures.
Where necessary, feedback will be given to the PI at the participating site regarding their operative technique and radiographic outcome. Any relevant issues will be discussed with the participating unit.

4.7.2 Telephone Interviews for Adapted Client Service Receipt Inventory (CSRI children version)

A telephone interview with the infant's parent/guardian(s) should be conducted by a member of the research team at site to complete the Adapted Client Service Receipt Inventory (CSRI children version) at 3-6-,12-, 18-months' and 2 years' corrected age listed in Table 3. These telephone interviews will be performed every 6 months. At each visit timepoint, at least four attempts to contact the infant's parent/guardian(s) should be made over the course of 48 hours, twice a day. On failure to obtain a response by telephone, the CSRI questionnaire will be sent out to the participants by post.

4.7.3 Questionnaire Completion by infant's parent/guardian(s)

The infant's parent/guardian(s) should complete the EuroQoL EQ-5D-5L, TNO-AZL TAPQOL, Q-CHAT, BITSEA questionnaires at the timepoints listed in Table 3. These should be completed and returned to a member of the research team during attendance at the relevant follow-up visits. In cases where it is not possible to complete the questionnaires during the follow-up visit, they can be returned to the research team by post using a self-addressed envelope.
Questionnaires should be completed at the start of the visit before any other procedures are performed. The completed questionnaire responses to the EQ-5D-5L must be reviewed during the visit to check for self-reported 'severe' or 'extreme' anxiety and depression. Parents/guardians reporting these symptoms should be signposted to access support from their healthcare provider e.g., their GP.
In cases where the questionnaires have been returned to the research team by post, the EQ-5D-5L responses must be assessed by a member of the research team as soon as they are received to check for self-reported 'severe' or 'extreme' anxiety and depression. Parents/guardians reporting these symptoms should be contacted and signposted to access support from their healthcare provider e.g., their GP.

4.8 Eligibility Criteria for Individuals Performing the Interventions

NEL for this indication has undergone an evolution from its initial descriptions. All participating surgeons have been involved in a consensus meeting where the steps of the procedure, permitted variations and endpoints were agreed upon to ensure internal consistency (28) Participating surgeons are experienced neurosurgeons and endoscopists who routinely use endoscopic techniques in their clinical practice.

Paediatric neurosurgeons performing the surgical interventions for ENLIVEN-UK must be experienced in infant neuro-endoscopy and NEL and must attend a dedicated trial training session on the NEL procedure arranged by the sponsor. UCL CCTU will maintain a central training log for all investigators delegated to perform surgical procedures in the trial.
Nursing staff, medical staff, and any other delegated members of the clinical trial team at participating sites should have the appropriate qualifications to manage patients with IVH and PHVD. Protocol-specific training will be provided to participating sites by the ENLIVEN-UK Trial Manager or delegate at UCL CCTU prior to site activation, or during a Site Initiation Visit (SIV). New site staff who start work on the trial after site activation occurs will be provided with protocol specific training prior to performing trial related procedures.
Each member of the trial team at each participating site will have roles delegated by the PI and documented on the ENLIVEN-UK site delegation log. Current CVs and GCP certificates of all individuals working on the trial will be collected by the ENLIVEN-UK trial team at UCL CCTU to document their qualifications and relevant experience.

5 Assessments & Follow-Up

5.1 Outcomes

5.1.1 Primary Outcome(s)

The primary outcome measure is the CQ measured at 2 years' corrected age following addition of NEL to the standard of care. We aim to detect a 20-point (clinically significant) difference in CQ at this timepoint. The CQ is measured by dividing the age equivalent cognitive score on the Bayley Scales of Infant and Toddler Development (4th edition) (Bayley IV) by the corrected age at assessment (both in months) multiplied by 100. A 20-point difference is the equivalent of 4.8 months' advantage at 2 years of age (and two years' difference at 10 years of age).
The Bayley Scale will be administered by a qualified and validated independent clinical development specialist blinded to the treatment arm and performed at its own separate visit.

5.1.2 Secondary Outcomes

The secondary outcome measures are:

1. Developmental Measures:
    a. Motor quotient (MQ): Age equivalent motor score of the Bayley IV divided by corrected age at assessment, measured at 2 years' corrected age
    b. Language quotient (LQ): Age equivalent language score of the Bayley IV divided by corrected age at assessment, measured at 2 years' corrected age
2. Other neurological and functional assessments conducted during the 2-year follow-up visit:
    a. Presence of seizures during the first 2 years and use of anticonvulsant medication at 2 years.
    b. Presence of cerebral palsy (+ accompanying Gross Motor Function Classification System (GMFCS) grade and deficit distribution map using the Classification of SCPE
    c. Assessment of hearing and vision (British Association of Perinatal Medicine classification)
    d. Parent report:
        i. Brief Infant Toddler Social Emotional Assessment (BITSEA)
        ii. Quantitative Checklist for Autism in Toddlers (Q-CHAT)
3. Mortality up to 2 years corrected age.
4. NEL & VP shunt related outcomes:

a. Safety of NEL: Number of Adverse Events, where Adverse Events would include (and not limited to) secondary bleeding in the brain, post-operative infections, temporising device survival, mortality, stroke, seizures, electrolyte disturbances, CSF leak, unexpected readmissions or return to theatre.
b. Number and type of further surgical procedures, including revision of the temporising drainage device (VAD or VSG), addition of a second temporising device, surgery for loculated or isolated ventricles, and revisions of the VP shunt, if implanted, until two years' corrected age. These infants often need multiple shunt revisions during their first two years of life. We will have a separate CRF to record data related to these unexpected presentations and procedures.
c. Requirement for permanent VP shunt insertion at 6 months' corrected age. (This is at the discretion of the treating team in the participating centre, according to routine clinical care).

5. Quality of life and health economic assessments:
    a. Health-Related Quality of Life (HRQoL) in children: TNO-AZL Preschool Children's Quality of Life (TAPQOL) to be assessed at 12-months and 2 years' corrected age
    b. HRQoL in primary caregiver: EuroQoL EQ-5D-5L to be assessed at baseline, 6 months, 12 months- and 2 years' corrected age
    c. Healthcare resource use costs (CSRI (adapted) children version)[45] (via telephone assessment) at 3 -6-,12-, 18- months and 2 years' corrected age.
    d. Subsequent cost-effectiveness analysis & cost-benefit analysis of impact on carers based on responses to the EQ-5D-5L

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5.2 Participant Timeline

Table 1. ENLIVEN-UK Participant Schedule of Assessments

	Screening Visit[1]	Baseline Visit [3]	Surgery (t=0)	Post-Operative Follow Up (t=24-48h)	First Clinical Follow Up (t=term equivalent	VP Shunt Insertion (if required)	3-6 Months Clinical Follow Up Visit	Age 1 Year Clinical Follow Up	18 Month Follow Up 	2 Years corrected Age Clinical Follow Up [14]	Unscheduled Visit to Neuro-surgical Unit[15]
		Within 7 days prior to surgery (t=0)			+/- 1 month		+/- 2 months	+/- 2 months	+/- 2 months	+/- 2 months	
Informed consent	X										
Eligibility[2]	X	X									
Papile grade		X									
Birth Weight		X									
Cranial ultrasound[4]		X		X		X					
Haematology[5]		X		X							
Biochemistry[6]		X		X							
Coagulation/Clotting [7]		X		X							
Imaging History[17]		X									
Signs of raised ICP		X									
Randomisation			X								
Physical Examination[8]											X
Study Procedure (NEL+TD / TD alone)[11]			X								

	Screening Visit[1]	Baseline Visit [3]	Surgery (t=0)	Post-Operative Follow Up (t=24-48h)	First Clinical Follow Up (t=term equivalent	VP Shunt Insertion (if required)	3-6 Months Clinical Follow Up Visit	Age 1 Year Clinical Follow Up	18 Month Follow Up	2 Years corrected Age Clinical Follow Up [14]	Unscheduled Visit to Neuro-surgical Unit[15]
		Within 7 days prior to surgery (t=0)			+/- 1 month		+/- 2 months	+/- 2 months	+/- 2 months	+/- 2 months	
Discharge Information				X							
Head Circumference		X		X	X	X	X	X		X	X
Incidence of Seizures										X	
Wound Site Check				X	X					X	X
CSF sample collection (optional)[16]			X			X					X
Research Blood sample collection (optional)[16]			X			X					X
Clinical Assessment[12]		X		X	X	X	X	X		X	X
Shunt/Temporising Device Information				X	X	X	X	X		X	X
Adverse events Review			X	X	X	X	X	X	X	X	X
Concomitant Medication Review[13]			X	X	X					X	
MRI (as per Standard of Care)[4]					X						X
EuroQoL EQ-5D-5L[19]		X					X[18]	X		X	
Adapted CSRI (children version)							X	X	X	X	
TNO-AZL TAPQOL								X		X	
Bayley IV Scales[9]										X	

	Screening Visit[1]	Baseline Visit [3]	Surgery (t=0)	Post-Operative Follow Up (t=24-48h)	First Clinical Follow Up (t=term equivalent	VP Shunt Insertion (if required)	3-6 Months Clinical Follow Up Visit	Age 1 Year Clinical Follow Up	18 Month Follow Up	2 Years corrected Age Clinical Follow Up [14]	Unscheduled Visit to Neuro-surgical Unit[15]
		Within 7 days prior to surgery (t=0)			+/- 1 month		+/- 2 months	+/- 2 months	+/- 2 months	+/- 2 months	
Cerebral palsy assessment [9, 10]										X	
Vision and hearing assessment (BAPM classification)[9]										X	
Brief Infant Toddler Social Emotional Assessment (BITSEA)										X	
Quantitative Checklist for Autism in Toddlers (Q-CHAT)										X	

[1] *Screening and baseline visit can occur on the same day if the infant's parent/guardian(s) have been given time to reflect on the information in the PIS and following a discussion with a medically qualified investigator where they have and been given the opportunity to ask questions.*

[2] *Review inclusion and exclusion criteria and ensure eligibility prior to enrolment and randomisation.*

[3] *Baseline Visit assessments to confirm eligibility for trial should be performed within 7 days of Surgery (t=0). Baseline EuroQoL EQ-5D-5L Quality of Life questionnaire can be completed within 28 days prior to randomisation as it is not required to confirm eligibility.*

[4] *Investigators are required to submit images of Ultrasound scans for review and storage for all infants.*

Standard of care MRI scans may be submitted for review and storage for all infants where available and if performed as standard of care assessment ***only.***

Please see Imaging Transfer Guidelines for further details.

[5] *Haematology – including Haemoglobin, White Blood Cell Count, platelets as per routine standard of care*

[6] *Biochemistry – including Sodium, Potassium, as per routine standard of care*

[7] *Coagulation: including INR or APTT as per routine standard of care*
[8] *Physical Examination: Including heart rate, temperature, Glasgow Coma Score. Results of routine* ***Blood tests for Neutrophils Erythrocyte Sedimentation Rate and C-Reactive Protein should be collected if performed as part of routine care.***
[9] *Assessments will be performed by a qualified and validated independent clinical development specialist* ***blinded to the treatment arm.***
[10] *CP subtype (SCPE) & Gross Motor Function Classification System (GMFCS) grade will be assessed*
[11] *For Arm A (Intervention) patients, details of the NEL procedure will be recorded in addition to Temporising device information*
[12] *Clinical assessment – including weight, review of parental concerns*
[13] *Review of Concomitant medications for prophylactic antibiotics and anti-epileptic medications prescribed.*
[14] *See section 5.2.1 for details about the performing the 2-year clinical follow-up visit*
[15] *Unscheduled visits will be performed as deemed clinically necessary (i.e. all returns to the neurosurgical unit occurring in between scheduled visits until completion of 2-year follow-up)*
[16]*Research blood and CSF sample collection is optional. Please see Appendix 9 and the Laboratory Manual for further details.*
[17] *Imaging History: Previous Imaging scans performed (including Ultrasound, CT and MRI)*
[18] *Please ensure parent/guardian(s) are reminded to complete the EQ-5D-5L at 6-months. If the visit is scheduled earlier than 6 months, please ask parent/guardian(s) to take this questionnaire away for completion and return by post or at their next trial visit.*
[19] *Responses to the EQ-5D-5L must be reviewed during the visit to check for parent/guardian self-reported 'severe' or 'extreme' anxiety and depression. Parents/guardians reporting these symptoms should be signposted to access support from their healthcare provider e.g., their GP.*

5.2.1 2-years' corrected age Assessment

Table 2.

Visit Name:	2 Years corrected age Clinical Follow-up (+/- 2 MONTHS)	
Completed by:	Independent Blinded Assessor	Completed at Neurosurgical follow-up
Bayley IV Cognitive Quotient, Motor and Language Quotient	X	
Vision and hearing assessment (BAPM classification)	X	
Cerebral palsy assessment (SCPE & GMFCS)	X	
Clinical Assessment		X
Head Circumference		X
Incidence of seizure		X
Wound Site Check		X
Shunt/Temporising Device Information		X
Review of AEs, NAEs and SAEs		X
Concomitant Medication Review		X
EuroQoL EQ-5D-5L*		X
Adapted Client Service Receipt Inventory (CSRI children version)		X
TNO-AZL TAPQOL		X
Brief Infant Toddler Social Emotional Assessment (BITSEA)		X
Quantitative Checklist for Autism in Toddlers (Q-CHAT)		X

**Responses to the EQ-5D-5L must be reviewed during the visit to check for parent/guardian self-reported 'severe' or 'extreme' anxiety and depression. Parents/guardians reporting these symptoms should be signposted to access support from their healthcare provider e.g., their GP.*

5.3 Assessments during trial

5.3.1 Imaging: Ultrasound/MRI

- Investigators are required to submit images of Ultrasound scans (as listed below) for review and storage for all infants.
- *Standard of care MRI scans may be submitted for review and storage for all infants where available and if performed as standard of care assessment* ***only.***
- A copy of all ultrasound/MRIs will be kept at the participating unit and will also be sent to UCL where it will be uploaded to the Data Safe Haven (DSH). Images will be pseudonymised by sites, with participant's names and hospital/NHS numbers removed before transfer to UCL. Please see Imaging Transfer Guidelines for further details.

Ultrasound scans:

- At Baseline Visit: The baseline ultrasound scan will be used to confirm eligibility.
- At Post-Operative Follow-Up (t=24-48 hours)

  Arm A (Intervention) Post-operative cranial ultrasound: will be carried out within 48 hours of NEL. Post-NEL cranial ultrasound scans will be reviewed

regularly by the TMG at least quarterly, which may provide feedback to the participating centre on operative technique and radiographic outcome.
Arm B (Control) Post-operative cranial ultrasound: This should be carried out within 48 hours of temporising device insertion.

- At VP Shunt insertion (if required)

MRI Scans:
*Where available and when MRI scans are performed as part of standard of care assessment at the timepoints listed below **only**.* A copy should be kept at participating sites and sent to UCL for upload to the Data Safe Haven:

- At First Clinical Follow-Up (t=term equivalent +/- 1 month)
- At Unscheduled Visits to Neurosurgical Unit

Other MRI/Ultrasound/CT scans
If an infant undergoes any other MRI, CT, or Ultrasound scans as part of their standard of care in addition to those listed above and where available, these should also be sent to UCL. They will be uploaded to the Data Safe Haven (DSH).

5.3.2 Questionnaires

The infant's parent/guardian(s) should complete the EuroQoL EQ-5D-5L, TNO-AZL TAPQOL, Q-CHAT, BITSEA questionnaires at the timepoints listed below.
A telephone interview with the infant's parent/guardian(s) should be conducted by a member of the research team at site to complete the Adapted Client Service Receipt Inventory (CSRI children version) at 3 -6-,12-, 18- months' and 2 years' corrected age.

Table 3. Questionnaires completed by infant's parent/guardian(s)

	Baseline Visit	**3-6* Months Clinical Follow-Up Visit (+/-2 months)**	**Age 1 Year Clinical Follow-Up (+/- 2 months)**	**18 Months of Age (+/- 2 months) – (Telephone Follow-Up)**	**2 Years corrected Age Follow-Up (+/- 2 months)**
Adapted Client Service Receipt Inventory (CSRI children version) – (*Telephone Interview*)		X	X	X	X
Brief Infant Toddler Social Emotional Assessment (BITSEA)					X
Quantitative Checklist for Autism in Toddlers (Q-CHAT)					X
EuroQoL EQ-5D-5L¥	X	X*	X		X
TNO-AZL TAPQOL			X		X

Please ensure parent/guardian(s) are reminded to complete the EQ-5D-5L at **6-months. If the visit is scheduled earlier than 6 months, please ask parent/guardian(s) to take this questionnaire away for completion and return by post*

¥ *Responses to the EQ-5D-5L must be reviewed during the visit to check for parent/guardian self-reported 'severe' or 'extreme' anxiety and depression. Parents/guardians reporting these symptoms should be signposted to access support from their healthcare provider e.g., their GP.*

5.4 Participant Transfers

If a participant moves from the area, every effort should be made for them to be seen at another participating trial site. Access to participant's CRFs will be given to the new site and the parent/legal guardian(s) will need to sign a new consent form. Once this has been done, the new site will take over responsibility for the participant; until this has been completed, responsibility for the participant lies with the original site.

5.5 Early Stopping of Follow-up

Infant's parent/guardian(s) may withdraw from the trial intervention between time of consent and prior to surgery. After this point, the infant will have received the trial intervention or control (depending on the arm they were randomised to).
If a parent/legal guardian(s) chooses to discontinue their infant's participation in the trial, they should always be followed up they should continue to be followed up as closely as possible to the follow-up schedule defined in the protocol, providing they are willing. They should be encouraged and facilitated not to leave the whole trial. If they do not wish to remain on trial follow-up, however, their decision must be respected, and the participant will be withdrawn from the trial completely. The CCTU should be informed of this in writing using the appropriate documentation. Participants stopping early may have a negative impact on trial data integrity and the ability to reach the stated outcome measures. Every appropriate effort will be made by the investigators to encourage participants to agree to completion of the primary outcome assessment.

Data already collected during the infant's participation in the trial will be kept for analysis. Any optional consent e.g., future use of stored samples already collected can be refused when leaving the trial early (but this should follow a discussion).

Parent/legal guardian(s) may change their minds about stopping their infant's trial follow-up at any time and re-consent to participation in the trial.

Participants who cease post-randomisation trial follow-up early will not be replaced.

5.6 Loss to Follow-up

If a participant's parent/legal guardian(s) is no longer contactable and has missed at least one follow-up visit within the protocol defined visit window (please refer to Participant Timelines for specific follow-up visit windows), then site staff should attempt to contact the participant's parent/legal guardian(s) at least three times over three months before they are declared as lost to follow-up. Attempts should be made to contact the participant's parent/legal guardian(s) via two different methods of contact (i.e., telephone and letter). Site staff may identify and contact the participant's registered GP to obtain up to date contact information and may also contact their paediatrician at their local hospital and/or neonatal unit. A death form should be submitted if the site becomes aware that the patient has died.

5.7 Completion of Protocol Follow-Up

Participants will complete protocol follow-up upon completion of the final visit CRF for the 2-years' corrected age developmental assessment.

6 Safety reporting

The principles of GCP require that both investigators and Sponsors follow specific procedures when notifying and reporting adverse events or reactions in clinical trials. These procedures are described in this section of the protocol. **Section 6.1** lists definitions, **Section 6.3** gives details of the investigator responsibilities and provides information on CCTU responsibilities.

6.1 Definitions

Definitions of harm of the EU Directive 2001/20/EC Article 2 based on the principles of GCP apply to this trial.

Table 4: Definitions

Adverse Event (AE)	Any untoward medical occurrence in a study participant, which does not necessarily have a causal relationship with the study intervention (NEL).
Notifiable Adverse Event (NAE)	Any AE that: •is listed in section 6.2 (Notifiable Adverse Events) These events should be reported within 5 working days of site becoming aware.
Serious Adverse Event (SAE)	Any AE that: • results in death • is life threatening* • requires hospitalisation or prolongs existing hospitalisation** • results in persistent or significant disability or incapacity • is a congenital anomaly or birth defect • or is another important medical condition***
Foreseeable (Expected) SAE	Any AE that: • results in death • is life threatening* • requires hospitalisation or prolongs existing hospitalisation** • results in persistent or significant disability or incapacity • is a congenital anomaly or birth defect • or is another important medical condition*** **AND** •is listed in section 6.1.2 (Foreseeable Adverse Events) These events must be reported **within 5 days** of site becoming aware if there is **no causal relationship** to trial intervention (NEL) **These events must be reported within 24 hours of site becoming aware if causally related to trial intervention (NEL).**
Unforeseeable (unexpected) SAE	Any AE that: • results in death • is life threatening* • requires hospitalisation or prolongs existing

	hospitalisation** • results in persistent or significant disability or incapacity • is a congenital anomaly or birth defect • or is another important medical condition*** **AND** •is **not** listed in section 6.1.2 (Foreseeable Adverse Events) **These events must be reported within 24 hours of site becoming aware if causally related or unrelated to trial intervention (NEL).**

* The term life threatening here refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that might hypothetically cause death if it was more severe (e.g., a silent myocardial infarction)

** Hospitalisation is defined as an in-patient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisation for pre-existing conditions (including elective procedures that have not worsened) do not constitute an SAE. Hospitalisation for the trial procedure does not constitute an SAE. As infants will be remain in hospital following the trial procedures this specifically refers to additional or prolonged admissions to those expected as per standard of care.

*** Medical judgement should be exercised in deciding whether an AE is serious in other situations. The following should also be considered serious: important AEs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above (e.g., an allergic bronchospasm requiring intensive emergency treatment, seizures or blood dyscrasias that do not result in hospitalisation, or development of drug dependency).

6.1.1 Adverse Events

Adverse events include:

- an exacerbation (i.e., increase in the frequency or intensity) of a pre-existing illness, episodic event or symptom (initially recorded at the screening/baseline visit), that is detected after trial intervention
- occurrence of a new illness, episodic event or symptom, that is detected after trial intervention

Adverse events do NOT include:

- Medical or surgical procedures: the condition that leads to the procedure is the adverse event
- Pre-existing disease or a condition present before treatment that does not worsen
- Hospitalisation where no untoward or unintended response has occurred

Reporting of Adverse Events

The patient population includes preterm infants who are cared for on a neonatal intensive care for a prolonged period. Due to the nature of the patient population, a high incidence of adverse events can be foreseeable during their hospital stay. Only adverse events deemed as serious (see section 6.1.2) or as notifiable event (see section 6.2) will be recorded for the trial.

6.1.2 Serious Adverse Events

6.1.2.1 Foreseeable (expected) SAEs

The following are 'Foreseeable SAEs' that could be reasonably anticipated to occur in this population of infants during the course of the trial or form part of the outcome data.
They do not require expedited reporting by trial centres as SAEs **unless considered causally related** to the intervention (NEL) in which case they should be reported within 24 hours of site staff becoming aware of them as detailed in section 6.3.2.
'Foreseeable SAEs' that are **casually related** to the trial intervention (NEL) should be reported within 24 hours of site staff becoming aware of them using the SAE report form.
Foreseeable SAEs that are **not considered causally related** to the trial intervention (NEL) should be reported within 5 working days. Therefore, all Foreseeable SAEs occurring for patients in Arm B (Temporising device alone) will be not related to NEL and should be reported within 5 days.

Foreseeable SAEs:

- Necrotising enterocolitis or gastrointestinal perforation
- Intracranial abnormality (intraventricular haemorrhage or white matter damage) on cranial ultrasound scan or other imaging
- Seizures outside of 48 hours the procedure
- Pulmonary hypertension
- Hydrocephalus
- Respiratory distress syndrome
- Bronchopulmonary dysplasia or chronic lung disease
- Retinopathy of prematurity
- Early or late-onset Sepsis
- Patent ductus arteriosus (PDA)
- Pulmonary haemorrhage
- Pneumothorax
- Anaemia
- Hyperbilirubinaemia/jaundice
- Hypoglycaemia
- Hyperglycaemia
- Coagulopathy
- Liver cholestasis
- Liver failure
- Hypotension
- Hypertension
- Impaired renal function
- Extravasation injury
- Fractures
- Return to hospital for suspected or actual shunt malfunction or other neonatal condition unrelated to hydrocephalus after discharge from the neonatal unit, (unless readmission following initial discharge from hospital for grade 3 and above events)

6.1.2.2 'Unforeseeable SAEs' – (All SAEs not listed as 'Foreseeable SAEs')

All other SAEs occurring in trial participants which are not listed as Foreseeable SAEs in Section 6.1.2.1 are classed as unforeseeable SAEs and must be reported immediately after site staff become aware of the event (in no circumstances should this notification take longer than 24 hours) (see section 6.3).

6.2 Notifiable Adverse Events

The following adverse events should be reported within 5 working days using the Notifiable AE CRF:

1. New bleed identified on post-operative cranial ultrasound (CTCAE grade 2 and above)
2. Unexpected return to theatre for temporising device dysfunction, infection or CSF leak (CTCAE grade 3 and above). CSF infections will be monitored closely and reviewed at Trial Management Group meetings.
3. Return to theatre for insertion of an additional temporising device to treat loculated hydrocephalus (CTCAE grade 3 or above) or for a second endoscopic procedure to deloculate the ventricles
4. Confirmed or presumed infection associated with the trial procedure (grade 3 and above). This will include superficial (wound) and deep (CNS) infection. Confirmed infection will be where a micro-organism thought to be causative is isolated and presumed is when a micro-organism is not isolated, but the treating clinical team commences antibiotics. Of note, preterm infants may have many sources of infection and the **reporting here is confined to infection associated with the procedure (grade 3 and above).**
5. New development of seizures within 48 hours of the intervention (NEL) (grade 3 and above)
6. New development of focal neurological deficits within 48 hours of the intervention (NEL) (grade 3 and above)
7. Abandoned NEL procedure

Only non-serious AEs which constitute a notifiable event (listed above) should be reported to CCTU (via the trial database) within 5 working days.

6.3 Decision for withdrawal of all Medical Care

There may be a small number of cases where the decision is made to withdraw all medical care, resulting in participant death. If this occurs after the time of randomisation, an SAE report should be submitted immediately after site staff become aware of the event (in no circumstances should this notification take longer than 24 hours) (see section 6.3). All infant deaths will be reported to the IDMC promptly, as and when they are reported to CCTU, to review on a case-by-case basis

6.4 Investigator responsibilities

All non-serious AEs, whether expected or not, should be recorded in the patient's medical notes. Only non-serious AEs which constitute a notifiable event (listed in section 6.2) should be reported to CCTU (via the trial database) within 5 working days.

All Foreseeable SAEs that are **casually related** to the trial intervention (NEL) or trial procedures should be reported to CCTU immediately and no later than 24 hours after the site staff becomes aware of the event.

All Unforeseeable SAEs (regardless of causal relationship to trial intervention NEL or trial procedures) should be reported to CCTU immediately and no later than 24 hours after the site staff becomes aware of the event.

Please refer to Appendix II for Safety Reporting Flowchart.

6.4.1 Investigator Assessment

6.4.1.1 Seriousness

When an AE occurs, the investigator responsible for the care of the participant must first assess whether or not the event is serious using the definition given in Table 4. If the event is classified as 'serious' then an SAE form must be completed and CCTU notified immediately (within 24 hours) unless the event is listed in section 6.1.2.1 as a 'foreseeable

SAE' which is **not causally related** to the trial intervention (NEL) in which case, it should be reported within 5 working days.

6.4.1.2 Severity or Grading of Adverse Events

The severity of all AEs (serious and non-serious) in this trial should be graded using the gradings in the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (2017):

Grades for AEs according to the CTCAE are:

Grade 1: Mild; asymptomatic or mild symptoms; clinical diagnostic observations only; intervention not indicated.

Grade 2: Moderate; minimal, local or non-invasive intervention indicated.

Grade 3: Severe or medically significant but not life threatening; hospitalisation or prolongation of hospitalisation indicated; disabling.

Grade 4: Life threatening consequences; urgent intervention indicated.

Grade 5: Death related to AE.

6.4.1.3 Causality

The investigator must assess the causality of all serious events in relation to the intervention (NEL) using the definitions in Table 5.

Table 5: Causality Definitions

Relationship	Description
Unrelated	There is no evidence of any causal relationship
Related	There is clear evidence to suggest a causal relationship to the intervention and other possible contributing factors can be ruled out

6.4.1.4 Expectedness

If there is at least a possible involvement of the trial intervention (NEL), the sponsor will assess the expectedness of the event. If information of expectedness is provided by the investigator this should be taken into consideration by the sponsor. An unexpected adverse event is one not reported in Table 6 NEL Risks and mitigations (**Section 6.3.1.5**).

6..1.5 Risks associated with NEL

The risks associated with NEL for the ENLIVEN-UK trial are listed in Table 6 (NEL risks and mitigations) below:

Table 6. NEL risks and mitigations.

POTENTIAL RISK	RISK MANAGEMENT
Infection	Procedure in strict sterile conditions in operating theatre as per standard practice. Peri-operative antibiotics are given and the choice of agent and duration will vary according to local guidelines.
Secondary bleeding	There is a clear consensus on surgical protocol to ensure maximal safe washout without causing secondary bleeding in the ventricles or in the brain. The surgeon should stop when they feel they have achieved a 'maximal safe washout' as defined in the consensus guideline (28).
Stroke	Procedure-related brain injury risk has not been reported with NEL and therefore, the

	risk is low. It will be identified if it occurs on the post-operative ultrasound scan.
CSF leak	Standard closure techniques will be used to protect against CSF leak and, if it develops, will be managed at the discretion of the treating surgeon.
Seizures	Seizures (up to CTCAE Grade 3) can arise as a result of the initial IVH or procedure-related brain injury. These have been reported with NEL but the risk is low. If it occurs, it will be managed at the discretion of the treating medical team including neurosurgeon and neonatologist.
Temporising device dysfunction	The TD may stop working adequately due to either blockage, insufficient drainage or infection. At this stage, the clinical team will make an assessment as to whether it needs to be revised or whether a permanent ventriculoperitoneal shunt needs to be placed. This management will remain at the discretion of the treating neurosurgical team.
Electrolyte/Sodium imbalance	The use of irrigating solution may lead to disturbances in the serum level of sodium and other electrolytes. This will be mitigated by using appropriate irrigating solutions, such as Ringer Lactate or artificial CSF and by monitoring electrolyte levels in the serum as in routine post-operative practice in neonatal care.

6.4.2 Notifications

6.4.2.1 Notifications by the Investigator to CCTU

CCTU must be notified of all SAEs excepting those listed in 6.1.2.1 - unless considered **causally related** to the intervention immediately after site staff become aware of the event (in no circumstances should this notification take longer than 24 hours).

The Foreseeable (expected) SAEs listed in section 6.1.2.1 must be reported within 24 hours of site staff becoming aware of them **if they are considered causally related** to the trial intervention (NEL).

'Foreseeable SAEs' that are **not considered causally related** to the trial intervention (NEL) should be reported within 5 working days using the SAE report form.

All 'Unforeseeable SAEs' i.e., all other SAEs occurring in trial participants which are not detailed in Section 6.1.2.1 should be reported within 24 hours of site staff becoming aware of them using the SAE report form.

All Notifiable AEs (NAEs) listed in Section 6.2 should be reported within 5 working days using the Notifiable Adverse Events (NAE) CRF.

Investigators should notify CCTU of any SAEs and Notifiable Adverse Events (NAEs) occurring from the time of randomisation until 2-year hospital visit follow up. From this point forward the site will not actively monitor SAEs or NAEs.

The SAE form must be completed by the site staff named on the delegation log with this responsibility assigned by the PI. The form should be reviewed and signed off by the investigator (listed on the delegation log) who is responsible for the participant's care with

attention paid to the grading and causality of the event. The responsible investigator should check the SAE form at the earliest opportunity, make any changes necessary and sign. Systems should be in place at the site to enable the investigator to check the form for clinical accuracy as soon as possible.
The minimum criteria required for reporting an SAE are the primary event term, participant's trial specific PIN, date of birth, name of reporting investigator and sufficient information on the event to confirm seriousness. Any further information regarding the event that is unavailable at the time of the first report should be completed as soon as it becomes available.
Follow-up: Participants must be followed up until clinical recovery is complete, laboratory results have returned to normal or baseline values, or until the event has stabilised. Follow-up should continue after completion of 2-year trial follow-up if necessary. If there are ongoing SAEs at the study end this should be discussed with TMG. Follow-up SAE forms should be completed as further information becomes available. Additional information and/or copies of test results etc may be provided separately. The participant must be identified by trial specific PIN, date of birth and initials only. The participant's name should not be used on any correspondence and should be blacked out and replaced with trial identifiers on any test results.

SAE REPORTING (For all causally related Foreseeable and all Unforeseeable SAEs)
Within 24 hours of investigator becoming aware of an SAE:
The SAE must be entered on to the sponsor's central database and the trial team at CCTU notified at cctu.enlivenuk@ucl.ac.uk
.

6.4.2.2 UCL CCTU responsibilities
Clinical reviewer (Chief Investigator, or a medically qualified delegate) will review all SAE reports received. The causality assessment given by the local investigator at the hospital cannot be overruled; in the case of disagreement, both opinions will be provided in any subsequent reports.
The clinical reviewer will complete the assessment of expectedness using table 6 (NEL risks and mitigations) in **section 6.3.1.5.**
CCTU is undertaking the duties of trial sponsor and is responsible for the reporting of SAEs occurring to research participant where in the opinion of the clinical reviewer the event was related and unexpected, to the REC within 15 days of the sponsor becoming aware of the event.
CCTU will keep investigators and the IDMC informed of any safety issues that arise during the course of the trial.
In the UK, an Annual Progress Report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended.

6.4.2.3 Urgent Safety Measures
The CCTU or investigator may take appropriate urgent safety measures in order to protect research participants against any immediate hazard to their health or safety.
In the UK, if any urgent safety measures are taken the CCTU shall immediately (no later than 3 days from the date the measures are taken), give written notice to the REC of the measures taken and the circumstances giving rise to those measures, according to the relevant CCTU SOP.

6.5 Safety Monitoring

The Independent Data Monitoring Committee (IDMC) will review the study data and outcomes including SAEs. All infant deaths will be reported to the IDMC promptly, as and when they are reported to CCTU, to review on a case-by-case basis. The IDMC will ensure the safety and wellbeing of the trial participants and, if appropriate, make recommendations to the Trial Steering Committee (TSC) regarding continuance of the study or modification of the Protocol. The TSC will have ultimate responsibility for deciding whether the trial should be stopped on safety grounds.
CCTU will also provide safety information to the Trial Management Group on a periodic basis. Notifiable events including CSF infections will be monitored closely and reviewed at TMG meetings.
Trial Intervention (NEL) compliance:

Non-compliance with the intervention (NEL) is not anticipated but trial data will be reviewed on a monthly basis and post-operative ultrasound scans, will be reviewed at least quarterly by the TMG to evaluate any variability in the surgical procedures.
Where necessary, feedback will be given to the PI at the participating site regarding their operative technique and radiographic outcome. Any relevant issues will be discussed with the participating unit.

7 Quality Assurance & Control

7.1 Risk Assessment

The Quality Assurance (QA) and Quality Control (QC) considerations for the ENLIVEN-UK trial are based on the standard CCTU Quality Management Policy that includes a formal Risk Assessment, and that acknowledges the risks associated with the conduct of the trial and proposals of how to mitigate them through appropriate QA and QC processes. Risks are defined in terms of their impact on the rights and safety of participants; project concept including trial design, reliability of results and institutional risk; project management; benefit risk of the trial (see section 1.4); and other considerations.
QA is defined as all the planned and systematic actions established to ensure the trial is performed and data generated, documented and/or recorded and reported in compliance with the principles of GCP and applicable regulatory requirements. QC includes the operational techniques and activities performed within the QA system to verify that the requirements for quality of the trial related activities are fulfilled.
The ENLIVEN-UK Risk Assessment has been reviewed by the CCTU's Quality Management Group (QMG).

7.2 Central Monitoring at CCTU

CCTU staff will review data and other information provided by investigators to identify trends, outliers, anomalies, protocol deviations and inconsistencies. The frequency and type of central monitoring will be detailed in the ENLIVEN-UK Quality Management and Monitoring Plan (QMMP).

7.3 Monitoring

The frequency, type and intensity of routine on-site monitoring and the requirements for triggered on-site monitoring will be detailed in the ENLIVEN-UK QMMP, including any provision for remote or self-monitoring. The QMMP will detail the procedures for review and sign-off of monitoring reports. In the event of a request for a trial site inspection by any regulatory authority UCL CCTU must be notified as soon as possible.

7.3.1 Direct access to Participant Records

Participating investigators must agree to allow trial-related monitoring, including audits, EC review and regulatory inspections, by providing access to source data and other documents as required. Participant consent for this must be obtained as part of the informed consent process for the trial.

7.3.2 Confidentiality

CCTU plan to follow the principles of the UK DPA regardless of the countries where the trial is being conducted.

Participant's data will be collected and kept securely. Confidentiality of participant's personal data is ensured by not collecting participant names and other personally identifiable information on CRFs and receiving only pseudonymised data. At the time of consent, participants will be allocated a Participant Identification Number (PIN), which will be used on all trial related paperwork sent to UCL CCTU and in the trial database.

Any documents (e.g., screening and enrolment logs) linking trial specific PIN to participant's personally identifiable information will be kept securely at site; only redacted copies will be sent to Sponsor if requested.

Copies of participant's trial data will be kept at the participating site in a secure location with restricted access. Unless working at a site, CCTU staff will only have access to the data collected on the trial CRFs (i.e., they will not have access to any other personal data) and applicable source data, moreover only staff working on the trial will have access to these data. Data stored electronically are held on secure servers, that have restricted access.

The informed consent form will carry the participant's name and an appropriate signature; these will be retained at the trial site (participant's hospital). The consent forms will only be accessed by UCL CCTU staff for purposes of monitoring the consent procedure at the site.

Trial-specific samples will be labelled 'ENLIVEN-UK', with the trial specific participant PIN, visit name and date of birth.

7.4 Source Data

The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial participants. Source data are contained in source documents and are defined by EU guidelines as all information in original records that are used for the reconstruction and evaluation of the clinical trial. Source documents are the first place where the source data are recorded. These can include hospital records, clinical and office charts, surgical and laboratory notes, scans and source data worksheets.

Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail). Each data element should only have one source.

For this trial the CRFs/eCRFs will not be the source document for any data elements.

The following data should all be verifiable from source documents, which may include paper notes and electronic health records:

- signed consent forms
- dates of visits including dates any trial specimens were taken and processed in the laboratory
- eligibility and baseline values
- adverse events of any grade that lead to treatment modification and adverse events judged as related to the intervention
- Serious adverse events – Foreseeable SAEs, Unforeseeable SAEs and Notifiable AEs (please refer to section 6.1 for definitions)
- Ultrasound and MRI scans*
- Bayley Scales of Infant and Toddler Development (4th edition) (Bayley IV)

- Adapted Client Service Report Inventory (CSRI) Children version
- Quantitative Checklist for Autism in Toddlers (Q-CHAT)
- Brief Infant Toddler Social Emotional Assessment (BITSEA)
- TNO-AZL TAPQOL Preschool Children's Quality of Life Questionnaire
- EuroQoL EQ-5D-5L Questionnaire

*Ultrasound and MRI scans will be transferred to University College London (UCL) and then uploaded to the Data Safe Haven facility at UCL. Please refer to the Imaging Transfer Guidelines for further details.

Paper CRFs (pCRFs) will be provided to the site to be used as a back-up for instances when the EDC is unavailable (e.g., system updates, build maintenance, system failures). pCRFs will be provided to sites and should only be used as a temporary measure until the EDC is restored.

A Source Data Agreement will be put in place as part of the site activation process with each site. This will define the source documents and the data therein, together with location of these source documents and any applicable plans for transmission of source data between the site and CCTU.

7.5 Data Collection and Transfer Methods

Data collected will need to be directly entered by the research team at the local hospital onto the Sponsor's central database (eCRFs). Data collected by the blinded independent clinical development specialist will be directly entered onto the Sponsor's central database (eCRFs). Blinded independent clinical specialists will be given restricted access to the central database in order to prevent unblinding.

Imaging scans (MRI, CT and ultrasounds) will be transferred by sites to University College London (UCL) where they will be uploaded to the Data Safe Haven portal. Please refer to the trial specific SOP for details.

Training on data collection, secure data transfer and storage for site staff listed on the delegation of responsibilities log will be provided at the site initiation meeting(s).

7.6 Data Management

Data will be collected at the time-points indicated in the Participant Timeline (Section 5.2). Data will be entered under each participant's assigned trial specific PIN onto the central database. The database software provides a number of features to help maintain data quality, including maintaining an audit trail, allowing custom validations on data, allowing users to raise data query requests, and search facilities to identify validation failure and missing data.

Data collection, data entry, queries raised by a member of the ENLIVEN-UK trial team and database lock(s) will be conducted in line with the CCTU SOPs and trial-specific Data Management Plan.

The database will be password protected and only accessible to members of the ENLIVEN-UK trial team at CCTU, delegated site staff and external regulators if requested. Database users will only be granted permissions to use the database functionality appropriate to their role in the clinical trial.

Identification logs, screening logs and enrolment logs will be completed and held at the trial site.

7.6.2 Handling of imaging data

Ultrasound and MRI scans will be performed at the timepoints indicated in Section 5.3.1. Investigators are required to submit images of Ultrasound and standard of care MRI and CT scans for review and storage for all infants. Once ultrasound scans are performed the images will be transferred to UCL for secondary outcome analysis. Images will be pseudonymised by sites, with participant's names and hospital/NHS numbers removed.
A quality control (QC) check will be performed at UCL to ensure that all identifiable data has been redacted before the scan images are transferred using a secure method to the dedicated project area in UCL Data Safe Haven Pseudonymised images will be stored in a dedicated project area on the UCL Data Safe Haven.

All data will be handled in accordance with the Data Protection Act 2018, the EU General Data Protection Regulation (GDPR) 2016 (and subsequent updates and amendments).

7.7 Data Storage

Trial data will be stored in a database created specifically for the ENLIVEN-UK trial.
The database is hosted by OpenClinica. The data are stored on secure, GDPR-compliant, cloud-based servers held within UK and EU: https://www.openclinica.com/privacy-policy/

The randomisation service is hosted by Sealed Envelope LTD. The data are stored on a secure, GDPR-compliant, cloud-based servers held within the EU: https://www.sealedenvelope.com/security/

The identification, screening and enrolment logs, linking personally identifiable information to the participant's trial specific PIN, will be held locally by the trial site. This will either be held in written form in a locked filing cabinet or electronically in password protected form on hospital computers. After completion of the trial the identification, screening and enrolment logs will be stored securely by the sites for 15 years after trial closure unless otherwise advised by CCTU.

7.8 Data Archiving

Once all primary and secondary analysis has been completed the trial data will be archived. Once the trial data has been archived the trial database will be decommissioned and will no longer be available. Any subsequent/further analysis will be performed using the archived data.

7.9 Quality Issues

Quality Issues are issues that can have an impact on patient safety, rights, and well-being; data integrity and/or scientific rigor; and compliance with regulatory requirements; these can be classified as protocol deviations, potential serious breaches, near misses etc.

A protocol deviation is any departure from procedures documented in this protocol, this includes deviations that cannot be predicted. If a protocol deviation is identified, the Trials team should be contacted and CCTU's protocol deviation reporting process will be followed.

A 'serious breach' is a deviation from procedures documented in this protocol, GCP or other clinical trial regulations that is likely to affect to a significant degree:

1. The safety or physical or mental integrity of the participants in the trial, or
2. The scientific value of the trial.

If a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the CI, the serious breach will be reviewed by the Sponsor and, if

appropriate, the Sponsor will report it to the REC committee within 7 days of classification of a serious breach.

8 Statistical Considerations

8.1 Sample Size

The sample size required for the ENLIVEN-UK trial utilised individual patient data from the DRIFT trial, which showed that the distribution of cognitive quotient (CQ) in the 'standard treatment' arm at 2 years' corrected age was approximately uniform in the 0—100 interval with a median of approximately 50 (Figure 2a) (19). The distribution in the DRIFT arm was more skewed, with a median of approximately 70 (Figure 2a) (19). This was evident at 10 years, with a median difference of 25.6 (46.7 in the control arm vs 72.3 in the DRIFT arm) (13). We hypothesise that, mechanistically, NEL would achieve the same effect as DRIFT. We therefore estimate a median difference of 20 points between our treatment arms. A difference of 20 points is considered clinically significant, representing approximately a 5-month difference in developmental age at 2 years and a 2-year difference at 10 years. That this was also considered a significant and valuable difference to parents, as confirmed by a focus group led by our parent co-applicant Galland.

To reflect results shown in DRIFT, the distribution of CQ in the control arm was modelled using a Beta(1,1) distribution, equivalent to the uniform distribution. The distribution in the experimental arm was modelled to be a Beta(10, 4.25). Both distributions were multiplied by 100 to reflect the 0—100 CQ scale (Figure 2b). Using simulations performed in R with 1000 replications, we established that 45 patients in each arm, totalling 90 patients, would provide 90% power to detect the hypothesised treatment effect, based on a Wilcoxon-test with two-sided alpha of 5%. To account for a 10% loss to follow-up and other methodological challenges during the study, we aim to recruit 100 patients in this study, 50 in each arm.

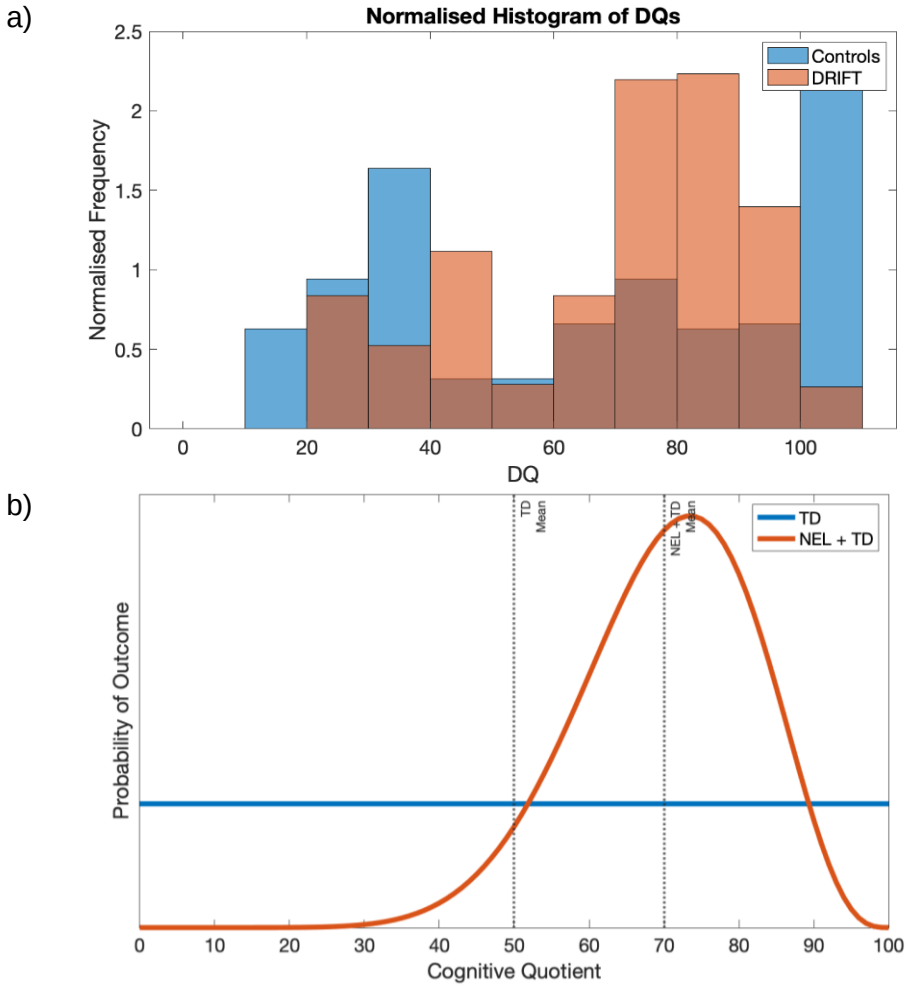

Figure 2: (a) Developmental quotient (old name for cognitive quotient on Bayley II) distributions in control (TD) and intervention (DRIFT) arms of the DRIFT trial. (b) Estimated distributions of cognitive quotient scores at 2 years in the control (TD) and intervention (NEL + TD) arms of the ENLIVEN-UK Study.

8.2 Assignment of Intervention

8.2.1 Randomisation Procedures

Following the Screening visit, the PI or delegate will enter the initials, gestational age at birth, sex, grade of IVH, site, re-confirm participant eligibility on the SealedEnvelope.com secure online system and allocate the appropriate trial specific PIN to the patient. Delegated staff at participating sites will be provided with a secure login to the SealedEnvelope.com website, according to their role in the trial. The randomisation result will be shown directly online as an arm allocation to the user in additon to an email, with an unblinded email confirmation of a successful randomisation sent to the CCTU trial team. Randomisation will be considered completed after intervention allocation has been assigned by the randomisation system.

8.2.2 Randomisation Methodology and Sequence Generation

A computer-generated randomisation sequence, using the SealedEnvelope.com system, will be used to assign the participants to one of the two treatment arms using a 1:1 ratio. The adaptive minimisation approach will be the treatment allocation methodology used to allocate treatment arms; while not allocating at random will be referred to as a 'randomisation method' here in ENLIVEN-UK. As per ICH E9 guidelines this will incorporate a random element into

each treatment allocation to avoid this approach being deterministic. This procedure will use a 'biased coin' approach where it will favour balance of arms with a high (80%) chance. The factors minimised on will not be provided here to reduce the chance of bias, but will be listed in the standalone Statistical Analysis Plan (SAP).

8.2.3 Allocation concealment mechanism and Blinding

This is a trial in which the primary outcome assessor, the Trial Statistician and the Clinical Project Manager will be blinded to the treatment allocation. The treating neurosurgeon and associated team cannot be blinded to treatment allocation due to nature of the study. Parents/legal guardians will be informed of the allocation after the procedure is completed. Parents will be informed by study team prior to the assessment that the assessor will be blinded to the treatment allocation, and they should therefore not divulge this information to the assessor inadvertently, which will be reinforced by the assessor before evaluation commences. All users of the Sealed Envelope system, with the exception of the Trial Statistician and the Clinical Project Manager, will be unblinded to treatment allocation via email and with the treatment allocated accessible through a secure portal, prior to the procedure being performed.

Given the study design, the treating neurosurgeon and associated research team cannot be blinded to treatment allocation. The increased operating time will also result in the Neonatal Intensive Care Unit (NICU) team being aware of the treatment arm. Previous Patient Advisory Group (PAG) work has identified that parents would like to be informed of the allocation and, failing to do so may result in many parents not taking part.

However, the primary outcome measure and other components of the Bayley IV developmental outcomes at 2 years' corrected age will be carried out by assessors blind to the treatment allocation.

8.2.5 Allocation Implementation

Following confirmation of participant eligibility, eligible participants will be randomised at the 'Surgery (t=0)' visit by a clinical investigator or delegated member of the research team using the Sealed Envelope web-based service.

The responsibility for enrolling and performing the allocated surgical intervention (as per the procedures outlined in Section 4) for the participant lies with the PI at each recruiting participating site, however this can also be undertaken by other delegated clinicians who have been delegated the task and which has been recorded on the ENLIVEN-UK Delegation Log. Secure login usernames and passwords for Sealed Envelope will be provided to delegated staff prior to site activation and/or as required. A complete list of users can be obtained from UCL CCTU.

The users will be required to log in and answer eligibility questions before entering minimisation data and being permitted to randomise a participant. The randomisation result will be shown directly online, with an email confirmation to the user.

8.3 Statistical Considerations

8.3.1 Statistical Analysis Plan

This section should be considered as version 0.1 of the statistical analysis plan (SAP). Further detail will be provided in a standalone SAP document, written by the trial statistician and approved by the TMG and Data Monitoring Committee (DMC) prior to any substantial analysis of the data.

The SAP will be pre-specified and will be stored within the electronic Statistics Master File (SMF) in an access-protected network drive. It will contain the following sections:

I. Introduction
II. Study Methods
III. Statistical Principles
IV. Trial Population
V. Analysis of Primary and Secondary Outcomes (including statistical models and method of dealing with missingness)

8.3.2 Summary of baseline data and flow of participants

A CONSORT diagram will be produced to report the flow of participants in the study.
Summaries of baseline characteristics, by trial arm, will be presented using frequency and percentage for categorical variables, and for continuous variables by mean and standard deviation (or median and inter-quartile range for non-normally distributed data).
The results of the analyses will be reported following the principle of the ICH E3 guidelines on the Structure and Content of Clinical Study Reports (30). The pilot/feasibility stage will take guidance from the dedicated CONSORT extension for trials of that type (31).

8.3.3 Interim Analyses

No formal interim analyses are currently planned beyond regularly scheduled Independent Data Monitoring Committee (IDMC) meetings and an internal pilot study focussed on recruitment and adherence. The IDMC has responsibility for safeguarding the interests of trial participants and advises the Trial Steering Committee (TSC). This is done by providing the IDMC with reports on safety and efficacy to assess benefit/risk ratio on trial conduct to ensure that the study can achieve its goals. The IDMC and its delegates will have unrestricted access to unblinded data and will direct the unblinded statistician to facilitate reports as they require.

8.3.4 Internal Pilot

An internal pilot study will be conducted over the first 12 months of recruitment, beginning when the first centre opens. This pilot study will have specific aims of assessing recruitment feasibility, barriers to recruitment and protocol adherence with clear ‘traffic light’ progression criteria (Table 7). The progress of the trial will be reviewed by the TSC and Funder against the traffic light progression criteria. However, the Funder will be central to decision-making at the end of the pilot phase under all scenarios described below:

- Red: No progression to substantive phase
- Amber: A 'Recovery Plan' will be drafted in consultation with the TSC and the IDMC, ahead of consultation with the Funder over the terms of progression (or not) to the main phase of the study
- Green: Only a 'green' outcome would automatically qualify for automatic 'progression without change’.

An IDMC meeting will also be scheduled prior to progression past the pilot to ensure there are no safety concerns.

Table 7. Red/Amber/Green progression criteria for 12-month internal pilot study

	Red No progression to substantive phase	**Amber** A 'Recovery Plan' will be drafted over the terms of progression (or not) to the main phase of the study	**Green** Automatic progression to substantive phase
Total sites opened	<5	5 to 7	8+

Patients screened per site per 6 months open	<1	1 to <2	2+
Patients recruited per site per 6 months open	<0.3	0.3 to <1	1+
Total patients recruited	10	11 to 19	20+
Adherence to randomised arm	<70%	70 to 90%	>90%

In addition, specific barriers to recruitment will be assessed:

- Screening logs will be scrutinised to assess whether eligible patients have been missed or not approached by study teams and structured questionnaires will be conducted with the PI and Associate PI at each site to identify any reasons or barriers. Parents who decline participation will be asked to volunteer the reason for not taking part.

Any modifiable barriers (e.g., nature of approach, information sheets) will be addressed prior to commencement of the substantive phase of the trial.

8.3.5 Statistical Methods – Primary Outcome

As described in the sample size section the primary outcome measure will be the cognitive quotient (CQ) scale rescaled to range from 0—100. The outcome measure will be assessed at the infant's 2 years corrected age timepoint only and we anticipate that the shapes of the two response distributions will differ. As this continuous outcome scale is not normally distributed and the sample sizes are of moderate size the non-parametric Mann Whitney U test will be used to compare the two independent arms. This will test the alternative hypothesis that responses in the two arms are not equal. This test will be performed two-sided and at a 5% alpha level. The test statistic for the Mann Whitney U Test is denoted by U and is derived using the sums of the ranks within arms of responses in both groups. U_1 (NEL with Temporising Device) and U_2 (Temporising Device Alone) will then be compared. An exact p-value will be calculated rather than a normal approximation. The effect measure will be the median difference in rescaled CQ score along with a 95% Confidence Interval. Sensitivity analyses will be performed adjusting for the minimisation factors to assess the robustness of the primary analysis, and separately the bootstrap means will also be calculated and compared between randomised groups.

8.3.6 Analysis Population and Missing Data

It is only possible to include those randomised infants with 2 year response data in the primary analysis. This is effectively what is termed a 'complete case analysis'. Naturally, it is key that missing data, for the Bayley-IV questionnaire in particular, at the two year timepoint is kept to the absolute minimum due to its potential to undermine the primary conclusions to be drawn from the trial. Multiple Imputation of missing values is possible, though consideration will need to be taken as to the volume and mechanism behind the missing data and its consequent effect on the interpretation of the outcome measure. This will be expanded upon further using the estimand framework in further iterations of the SAP. All infants randomised to one of the two arms will be included in other analyses where possible, irrespective of the successful completion of the procedure as intended – following the Intention to Treatment principle and analysis set. Any infants withdrawn after consenting, but prior to randomisation and surgery, will be summarised clearly and openly separately. Exploratory analyses may be produced using only those that adhered to the protocol as intended (Per Protocol) should the analysis aid interpretation.

8.3.7 Additional Analyses – Secondary

The secondary outcome measures are listed in Section 5.1.2. All measures will be analysed using methods appropriate to their data structure. As a general principle summary statistics

for continuous variables used will be mean, median, SD, lower quartile, upper quartile and reported appropriately according to distribution. Summary statistics for binary and categorical variables will be n (%).
Notable analysis points:

- Motor quotient and Language quotient will use the same approach as the primary outcome measure.
- Mortality up to 2 years will be analysed using survival analysis techniques – the Log-Rank test will be used to test for a difference and non-proportional hazards will be assessed to decide the most appropriate modelling technique, displayed using a Kaplan-Meier plot.
- Graphical representations of the harm profile will be guided by the Phillips et al. Publication (32)

8.3.8 Additional Analyses – Subgroup

Supplemental, exploratory subgroup analyses will be considered for gestational age at birth, sex, grade of IVH and site dependent upon infant numbers within each category.

9 Economic Evaluations

9.1 Health Economic Analysis Plan

A Health Economics Analysis Plan (HEAP) will be developed before accessing unblinded data. The purpose of the HEAP will be to set out in detail the analysis and reporting procedure intended for the economic analyses to be undertaken in the trial. The HEAP will also describe the circumstances under which amendments are permitted and the documentation of such changes; any deviations will be justified in the final report. The HEAP will be designed to ensure that there is no conflict with the protocol and the statistical analysis plan (SAP).

9.2 Within-trial analysis

An economic evaluation will be conducted over the trial period with a primary analysis from the NHS and personal social services (PSS) perspective and a secondary analysis from the societal perspective that will include the impact on quality of life and productivity of parents/carers contributing to the infant's care. Discount rate of 3.5% currently recommended for health technology appraisal in the UK (33) will be applied to costs and health effects accruing beyond the first year. The overall economic evaluation will comprise:

1. **Cost-Effectiveness Analysis:** mean incremental costs and incremental effectiveness of NEL + temporising device compared with temporising device alone. Incremental costs will be measured from the NHS and PSS perspective. Incremental effectiveness will be estimated as the difference in cognitive disability at 2 years' corrected age. Data on delivery of the NEL intervention (e.g., staff time, consumables) will be collected to calculate the cost of the intervention using micro-costing methods (34). Additional healthcare resource use such as days in hospital, number of planned and emergency admissions will be collected at 3-6, 12, 18 months and 2 years' corrected age through purpose designed parent-completed questionnaires (telephone assessment). Unit costs will be obtained from most recent published sources (35,36). Incremental cost-effectiveness ratios will be reported, and uncertainty explored using cost-effectiveness acceptability curves (37,38)

2. **Health-Related Quality of Life (HRQoL):** measuring the overall impact of a health condition requires preference-based methods. Efforts to evaluate HRQoL and calculate quality-adjusted life years (QALYs) for infants less than 12 months of age are restricted by the lack of preference-based HRQoL instruments for this group (39,40). Because of methodological concerns surrounding the use of preference-based

measurement in early childhood, the QALY metric will not be used. However, we will assess the HRQoL (at 1 year and 2 years' corrected age) using the TAPQOL (TNO-AZL Preschool Children's Quality of Life) a reliable and valid instrument for measuring parent's perceptions HRQoL for children aged between 1 and 5 years (41).

3. **Cost-Benefit Analysis of the Impact on the Parents/Carers**: Responses to EQ-5D-5L and the associated algorithm mapping the 5L descriptive system data onto the 3L valuation set, as recommended by NICE, will be used to calculate QALYs in a standard format and valued as a willingness-to-pay (WTP) for a QALY gained (42,43). Information on productivity losses will be collected and costed using the human capital approach (44). As caring responsibilities of parents/carers are complementary to state funded caring, we shall also calculate the societal value of caring provided by parents/carers.

10 Regulatory & Ethical Issues

10.1 Compliance

10.1.1 Regulatory Compliance

This trial will adhere to the principles and conditions of Good Clinical Practice.
In conducting the trial, the Sponsor, UCL CCTU and sites shall comply with the protocol and with all relevant guidance, laws and statutes, as amended, applicable to the performance of clinical trials and research including, but not limited to:

- UK Policy Framework for Health and Social Care Research, issued by the Health Research Authority
- Declaration of Helsinki 1996
- Data Protection Act 2018 (DPA number: Z6364106),
- General Data Protection Regulation (EU)2016/679 (GDPR)
- Human Tissue (Quality and Safety for Human Application) Regulations 2007
- EU Tissue and Cells Directives 2004/23/EC, 2006/17/EC and 2006/86/EC

10.1.2 Site Compliance

Agreements that include detailed roles and responsibilities will be in place between participating sites and CCTU.
Participating sites will inform CCTU as soon as they are aware of a possible serious breach of compliance, so that CCTU can fulfil its requirement to report the breach if necessary (see section 7.9).

10.1.3 Data Collection & Retention

Clinical notes and administrative documentation should be kept in a secure location (for example, locked filing cabinets in a room with restricted access) and held for a minimum of 15 years after the end of the trial. During this period, all data should be accessible, with suitable notice, to the competent authorities, the Sponsor, and other relevant parties in accordance with the applicable regulations. The data may be subject to an audit by the competent authorities. Medical files of trial participants should be retained in accordance with the maximum period of time permitted by the hospital, institution or private practice.

10.2 Ethical Approvals

10.2.1 Ethical Considerations

The trial has been designed to mirror standard clinical care, and only a few aspects of the trial are in addition to this. These aspects include the quality of life and assessments of health resources which will be carried out at 3-6, 12, 18 months and 2 years' corrected age. The final assessment at two years of age also mirrors the standard developmental and cognitive assessment that is routinely carried out in the UK at this time.

As this is a randomised trial, parents will not be able to choose the treatment their child will receive after they give consent to inclusion in the trial. This will be explained in detail at the point of recruitment. The clinical equipoise of both arms and the rationale for the trial will also be explained. Parents will be informed which arm their child is randomised to after the procedure.

We do not envisage any additional risks to participation in the trial, except in relation to the potential surgical complications detailed in section 4.2.1.

A summary of the results from the trial, as published in the medical literature, will be made available in lay language to the participants if requested.

10.2.2 Ethics Committee Approval

Following main REC approval and Health Research Authority (in England) approvals and before initiation of the trial at each clinical site, the local information pack will be submitted to each Trust's Research and Development (R&D) office by UCL CCTU. The local information pack will contain the protocol, all informed consent forms, and information materials to be given to the prospective participant, the Clinial Trial Site Agreement, the Organisation Information Document (OID), and the validated Schedule of Events Cost Attribution Template (SoECAT). In Wales and Scotland, the R&D office will be asked to give approval. In England, the R&D office will be asked to confirm capacity and capability. Any further substantial amendments will be submitted and approved by the main REC and HRA.

The rights of the participant's parent/legal guardian(s) to refuse to their child to participate in the trial without giving a reason must be respected. After the participant has entered the trial, the clinician must remain free to give alternative treatment to that specified in the protocol, at any stage, if s/he feels it to be in the best interest of the participant. The reasons for doing so, however, must be recorded; the participant will remain within the trial for the purpose of follow-up and data analysis according to the treatment option to which they have been allocated. Similarly, the participant's parent/legal guardian(s) must remain free to change their mind at any time about the protocol treatment and trial follow-up without giving a reason and without prejudicing their further treatment.

10.3 Competent Authority Approvals

This is not a Clinical Trial of an Investigational Medicinal Product (IMP) as defined by The Medicines for Human Use (Clinical Trials) Regulations 2004/1031 for UK only. Therefore, a Clinical Trial Authorisation (CTA) is not required in the UK.

10.4 Other Approvals

The protocol will be submitted by those delegated to do so to the relevant R&D department of each participating site or to other local departments for approval as required in each country. A copy of the local permissions (or other relevant approval as above) and of the Participant Information Sheet (PIS) and consent form on local headed paper must be forwarded to the CCTU before participants are entered.

10.5 Trial Closure

Trial closure is defined as the date when all data have been received, cleaned and all data queries resolved at all sites and the database locked for primary analysis.

The REC/HRA will be notified within 90 days of trial completion. Within one year of the end of the trial, the CCTU will submit a final trial report with the results of the trial, including any publications/abstracts of the trial, to the HRA. In case the trial is ended prematurely, the CCTU will notify the HRA within 15 days, including the reasons for the premature termination.

11 Indemnity

UCL holds insurance to cover participants for injury caused by their participation in the clinical trial. The parent/legal guardian(s) of the participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant in the clinical trial. UCL does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or not. This does not affect the participant's right to seek compensation via the non-negligence route.

The parent/legal guardian(s) of the participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of UCL or another party. The parent/legal guardian(s) of the participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to UCL's insurers, via the Sponsor's office.

Hospitals selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to UCL, upon request.

12 Finance

This trial is funded by the NIHR HTA Programme (Project reference NIHR151288). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care. External funding for future ethically approved projects using the samples/data will be sought. Data Sharing Agreements will be put in place prior to transfer of data.

13 Oversight & Trial Committees

Trial oversight is intended to preserve the integrity of the trial by independently verifying a variety of processes and prompting corrective action where necessary.
There are number of committees involved with the oversight of the trial. These committees are detailed below, and the relationship between them expressed in the figure.

13.1 Trial Management Group

A Trial Management Group (TMG) will be formed comprising the Chief Investigator, other lead investigators (clinical and non-clinical) and CCTU staff and PPI contributors. The TMG will be responsible for the design, coordination and strategic management of the trial. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TMG Terms of Reference.

13.2 Trial Steering Committee

The Trial Steering Committee (TSC) is the independent group responsible for oversight of the trial in order to safeguard the interests of trial participants The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chair. The ultimate decision for the continuation of the trial lies with the TSC. The membership, frequency of meetings, activity and authority will be covered in the TSC Terms of Reference.

13.3 Independent Data Monitoring Committee

The Independent Data Monitoring Committee (IDMC) is the only oversight body that has access to the confidential, accumulating data for the trial. The IDMC is responsible for safeguarding the interests of trial participants, monitoring the accumulating data and making recommendations to the TSC on whether the trial should continue as planned. The membership, frequency of meetings, activity and authority will be covered in the IDMC Terms of Reference. The IDMC will advise the TSC through its Chair.

13.4 Trial Sponsor

The role of the sponsor is to take on responsibility for securing the arrangements to initiate, manage and finance the trial. UCL is the trial sponsor and has delegated the duties as sponsor to CCTU via a signed letter of delegation.

14 Patient & Public Involvement

Patient and Public Involvement (PPI) in research is defined by INVOLVE (an advisory group established by the NIHR) as research being carried out 'with' or 'by' members of the public rather than 'to', 'about' or 'for' them. INVOLVE intends 'public' to include patients, potential patients, carers and other users of health and social care services, as well as people from organisations that represent people who use services. In some cases, this may include involvement of the parent/legal guardian(s) of trial participants in guidance or oversight of the trial.

14.1 Potential Impact of PPI

PPI will help with the trial design and be able to provide parent/legal guardian perspectives and promote the trial. PPI will review the participant information sheet to ensure it has been written in lay terms for the understanding of the parent/legal guardian(s) infant enrolling in this trial. With the PPI involvement in this trial, it is hoped that recruitment strategies will be optimised to aid in reaching recruitment targets. PPI will help with the dissemination of trial results and feedback to participants parents/legal guardians and the public.

14.2 Identifying PPI Contributors

A Participant Advisory Group (PAG) will be set-up for the trial and will include a PPI lead. Terms of Reference for the PAG will be created. Training for PPI members will be provided where required and courses identified as helpful. PPI members will be reasonably reimbursed for their time and travel.

14.3 Protocol Design & Trial Set Up

PPI representatives have been involved in the trial design since the funding application stage, and one of the co-applicants is a parent with lived experience. PPI work has identified that parents would like to be informed of the intervention allocation and, failing to do so may result in many parent/legal guardians not taking part.

The PPI group has contributed throughout the study development by aiding in the design of the trial and by advising on the appropriateness of any parent/guardian- facing documentation.

14.4 PPI in the Ongoing Running of the Trial

The PPI lead will chair the PAG, and this group will meet at regular intervals throughout the trial duration. The PAG will evaluate feedback on recruitment and retention of participants. The PPI lead will be a member of the TMG and will report back to the TMG any outcomes of the PAG meetings. A PPI representative will also sit on the TSC as a lay member of the committee.

15 Publication & Dissemination of Results

15.1 Publication Policy

15.1.1 Trial Results

The results of the trial will be disseminated regardless of the magnitude and interpretation of any effect of the intervention. The publication of the results will comply with the UCL CCTU Publication Policies.

A lay summary of the results will also be produced to be disseminated to those participants who took part who express an interest in the findings.

A summary of results will be submitted to the REC via the HRA (https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/ending-your-project/final-report-form/) and published through an open-access mechanism in a peer-reviewed journal within 12 months of the trial closure.

15.1.2 Authorship

All individuals who have made substantial intellectual, scientific and practical contributions to the trial and the manuscript should, where possible, be credited as authors; all individuals credited as authors should deserve that designation. It is the responsibility of the Chief Investigator and, ultimately, the Sponsor to ensure that these principles are upheld.

15.1.3 Reproducible Research

The latest version of the protocol will be made available as supplementary material upon publication of the primary publication.

Applications for access to the trial dataset at the end of the trial, should be submitted formally in writing to UCL CCTU and will be considered and approved in writing after formal consideration by the trial oversight committees (if still in place) and the CI.

16 Data and/or Sample Sharing

Requests for access to trial data will be considered, and approved in writing where appropriate, after formal application to the TMG/TSC.

Data will be shared accordingly based on the following principles:

- No data should be released that would compromise the ongoing trial.
- There must be a strong scientific or other legitimate rationale for the data to be used for the requested purpose.
- Investigators who have invested time and effort into developing a trial or study should have a period of exclusivity in which to pursue their aims with the data before key trial data are made available to other researchers.
- The resources required to process requests should not be under-estimated, particularly successful requests which lead to preparing data for release. Therefore

adequate resources must be available in order to comply in a timely manner or at all, and the scientific aims of the study must justify the use of such resources.
- Data exchange complies with Information Governance and Data Security Policies in all of the relevant countries.

UCL shall ensure that the outcome of the Research is prepared for publication in a suitable peer-reviewed journal and shall ensure that it, and any other publication, including patent applications, of or resulting from research caried out by the grant shall acknowledge the NIHR's financial support and carry a disclaimer relevant to the programmes set out in the NIHR's research outputs and publications guidance as amended from time to time. Data will be available for sharing after the trial results have been published (within 12 months of the end of trial). Researchers wishing to access ENLIVEN-UK data should contact the Trial Management Group in the first instance.

17 Translational Research Collection

Two translational studies may arise from this trial. These will be carried out under separate funding arrangements and will require their own ethics applications. These are expected to be:

1. Radiological study – this is likely to involve correlation between the brain MRI scan undertaken at term-equivalent age and the primary and secondary outcomes of the trial.
2. CSF study – CSF, as well as a paired blood specimen, will be taken at the time of the index procedure and also, in some infants, at the time of insertion of a permanent VP shunt. Additional CSF and blood samples may be collected at any unscheduled visits to the Neurosurgical Unit if the patient has consented to these added studies.

In this study, funding is provided to transport these specimens and store them in the Liverpool Neuroscience Biobank at the Walton Centre in Liverpool. Additional funding will be sought to correlate the presence and level of biomarkers in the blood and CSF with the extent of intraventricular haemorrhage, PHVD and trial outcomes.

17.1 Consent for translational studies

Separate consent will be requested for the translational studies. Consent for collection of blood and CSF, as well as storage of radiological investigations, will be requested at the same time as the primary trial.

18 Protocol Amendments

Table 8. Summary of Protocol Amendments

Protocol version	Protocol date	Summary of changes
1.0	29Sep2023	N/A – Initial submitted protocol to REC (not approved)
2.0	08Dec2023	**Revisions to v1.0 following initial REC review and in response to Favourable Opinion with Conditions.** ○ **Sections 3.6, 4.7.3, 5.2, & 5.3**: Wording added to clarify that questionnaires should be completed at the start of the visit before any other procedures are performed. Where participants' parents/guardians self-report 'severe' or 'extreme' anxiety and depression in the EQ-5D-5L Questionnaire, they

		should be signposted to access support from their healthcare provider. ○ General administrative changes (e.g., staff and trial management membership) ○ Corrections, formatting, and minor amendments to the overall text. ○ Protocol version history updated.
3.0	20 September 2024	**Revisions to v2.0 of the protocol.** ○ **Section 3.5:** Clarification added that NICU Units (based at other NHS Trusts) will not be set-up as Participant Information Centres ○ **Section 3.6:** Wording added to clarify that participant's parent/legal guardian(s) should be informed which trial treatment arm was received by the participant after the procedure has taken place. At this point the trial information card should be given. ○ **Section 6.3:** Decision for withdrawal of all Medical Care: Wording added to clarify that there may be a small number of participant deaths following the decision to withdraw all medical care. ○ **Section 5.3.1 & 7.4/7.6.2:** Clarification added that pseudonymised imaging scans will be transferred directly to UCL and not to GOSH. ○ General administrative changes (e.g., staff and trial management membership) ○ Protocol version history updated.

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20 Appendices

20.1 Appendix I - Translational Research Sample Collection

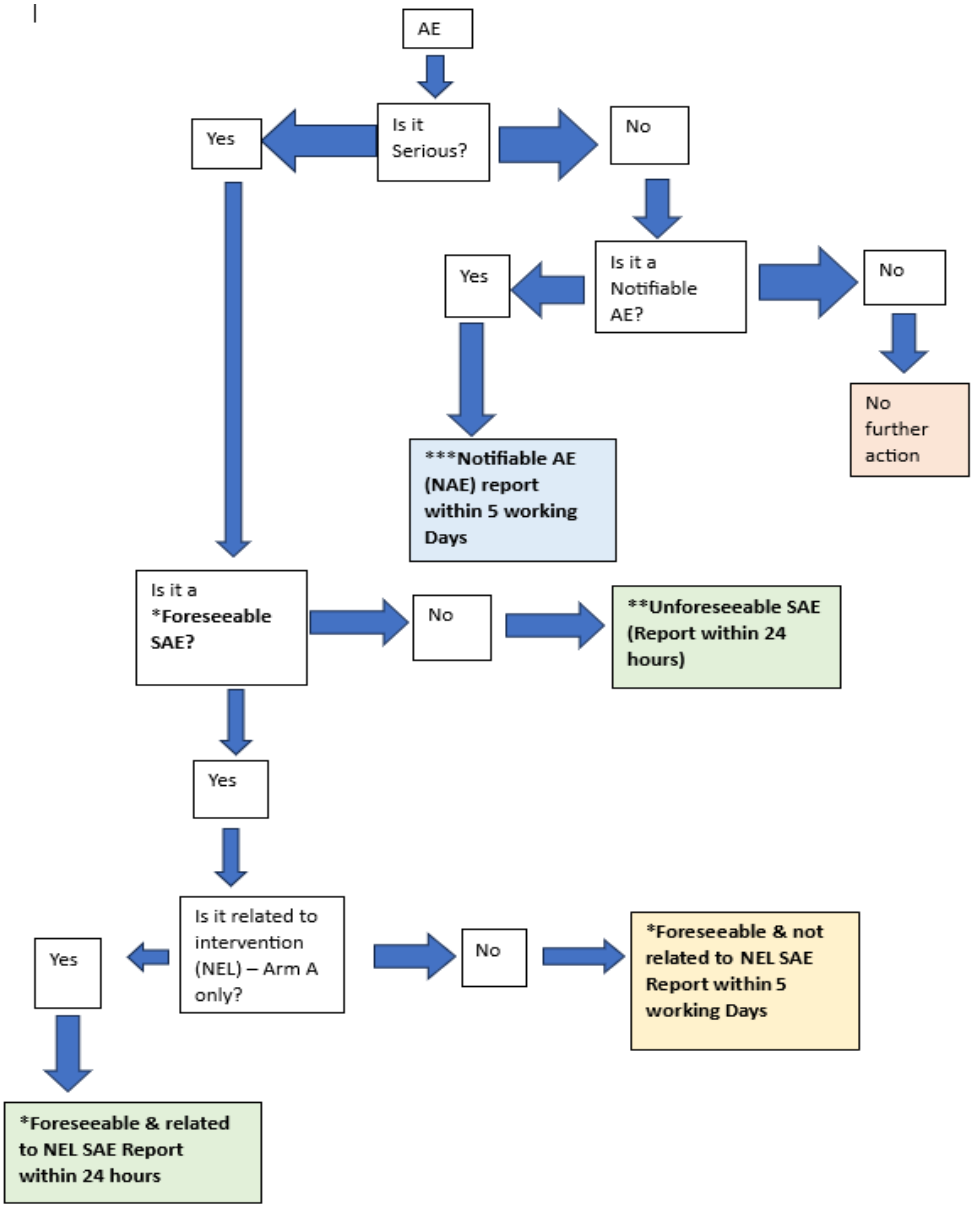
Translational research samples should be collected at the following timepoints where informed consent has been obtained.

Table 9: Translational Sample Collection Timepoints:

	Baseline Visit	**Surgery (t=0)**	**Post-operative Follow-Up**	**First Clinical Follow-up (t=term equivalent)**	**VP Shunt Insertion (if required)**	**Unscheduled Visit to Neurosurgical Unit**
OPTIONAL: CSF Sample Collection (up to 9ml)		X			X	X
OPTIONAL: Blood Sample Collection (up to 1.0.ml)		X			X	X

See Laboratory Sample Management Plan for full details on sample collection, labelling, processing, storage, and shipment.

20.2 Appendix II – Safety Reporting Flowchart



Key:

Foreseeable SAEs* – Please refer to **section 6.1.2.1 for a list of foreseeable SAEs.

***Unforeseeable SAEs* – Please refer to section **6.1.2.2** for the definition of an Unforeseeable SAE

****Notifiable AE (NAE)* – Please refer to section 6.2 for a list of NAEs.