STUDY PROTOCOL

Surgical drainage, irrigation and fibrinolytic therapy (DRIFT) in premature infants with post-haemorrhagic ventricular dilatation: Brain function and structure at school age

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1. AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
0	1.1	28 October 2014	K Luyt	Additional information about screening under study procedures
1	1.2		K Luyt	Addition of cognitive assessment approach to children with very severe disability.
2	1.3	23 Sept 2015	K Luyt	Adding option of assessment at home or school for children with severe mobility problems or for those that have emigrated to other countries.

2. SYNOPSIS

Study Title	Surgical drainage, irrigation and fibrinolytic therapy (DRIFT) in premature infants with post-haemorrhagic ventricular dilatation: Brain function and structure at school age
Internal ref. no.	2287
Study Design	Long term follow up of a multi-centre randomised controlled trial
Study Participants	Participants of the DRIFT Trial
Planned Sample Size	60
Follow-up duration	
Planned Study Period	01/09/2014 to 31/05/2016
Primary Objective	To compare cognitive function, visual function, sensorimotor ability and emotional well-being between the two treatment groups form the DRIFT trial, at school age
Primary Endpoint	Severe cognitive disability at school age
Intervention (s)	None

3. BACKGROUND AND RATIONALE

3.1 Summary Background and Rationale

3.1.1 Lay Summary:

Despite advances in newborn intensive care, infants born prematurely are at high risk of brain injury and major disabilities/neurodevelopmental impairments later in life. Bleeding into the fluid spaces (ventricles) of the brain is one of the most common consequences of being born very early. These bleeds, called Intraventricular Haemorrhage (IVH) are often further complicated by progressive enlargement of the ventricles, known as post–haemorrhagic ventricular dilatation (PHVD), which has a very high rate of serious disability such as cerebral palsy and learning difficulties.

Despite a number of different approaches to therapy, no intervention has been objectively shown to improve outcome. Drainage, irrigation and fibrinolytic therapy (DRIFT) was developed as a method of washing out the ventricles to clear the effects of the bleeding. The DRIFT randomised trial was conducted in 2003-2006. Eligible babies were preterm, had an IVH and expanded the cerebral ventricles over pre-determined limits. With parental consent, 54 babies were randomised in Bristol and a further 20 in Poland, to either DRIFT or standard therapy which consisted of fluid tapping to control excessive expansion.

Magnetic resonance (MR) brain imaging was carried out in 36 babies in the DRIFT trial and showed cerebral lesions and/or impaired brain growth in a large proportion of the infants. When neurodevelopment was assessed by “blinded” observers at 2 years, severe disability or death was significantly reduced in the DRIFT group. There was a large reduction in severe learning difficulties from 59% to 31% in the DRIFT group compared to the control group.

As cognitive testing at 2 years is limited and can be difficult in children with motor impairment, it is important to do more comprehensive testing at school age. Cerebral visual impairment concerns how the brain processes images and cannot be adequately tested at 2 years. Thus it is important to thoroughly assess vision including techniques that can detect and define cerebral visual impairment.

The children in the DRIFT trial are a unique study group with well-documented serious brain injury substantially different from the previous studies of preterm infants, most of whom have not had severe brain injury of this nature. The proposed MR imaging, visual assessment and cognitive assessment at school age will allow us to assess to what extent the brain has remodelled and adapted to the previous injury and will enable us to see if some functions (i.e. vision or language) have “moved” from their normal locations. This study may provide vital insights into how the brain repairs and adapts after injury from IVH in premature infants, enabling future refinement of treatments. The proposed research might ultimately lead to a reduction in disabilities in children born prematurely, with a long-term cost saving to health and education services, and improved quality of life.

In 2012, the investigators tested the feasibility of this protocol in a small group of children from the DRIFT trial. Ethical approval for this research was given by South West 3 Research Ethics Committee, and the study demonstrated that the children (now aged 7-10 years) coped extremely well and were able to cooperate with all the assessments and brain imaging undertaken.

3.1.2 Scientific Summary:

Background:

Haemorrhage into the ventricles of the brain is one of the most common and serious consequences of being born preterm, despite improvements in the survival of preterm infants. Large intraventricular haemorrhage (IVH) is often further complicated by progressive enlargement of the ventricles, post–haemorrhagic ventricular dilatation (PHVD), which has a

very high rate of serious disability, i.e. cerebral palsy and cognitive disability. In the neonatal Research Network 33% of infants with birth weights less than 1000g developed IVH, and of those 10% required implantation of a ventriculoperitoneal shunt for PVHD [1]. 40% of children with PVHD will develop cerebral palsy and approximately 25% of these will have multiple disabilities. The presence of haemorrhagic parenchymal infarction, in addition to PVHD, increases the risk of cerebral palsy to 80-90% [1].

The immature brain may be injured in a number of different ways in PHVD, including pressure, distortion, inflammation and free radical injury from iron [2].

Reducing the rate of shunt insertion in these infants has been an important long-term objective in the management of IVH and PVHD. The large amount of blood and protein in the cerebrospinal fluid (CSF) combined with the small size and instability of the patient makes early ventriculoperitoneal shunt surgery impossible. Shunt implantation at the generally accepted weight threshold of 2kg, usually around term-age, is still associated with a higher infection and malfunction rate [3] [4].

Despite a number of different approaches to therapy, no intervention has been objectively shown to improve outcome. Repeated lumbar puncture, drugs to reduce cerebrospinal fluid (CSF) production and intraventricular injection of streptokinase have been tested in randomised trials with either no benefit or worse outcome in the intervention group.

Drainage, irrigation and fibrinolytic therapy (DRIFT) was developed as a surgical approach of reducing iron and pro-inflammatory cytokines from CSF and reducing pressure and distortion early [2]. The procedure involves insertion of right frontal and left occipital ventricular catheters under anaesthesia. Tissue plasminogen activator (TPA), a fibrinolytic, is injected intraventricularly at a dose that is insufficient to produce a systemic effect and this is left for approximately 8 hours. Under continuous intracranial pressure monitoring the ventricles are irrigated by artificial CSF through the frontal catheter. The occipital ventricular catheter is simultaneously connected to a sterile closed ventricular drainage system and the height of the drainage reservoir adjusted to increase or decrease drainage to maintain intracranial pressure below 7 mm Hg and net loss of 60–100 ml CSF/day. The drainage fluid initially looks like cola but gradually clears, at which point irrigation is stopped and the catheters removed. This commonly takes 72 hours but can be up to 7 days.

After initial feasibility testing showed DRIFT was technically possible and promising, the DRIFT randomised trial started recruiting in 2003. Eligible babies were preterm, had an IVH and expanded the cerebral ventricles over pre-determined limits. With parental consent, 74 babies were randomised in Bristol and Katowice, Poland to either DRIFT or to standard therapy which consisted of non-surgical conventional management (lumbar punctures to control excessive expansion and pressure symptoms). If repeated lumbar punctures were needed, a ventricular reservoir was inserted to facilitate tapping CSF.

Short term outcomes in the DRIFT trial showed no difference in shunt surgery or death. There was a significant increase in secondary bleeding in the DRIFT group. Magnetic resonance (MR) imaging was carried out on clinical indications in 36 of the 50 Bristol survivors.

At 2 years post term, severe disability or death was significantly reduced in the DRIFT group, when neurodevelopment was assessed by “blinded” observers [2]. There was an important decrease in severe cognitive disability (Bayley mental development index 3 SDs below mean) from 59% to 31% (adjusted odds ratio: 0.17 [95% CI 0.05-0.57]) and the difference in median MDI was more than 18 points. Developmental quotient at 2 years correlated significantly with qualitative grading of MR brain images at term. Sensorimotor disability remained substantial at 2 years: overall, 48% were unable to walk, and 20% were unable to communicate. Ventricular enlargement is typically greatest in the occipital areas and 9% of the children had no useful vision. Severe sensorimotor disability was less common in the DRIFT group but without reaching statistical significance.

However, while (relatively) short term neurodevelopmental measures are essential in the initial management of perinatal interventions, longer term measures provide far greater validity in assessing long term functioning (and the medical, societal and financial implications of these).

Prematurely-born children have a higher prevalence of visual defects than do children born at term [5] and in particular the spectrum of vision problems known collectively as "cerebral visual impairment" (CVI) is a recognised complication of preterm brain injury, particularly if involving the periventricular white matter [6]. Visual functions correlate with neurodevelopmental outcome and brain volume in preterm infants [7]. Severe CVI is the leading cause for children being registered as blind in the UK [8] and developed world and may additionally be associated with ocular, optic nerve or refractive problems which cause further impairment. Less severe CVI can involve damage to visual skills which have an important effect on school performance and tasks of everyday life [9]. Clinical assessment of CVI is difficult before the age of 5 years, however a recent study found evidence of CVI in 89% of children with known central nervous system damage [10] thus it is important to assess this area of function to fully understand the impact of severe IVH, PHVD and/or the impact of DRIFT.

Every preterm infant with severe cerebral palsy or severe cognitive or visual impairment will require lifelong parental and social care. The cost to society due to the complications of prematurity is significant. Based on 2003 US figures [11] the estimated lifetime costs per infant with cerebral palsy, severe cognitive impairment and blindness is £614,000, £675,000 and £400,000 respectively. Data from the UK EPICure study indicate that by age 11 the annual health and social service costs of children with serious neurodevelopmental disability are almost double those of children without disability (£1,225 vs £695) [12]. This adds a significant additional economic burden on the NHS and social care.

As cognitive testing at 2 years is limited and can be difficult in children with motor impairment, it is important to do more comprehensive testing at school age. Cerebral visual impairment concerns more complicated aspects of vision than just visual acuity or strabismus and cannot be adequately tested at 2 years. Thus it is important to thoroughly assess vision including techniques that can detect and define cerebral visual impairment. The MR imaging performed at term showed cerebral lesions and/or impaired brain growth in a large proportion of the infants.

The number of new cases of PHVD annually is estimated to be in the region of 200. With increasing rates of premature birth and survival of extremely preterm infants the prevalence of PHVD and severe disability is likely to increase in the future. If the cognitive improvement seen with DRIFT at 2 years translates into a similar effect size at school-age, we can project that serious disability could be prevented in at least 60 infants per year. The projected annual cost saving to the NHS and social services will be about £600,000 per year, based on the additional cost of severe disability [13]. This estimation excludes the further substantial reduction in the economic burden of parents/carers, special educational services and public funds. The impact on individual quality of life and acquisition of independence would also be substantial.

The children in the DRIFT trial are a unique study group with well-documented serious brain injury substantially different from the previous studies of preterm infants, most of whom have not had severe brain injury of this nature. There is now the opportunity and facility for long term (late primary school age i.e. 8-11 years old) to assess cognitive and visual function, functional status, emotional wellbeing, preference based measures of health related quality of life and healthcare costs of the DRIFT trial participants to determine further evidence of clinical efficacy, safety and cost-effectiveness of DRIFT therapy. Two year developmental outcomes are important, but often limited to detecting substantial neurodevelopmental impacts and have limited role in measurement of functional outcomes. With an invasive technique such as DRIFT

it will be important to quantify any benefit or risk of the procedure in comparison to conservative treatment.

The children in the DRIFT trial have now reached the age where cognitive and visual abilities and functional impact on activities of daily living can be assessed definitively and where the children will be able to cooperate with neuroimaging, even in the presence of disabilities. The feasibility of conducting this research protocol has been tested in Bristol. Children from the DRIFT trial were successfully recruited and completed the required assessments and imaging studies and coped well during their participation.

4. AIMS AND OBJECTIVES

Our primary hypothesis is that neurosurgical drainage, irrigation, and fibrinolytic therapy (DRIFT), which aims to lower pressure, distortion, free iron, and cytokines, will reduce severe cognitive disability in children assessed at school age.

Our secondary hypotheses are that DRIFT will improve:

(a) cerebral visual dysfunction
(b) sensorimotor ability
(c) functional status
(d) emotional/behavioural difficulties
(e) preference based measures of health related quality of life
(f) and reduce the health, social care and broader societal costs at age 11.

The aims of this study:

1) To compare cognitive function, visual function, sensorimotor ability and emotional wellbeing, between the two treatment groups in the DRIFT trial at school age.
2) To quantify functional status and use of community and specialist health and educational services.
3) To estimate the economic cost and outcomes of the DRIFT intervention by age 11, and model long-term costs and outcomes.
4) To quantify degree of ventricular dilatation and neurosurgical sequelae in the two treatment groups by clinical neuroimaging.

4.1 Primary Outcome

Severe cognitive disability at school age.

4.2 Secondary Outcomes

- Cerebral visual function
- Sensorimotor disability
- Functional status
- Emotional/behavioural function
- Preference based measures of health related quality of life
- Costs of initial hospitalisation and treatment during the neonatal period (including emergency transportation, periods of intensive care, and readmissions based on hospital records in the UK cohort)
- Costs of subsequent health care in childhood (based on hospital records from the UK cohort)
- Health and social care costs and impact on family at age 11 (based on parent recall)

5. STUDY DESIGN

Study design: Long term follow up of a multicentre randomised controlled trial

5.1 Study Participants

Children previously enrolled in and randomised to the DRIFT trial in Bristol and Poland between 2003 and 2006.

Inclusion criteria of the DRIFT trial were:

(1) IVH documented on ultrasound;

(2) age no more than 28 days;

(3) progressive dilation of the both lateral ventricles with each side:

(a) ventricular width 4 mm over the 97th centile;
(b) all of the following: anterior horn diagonal width 4 mm (1 mm over 97th centile), thalamo-occipital distance 26 mm (1 mm over 97th centile), and third ventricle width 3 mm (1 mm over 97th centile); or
(c) measurements above (a) or (b) on 1 side combined with obvious midline shift indicating a pressure effect.

Exclusion criteria were a prothrombin time of >20 seconds or accelerated partial thromboplastin time of >50 seconds or platelets <50000/mL.

The DRIFT study achieved a high level of loyalty from those recruited as 100% follow-up was obtained at 2 years with 97% of the survivors having the full Bayley Scales of Infant Development administered. All the families received a copy of the paper reporting the two year findings of the trial. The families with a child in the DRIFT trial will be invited to take part.

5.2 Statistical Considerations

In total 74 children (54 from Bristol and 20 from Poland) were randomised to the DRIFT trial of which 66 survived. 16 children are available for assessment in Poland and 50 in Bristol. Based on a similar effect size documented with severe cognitive disability at 2 years of age a two group continuity corrected chi-square test with a 5% two-sided significance level will have 80% power to detect the difference in severe cognitive disability between a control group proportion of 59% and odds ratio of 0.17 (i.e. an intervention proportion of 19.7%) when the sample size in each group is 28. With 60 infants (30 in each group) we will have 97% power (with an alpha of 5%) to detect a mean cognitive difference of 1 standard deviation (commonly 15 points) between the DRIFT and control groups.

45 UK children will be assessed in Bristol, and 15 Polish children in Katowice, Poland, assuming a 90% follow-up rate. It is intended to recruit 45 Children (22 DRIFT, 23 Control) from the Bristol cohort and 15 (8 DRIFT, 7 Control) from the Poland cohort.

Funding is available for the study to be completed in the UK and in Poland. **This protocol describes the UK cohort only**. The Poland cohort will be completed under a separate protocol and in accordance with local governance and regulatory requirements.

5.3 Participant Selection

Inclusion Criteria:

- Children previously recruited to the DRIFT trial
- Parents/carers are willing and able to give informed consent and children willing to assent to participation in the study.

Exclusion Criteria

- Children with metal implants that are incompatible in MRI scanners will be excluded from the neuroimaging element of the study.

6. ASSESSMENTS

All assessments will be adapted to the child's abilities.

6.1 Cognitive Assessments

Assessment will be undertaken by child psychologists.

Cognitive testing in this group of children needs to use a method with a wide spread of abilities as some of the study children have very significant disabilities (Cognitive score below 55). The British Ability Scales (BAS III) comprise 21 short tests, each measuring particular types of knowledge, thinking and/or skills (Elliott and Smith. GL Assessment; London. 2012).The final type of score is "age equivalent". This is the age at which the score achieved by the child was average. The BAS III has a basal threshold at a developmental age of 3 years. In the event that children do not attain the basal scoring threshold of the BAS III, the cognitive and language scales from the Bayley Scales of Infant and Toddler Development III (BSID III) (Bayley N. Harcourt Assessment: San Antonio; 2006) will be administered. This test also yields Developmental Age Equivalent score from 1 month to 3 years. In order to compare scores in all children, developmental age scores will be converted into a developmental quotient score: [developmental age equivalent score ÷ biological age at assessment x 100] for each child. . This allows severely delayed children to have a cognitive score rather than being labelled as "untestable".[14] The final cognitive score for children of all abilities will therefore be a cognitive developmental quotient and a continuous variable.

The BAS_III and BSID III will be adapted for use in Polish speaking children.

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The individual scales for BASIII are:

- Block building
- Copying
- Early number concepts
- Matching letter-like forms
- Matrices
- Naming Vocabulary
- Number Skills
- Pattern Construction
- Picture Construction
- Picture Similarities
- Quantitative Reasoning
- Recall of Designs
- Recall of Digits Backwards
- Recall of objects

- Recognition of pictures
- Speed of information processing
- Spelling
- Verbal Comprehension
- Verbal Similarities
- Word definitions
- Word reading

The individual scales for BSID III are:

- Cognitive Scale
- Language Scale (receptive and expressive language)

6.2 Assessment of Visual Function

Children will be assessed by trained vision specialists. Analysis of all visual data will be undertaken by Dr Cathy Williams.

The UK visual assessments will comprise:

A standard protocol to explore a range of visual and visual cognitive functions, for all of which age and developmental normative data are available.

The general approach will be to obtain some information relating to a wide range of visual functions relating to:

- How well child can discriminate small objects
- How well child can move their eyes
- How well child can interpret and use visual information
- Focussing power of the eye
- Anatomical structure of the retinal and optic nerve

Specific tests:

(1) History relating to visual behaviour :

(2) CVI – inventory (51 Q version, including 12 Q mini-version used previously [9]) [15]

(3) Direct observations:

- Binocular and Monocular visual acuity: we will use Crowded LogMar, with matching card if needed, where possible or Cardiff Cards if not; +/- pinhole to approximate for “best corrected”
- Binocular and monocular Contrast sensitivity (Cardiff contrast cards)
- Stereopsis using the “Preschool” Randot test
- Motor and Sensory Fusion
- Ocular Alignment (Cover tests alternate cover tests)

- Ability to fix and follow a target –monocularly and binocularly (toy, lit-toy or noisy lit toy)
- Ability to shift attention to a competing object within the visual field (toy, lit toy or noisy lit toy)
- Pursuit eye movements horizontally and vertically, fast and slow
- Saccadic eye movements horizontally and vertically, fast and slow
- Full-field optokinetic nystagmus (OKN)
- Vestibulo-ocular reflex nystagmus (postrotational)
- Accommodation to a lit target (RAF rule) and dynamic retinoscopy
- Visual fields to confrontation
- Tests of visuoperceptual skills:
  - Post-box
  - Rectangles
  - Biological motion and form –in-motion (on a laptop or tablet)
  - Contour integration
  - Familiar pictures in unfamiliar aspects (on a laptop or tablet)

Finally anaesthetic (proxymotocaine 0.5%), then cycloplegic drops will be instilled and the child's refractive error measured by a Canon R50 autorefractor, unless these data are available from tests no more than 6 months previously.

A photograph (with/without drops) will be taken of each eye using a Topcon PR2000 non-mydriatic camera to document fundus appearance and allow analysis of optic nerve characteristics

It is estimated this will take up to 60 minutes per child (40 if no drops used, 60 if drops needed)

In Poland visual acuity results (with details of test used), motility, cover test and refraction results can be collected locally or obtained from existing records. The question battery will be sent for completion by the mother/carer.

Visual outcomes:

(i) Severe visual impairment will be defined according to WHO taxonomy: Blind - 3/60 or worse; Low vision =3/60 to 6/18

(ii) Additional functional impairment will be defined as significant field defect (e.g. hemianopia), nystagmus in primary position and/or contrast sensitivity below age-matched or developmental age-matched norms

(iii) Mild impairments will include strabismus, best binocular acuity < 6/6 and/or unilateral amblyopia (difference between eyes of 2 lines or more LogMAR or behavioural equivalent).

(iv) Significant refractive error will be defined as spherical equivalent (SE) > +2 or < -1 or >:1 D anisometropia or >1D astigmatism.

(v) CVI will be indicated by performance in perceptual test (postbox, rectangles, contours) worse than that of 95% of age-matched or developmental age-matched children with no known developmental problems and/or higher symptom score on question battery than population-based control sample [9].

6.3 Assessment of Motor Function and Disability

Children will be assessed by a paediatric physiotherapist:

- Full neurological assessment

- Classification of severity of cerebral palsy using the Gross Motor Classification System.
- Assessment of motor ability using the Movement ABC-2 test in mobile children. The test contains 8 tasks. The tasks cover the following 3 areas: Manual Dexterity, Ball Skills, Static and Dynamic Balance

- Head circumference, height and weight
- Clinical history (including any other identified disabilities such as hearing loss, epilepsy, feeding difficulties, subsequent neurosurgical procedures)

6.4 Emotional and Behavioural Difficulties

The Strengths and Difficulties Questionnaire will be used. This is a brief behavioural screening tool for children and adolescents aged between 4 and 16 years of age. It comprises 25 items divided between 5 scales: emotional symptoms; conduct problems; hyperactivity/inattention; peer relationship problems; prosocial behaviour. There is a supplement which assesses impact including, chronicity, distress, social impairment and burden to others [16].

6.5 Quality of life, productivity, health, social care and other resource use

The Study Researcher will ask parents to complete the following questionnaires on behalf of their child.

- Two generic preference based measures of the child's health related quality of life: The HUI3, and the EQ-5D-5L proxy versions.
- A modified version of the Client Service Receipt Inventory (CSRI) – Children's version [17] to assess parent/carer productivity (completed by both parents/guardians where applicable). The modified CSRI also assesses the child's use of hospital, and community based health services, social and supportive care, educational services in the past 12 months.

The Study Researcher will also extract information on hospital care from the hospital and primary care records since birth to estimate the cost of initial hospitalisation and subsequent readmissions.

6.5 Neuroimaging

MR imaging will be carried out on the UK based children in the University of Bristol Clinical Research and Imaging Centre (CRIC). A clinical 3 Tesla Siemens scanner will be used.

Brain anatomy and function will be imaged using standard clinical protocols. Conventional high spatial resolution T1 and T2 sequences (0.75 mm x 0.75 mm x 3 mm) will be acquired to assess brain anatomy and possible chronic abnormalities in brain parenchyma. T1-images will be used to determine total and partial brain volumes using both manual and automated segmentation.

Diffusion Tensor Imaging will be used to evaluate white matter integrity and projections of major fibre structures. To this end Fractional Anisotropy and Tractography will be acquired using MRI techniques provided by Siemens.

Blood Oxygenation Level Dependent (BOLD) Functional MRI (fMRI) will be used as readout for functional imaging. BOLD fMRI will be acquired using a standard T2*-weighted multi-slice technique (spatial resolution 3 mm^3 with whole brain coverage) in block-design experiments with one item from the verbal, spatial and pictorial reasoning clusters as a task in the British Ability Scales. The fMRI will be individualised to each child’s abilities and tolerance.

Great care will be taken not to over-tire the child, using breaks, drinks and changes of activity to maintain interest. The total time in the MRI scanner room will be around 35 - 45 minutes, the MR data acquisition itself will take 20-30 minutes.

7. 7. STUDY PROCEDURES

7.1 Informed Consent

The DRIFT trial PI (Professor Andrew Whitelaw) and staff have remained in contact with families and have forwarded the published results of the DRIFT trial. The families were all informed of the future school age follow-up and all were supportive of this.

Participants will be identified from the DRIFT trial database, which includes the NHS number. The majority of the children remain outpatients of UHBristol and North Bristol (NBT) NHS trusts, or their parents have remained in contact with Professor Whitelaw. Tracing their up to date address and phone numbers will be simple using the patient administration systems for each trust.

Where children are no longer patients of UHBristol or NBT and their survival status, latest address and telephone number are unknown a search will be performed using the NHS Care Record Service using the child's name, date of birth and NHS number. This will provide the current address, current GP and also if the child is still alive. In cases where survival status is unknown the Office of National Statistics will be approached to see if a death has been registered. In cases where the current address is not known the GP practice where they are registered will be contacted for information, to avoid information being sent to inappropriate addresses.

Parents of children from the DRIFT trial will be sent a letter of invitation by post to offer them the opportunity to be in the follow up study. This will be followed up by a telephone call 7 days later from the Study Coordinator (Dr Sally Jary), whom they all met at 2 years. The parents will be given the option to not receive a telephone call or any further contact if they so wish. If the parents and children have indicated that they are interested in the study a full information sheet for the parent, and an appropriate information sheet for the child will be forwarded. The study coordinator will contact the parents by their preferred method of communication 7 days later. At this time the parents can ask questions, share any special needs to accommodate and indicate if their child would like to participate or not. If parents and their child agree to take part, full consent will be taken in person from the parent and assent will be requested from the child.

On the day of the study assessments and MRI full informed consent will be taken from the parent with assent from the child.

Consent will be sought for the research team to access all the children's health records, routinely collected data and educational outcomes for this study and for future research use (subject to appropriate ethical approval), as well as for linkage of these data in the long term.

Families will be reimbursed for their expenses in taking part. The children will be given a gift voucher (£20) as a small token of thanks for their participation.

It is not intended to give the families individual feedback on full analysis of the assessments and images. A picture of the brain scan will be given to the child and parents if they wish. A summary of relevant findings will be sent in a letter with an offer to discuss them more fully on the telephone or face-to-face.

7.2 Assessment Visit

Families will be invited to attend a study Assessment Day at CRIC. Where travel to Bristol will be too burdensome for the children assessments will be performed at home or school as preferred by their parents. We know of a minority of cases that have moved to other countries. Where parents have indicated that they wish to participate and it is not possible for the assessment team to travel those distances alternative arrangements will be made for a

local child development team to perform at least the cognitive assessment, which is the primary outcome measure for the study.

After informed consent has been obtained, parents will complete the Strengths and Difficulties questionnaire [16]. This will allow the researchers to appropriately plan the assessment visit to the level of the child's abilities.

7.3 Withdrawal from the Study

Parents are free to withdraw consent for their child to continue to participate in the study at any time. Data collected to that point will be retained.

7.4 Data Analysis

Analysis will be performed by intention to treat and hence primary outcome (cognitive score) will be assessed by comparing mean scores, and analysed using the Student t-test (unpaired). Developmental Quotient derived from age equivalent cognitive scores will be used as a continuous variable, derived from either the BAS III or BSID Bayley III scales.

For the secondary outcomes with continuous outcomes (eg Movement ABC), these will also be analysed using Students t-test, unless found in this population to not follow a normal distribution, in which case either a suitable transformations will be sought or a non-parametric approach considered.

For the binary secondary outcomes (eg functional motor impairment, Strengths and Difficulties, use of specialised health, rehabilitative or educational services) the Chi-Square or 2-tailed Fishers exact test will be used. Output from the clinical neuroimaging will be transformed into either binary (in the case of radiology reports) or continuous data (in the case of quantitative measures) and analysed as above.

Any sensitivity analyses will be performed using multivariate linear regression analysis to control for variables of interest. Co-variate variable selection will be performed a-priori for the models, and included if clinically felt to represent potentially important cofounders. To provide consistent reporting, it is anticipated that at least one sensitivity analysis will be performed: adjusting for the pre-randomisation co-variates used in the initial DRIFT trial report.

For all tests a conventional level of statistical significance at 5% will be used.

8. PARTICIPANT SAFETY

An adverse event is any untoward medical occurrence in a research subject. An adverse event/reaction is **serious** if it:

results in death
is life threatening
results in persistent or significant disability/incapacity
requires hospitalisation
prolongs a current hospitalisation
results in a congenital anomaly or birth defect

Adverse events and incidents that may affect the safety of the participants during their attendance at the Assessment Visit will be recorded in the study records and reported to the Sponsor in accordance with University of Bristol policy and procedures.

9. ECONOMIC EVALUATION

The primary economic analysis will provide a preliminary assessment of the incremental NHS care costs of the DRIFT intervention compared to usual care based on data extracted from the hospital records combined with national and local unit cost data, discounted (at standard rates) over time. These data will be supplemented by a more detailed description of the broader impact of DRIFT on use of specialist rehabilitation services, education, informal care and family work patterns for children and their families at age 11. Due to the limited level of detail on quality of life and non-NHS resource use prior to age 11, we plan a cost consequence [18] analysis quantifying NHS resource use over the 11 year period and providing a more detailed snapshot of the broader perspective on economic (e.g. educational, rehabilitation costs, informal care, productivity) and quality of life impact at age 11. This will provide an estimate of whether the initial costs of DRIFT are counterbalanced by lower NHS secondary care costs during the first 11 years of life or lower societal costs and improved quality of life at age 11.

Modelling of long-term costs and outcomes: In secondary economic analysis, we will develop a decision tree and Markov model to estimate the cost-effectiveness (cost per quality adjusted life year [QALY]) of DRIFT compared to standard care from birth to age 18. The primary perspective will be NHS and personal social services in accordance with the NICE methods guide. However, in secondary analysis we will broaden the perspective to include education, parental expenses and lost productivity. The structure of the model will be similar to that outlined by Petrou and Khan using a Markov model to stratify cohorts of surviving children by the degree of disability (none, mild, moderate, severe) with an annual cycle length [13].

Several parameters of the model will be derived directly from DRIFT trial data (i.e. cost of initial inpatient care to discharge and readmissions to age 11; probability of survival to discharge and at yearly intervals to age 11; disability status at age 2 and age 11; other NHS costs, educational, informal care, and productivity costs at age 11; health utilities at age 11. However, other parameters needed to interpolate between birth and age 11 and extrapolate to age 18 will be drawn from the literature or from expert opinion [19], [20]. Distributions will be assigned to all stochastic parameters within the model and a probabilistic sensitivity analysis will be conducted. Deterministic sensitivity analyses will be used to test the impact of various clinically plausible scenarios for the progression of disability beyond age 11. A 3.5% annual discount rate will be used for both costs and benefits. Results of the model will be summarised using incremental cost-effectiveness ratios, the net monetary benefit statistic and cost-effectiveness acceptability curves.

We will use the model to judge the probability that DRIFT is a cost-effective (compared to NICE threshold – currently £20-£30,000 per QALY) at age 11 and age 18. If the evidence is equivocal at age 11, we will use the model to calculate the expected value of sample information [21] to determine the value of further follow up of disability, quality of life and costs beyond age 11.

10. ETHICS

10.1 Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. All documents will be stored securely and only accessible by study staff and authorised personnel.

Participants will not be recognisable in the data base, or in any subsequent publications that will arise from the study.

The study will comply with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so.

10.2 Other Ethical Considerations

Children as participants:
Parents will be asked to consent on behalf of their child. The children will also be asked to provide assent to take part.

Risks, burdens and benefits:

There is no risk to participants in the study. Extensive research has been conducted into whether the magnetic and radio waves that are used in MRI could pose a risk to the human body. No evidence that there is a risk has ever been found. This means that MRI is one of the safest medical procedures currently available.

There is no direct benefit to children enrolled in the study. There are potential benefits to the paediatric population as a whole (i.e. infants affected by the same disease in the future), in terms of increased knowledge of the condition, which would possibly translate into better/earlier diagnosis, treatment or prevention.

Where parents have indicated that children have severe mobility or emotional problems and travel to CRICBristol for assessments would be difficult the study team will be prepared to travel to perform the assessments at home or the school, whichever is least disruptive to the family. The same option will be offered where families have emigrated to other countries. For these participants MRI scanning will not be performed.

In the extremely unlikely event that an unexpected structural brain abnormality is found on MRI a referral will be made to a Paediatric Neurologist and the GP will be notified. In the event that unexpected visual impairment is found in participants, referrals will be made to a Paediatric Eye specialist.

11. DATA HANDLING AND RECORD KEEPING

Consent forms: Original copy (with participant specific details) will be locked away securely in the study office on NHS premises (St Michael's Hospital, UHBristol NHS Trust) that are only accessible by swipe card.

Participants will be allocated a specific numeric identifier for use in the database and for MRI image identification. A separate file linking patient specific details (Name, date of Birth, Hospital number and NHS number) and the study specific numeric identifier will be locked away securely by the CI in NHS premises (only accessible by swipe card).

All study data will be entered on a password protected database. The participants will be identified by the specific numeric identifier.

After the end of the study consent forms and data files will be archived securely.

Access to Data

The Sponsor, persons responsible for the audit, representatives of the Ethics Committee and of the Regulatory Authorities will be allowed to have direct access to source data / documents. This is reflected in the Participant Information Sheet (PIS). Study monitoring will be undertaken on behalf of the Sponsor by UH Bristol using their monitoring standard operating procedure.

12. FINANCING AND INSURANCE

Study Funding

The study is funded by a grant from the National Institute for Health Research (NIHR) Health technology Assessment (HTA) programme.

Insurance Arrangements

Insurance for the study has been arranged by the sponsor (University of Bristol).

13. PUBLICATION POLICY

All co-applicants (and where appropriate collaborators) will take an active part in the preparing and reviewing of all manuscripts and reports generated during or as a result of this study. In line with contractual agreements with NIHR the authors will inform NIHR of any publications at least 28 days prior to publication.

Dissemination Policy

In addition to provision of annual and final reports, as well as presentations at scientific meetings and publication of findings in scientific literature, all participants in the trial will be sent a summary of the final results of the trial which will contain a reference to the full paper. Participants will also have access to the study website.

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