Study Title: UK Chiari 1 Study

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Chief Investigator: Mr. Jayaratnam Jayamohan; Consultant Neurosurgeon; Department of Neurosurgery, John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust; Jayaratnam.JayaMohan@ouh.nhs.uk

Investigators: Mr. Rory J. Piper; Neurosurgical Trainee; Department of Neurosurgery, John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust; rory.piper@ouh.nhs.uk

Mr. Fardad T. Afshari; Neurosurgical Trainee; Department of Neurosurgery, Queen Elizabeth Hospital, Birmingham University Hospitals NHS Foundation Trust; fardad.afshari@nhs.net

Mr. Wai C. Soon; Neurosurgical Trainee; Department of Neurosurgery, Queen Elizabeth Hospital, Birmingham University Hospitals NHS Foundation Trust; wai.soon@nhs.net

Mr. Angelos G. Kolias; Clinical Lecturer in Neurosurgery, Department of Clinical Neurosciences, University of Cambridge, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust; angelos.kolias@addenbrookes.nhs.uk

Mr. Rodney Laing; Consultant Neurosurgeon; Department of Neurosurgery, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust; rodney.laing@addenbrookes.nhs.uk

Mr. William B. Lo; Consultant Neurosurgeon; Department of Neurosurgery, Birmingham Children's Hospital, Birmingham Women and Children's Hospital NHS Foundation Trust; william.lo@nhs.net

Sponsor: Oxford University Hospitals NHS Foundation Trust

Research and Development Department, Joint Research Office, Oxford University Hospitals NHS Foundation Trust, Second Floor
OUH, Cowley, Unipart House Business Centre, Garsington Road
Oxford, OX4 2PG; ouh.sponsorship@ouh.nhs.uk; 01865 572224

Funder: Ann Conroy Trust; www.annconroytrust.org

Chief Investigator Signature: 

Statistician Signature:

Not applicable

Conflicts of Interest

None to declare.

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

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Protocol signature page

The undersigned has read and understood the study protocol detailed above and agrees to conduct the study in compliance with the protocol.

Mr. Jay Jayamohan		Oxford	13.10.20
Principal Investigator	**Signature**	**Site name or ID number**	**Date**

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1. KEY CONTACTS

Chief Investigator	Mr. Jayaratnam Jayamohan; Consultant Neurosurgeon; Department of Neurosurgery, John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust; Jayaratnam.JayaMohan@ouh.nhs.uk; 01865 231507
Sponsor	Oxford University Hospitals NHS Foundation Trust Research and Development Department, Joint Research Office, Oxford University Hospitals NHS Foundation Trust, Second Floor OUH, Cowley, Unipart House Business Centre, Garsington Road Oxford, OX4 2PG; ouh.sponsorship@ouh.nhs.uk; 01865 572224
Funder(s)	The Ann Conroy Trust; www.annconroytrust.org Chair: Mr. Graham Flint; Consultant Neurosurgeon; Department of Neurosurgery, Queen Elizabeth Hospital, Birmingham University Hospitals NHS Foundation Trust; Graham.Flint@uhb.nhs.uk; 0121 371 5794
Committees	**UK Chiari 1 Study Steering Committee.** Co-chair: Mr. Rory J. Piper; Neurosurgical Trainee; Department of Neurosurgery, John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust; rory.piper@ouh.nhs.uk; 01865 231793. Co-chair: Mr. Fardad T. Afshari; Neurosurgical Trainee; Department of Neurosurgery, Queen Elizabeth Hospital, Birmingham University Hospitals NHS Foundation Trust; fardad.afshari@nhs.net; 07887932590 **British Neurosurgical Trainee Research Committee (BNTRC).** Chair for 2019: Mr. Rory J. Piper; Neurosurgical Trainee; Department of Neurosurgery, John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust; rory.piper@ouh.nhs.uk; 01865 231793

2. LAY SUMMARY

Background

Chiari 1 malformation (CM1) is a structural abnormality of the hindbrain characterised by herniation of the cerebellar tonsils through the foramen magnum. The investigation and management of CM1 remains contentious since there are currently no UK guidelines for clinicians. Practice varies widely between neurosurgical units and individual surgeons, but there is no robust evidence to bring consensus to the selection of surgical candidates or to the specific surgical technique for CM1. We therefore propose a collaborative, prospective, multi-centre study on the investigation, management and outcome of CM1 in the UK.

Objectives

Our primary objective is to determine the patient- or parent-reported, health-related quality of life (HRQoL) in patients with a new diagnosis of CM1 managed either conservatively or surgically at 12 months follow up. This will be measured using the 36-Item Short Form Health Survey (SF-36; UK version) in adults (16 years and above) and the age-appropriate parent-reported Pediatric Quality of Life Inventory™ (PedsQL™ ; UK version) in children (2 to 15 years). We also aim to i) assess the scope and variation of contemporary investigations and neurosurgical management for CM1 in the UK; ii) determine factors that are predictive of postoperative outcome; iii) to examine the outcomes of varying surgical strategies (including HRQoL 12-months following decompressive surgery); and iv) to investigate the natural history of patients managed conservatively.

Methods

The UK Chiari 1 Study will be a prospective, multicentre and observational study that will follow the British Neurosurgical Trainee Research Collaborative (BNTRC) model of collaborative research. Patients will be recruited after attending their first neurosurgical clinic. Afterwards data are collected from all patients undergoing decompressive surgery, other surgery or being treated conservatively for CM1 in participating UK neurosurgical units. Data will be both patient- or parent-reported (via digital questionnaires) and surgeon-reported (via digital questionnaires). Each participating site will complete the study within three years.

3. SYNOPSIS

Study Title	UK Chiari 1 Study		
Internal ref. no. / short title	UK Chiari 1 Study		
Study registration	Oxford PID 269739.		
Sponsor	Oxford University Hospitals NHS Foundation Trust/University of Oxford Research and Development Department, Joint Research Office, Oxford University Hospitals NHS Foundation Trust, Second Floor OUH, Cowley, Unipart House Business Centre, Garsington Road Oxford, OX4 2PG; ouh.sponsorship@ouh.nhs.uk ; 01865 572224		
Funder	The Ann Conroy Trust; www.annconroytrust.org Chair: Mr. Graham Flint; Consultant Neurosurgeon; Department of Neurosurgery, Queen Elizabeth Hospital, Birmingham University Hospitals NHS Foundation Trust; Graham.Flint@uhb.nhs.uk; 0121 371 5794		
Study Design	Prospective, observational, multicentre, cohort study.		
Study Participants	Adults and children referred to neurosurgery clinic for Chiari 1 malformation (CM1)		
Sample Size	500 patients		
Planned Study Period	Total study duration (per site): 36-months Total study duration (for entire study): 42-months Recruitment period duration (per site): 12-months Follow up data for all patients: 12-months following recruitment Additional follow up for patients undergoing decompressive surgery: 12-months following date of decompressive surgery End date (for entire study): 6th April 2024		
Planned Recruitment period	Participating sites may commence a 12-month recruitment period starting between 8th October 2020 to 7th April 2021.		
	Objectives	Outcome Measures	Timepoint(s)
Primary	To determine change in patient- or parent-reported, health-related quality of life (HRQoL) 12 months following first neurosurgical clinic	36-Item Short Form Health Survey (SF-36; UK version) in adults (16 years and above. Age-appropriate parent-reported Pediatric Quality of Life Inventory™ (PedsQL™; UK version) in children (2-15 years).	Baseline and 12-months following baseline
Secondary	To determine health-related quality of life 12-	HRQoL (as per baseline)	Baseline and 12-months following decompressive

	months following decompressive surgery [sub-set of patients undergoing decompressive surgery]		surgery
	To measure complications and need for re-operation 12-months following decompressive surgery [sub-set of patients undergoing decompressive surgery]	Rates of complications and need for further operations following decompressive surgery	12-months following decompressive surgery
	To determine the natural history of patients with CM1 treated conservatively without surgery [sub-set of patients who do not undergo surgery for CM1]	HRQoL (as per baseline)	Baseline and 12-months following baseline
	To determine the radiological correlates of presenting symptoms, signs and outcomes	Measure of cerebellar tonsillar herniation vs. baseline symptoms, baseline HRQoL and follow up HRQoL.	Baseline, 12-months and 12-months after decompressive surgery
Intervention(s)	None. This is an observational study.		

4. ABBREVIATIONS

BNTRC	British Neurosurgical Trainee Research Collaborative
BSCG	British Syringomyelia Chiari Group
CI	Chief Investigator
CM1	Chiari 1 malformation
CRF	Case Report Form
CSF	Cerebrospinal fluid
GCP	Good Clinical Practice
HRQoL	Health-Related Quality of Life
HRA	Health Research Authority
ICF	Informed Consent Form
NHS	National Health Service
NSU	Neurosurgical unit
PedsQL™	Pediatric Quality of Life Inventory™
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
RES	Research Ethics Service
SBNS	Society of British Neurological Surgeons
SF-36	36-Item Short Form Health Survey
SOP	Standard Operating Procedure

5. BACKGROUND AND RATIONALE

Chiari 1 malformation (CM1) is a structural abnormality of the hindbrain characterised by herniation of the cerebellar tonsils through the foramen magnum. It is one of six described Chiari malformations [1], but is the most common of these and has an estimated prevalence of approximately 8 in 1000 people [2]. CM1 affects patients of all ages, but more commonly presents in late childhood or early adulthood.

CM1 is a heterogeneous condition. Although the natural history is proposed by some to be relatively benign and whilst there are patients who are asymptomatic, CM1 may be accompanied by significant symptoms, deficits and complications [3]. A crowding phenomenon at the foramen magnum manifests as symptoms by causing a combination of brainstem, cerebellar and spinal cord compression. There may be disruption to the normal flow of cerebrospinal fluid (CSF) and around half of imaged patients will have an associated syringomyelia, and a minority of patients develop hydrocephalus [4].

Despite these malformations being classified by Hans Chiari in 1891 [5], CM1 remains poorly understood in aetiology, classification, diagnosis, natural history, investigation and management. There are currently no UK guidelines for the investigation or management of CM1 [6].

Surgery to decompress the cranio-cervical junction (often termed foramen magnum decompression (FMD) remains the mainstay of surgical management, however the surgical technique for decompressive surgery varies widely between centres and surgeons [7, 8] and others would advocate CSF diversion as primary strategy [9]. Common variations of decompressive surgery include bone-only decompression, dura splitting, tonsillar cauterisation, and durotomy with or without duraplasty. Recent single-centre studies from the UK suggest that there may be differences in efficacy and outcomes between these techniques [10, 11], but further evidence is required. The use of intraoperative technologies, such as ultrasonography, to inform surgical decisions also requires further evidence of benefit [12].

Current evidence in CM1 consists of relatively small, single-centre and/or retrospective studies and highly-powered and non-biased data is needed. There are no UK-wide studies that have reported or compared the scope or variability in contemporary neurosurgical workload, practice and outcomes. The lack of evidence in this field makes it difficult for surgeons to decide which patients to offer surgery and which surgical technique is most likely to achieve resolution of symptoms and associated conditions (such as syringomyelia) with minimal complications.

We therefore propose a collaborative, multi-centre and prospective study of the investigation and management of CM1 in the UK.

6. OBJECTIVES AND OUTCOME MEASURES

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Primary Objective To determine change in patient- or parent-reported, health-related quality of life (HRQoL) 12 months following first neurosurgical clinic	Health-related quality of life (HRQoL)[1]	12-months following baseline
Secondary Objectives [1] To determine health-related quality of life 12-months following decompressive surgery [sub-set of patients undergoing decompressive surgery]	HRQoL*	12-months following decompressive surgery
[2] To measure complications and need for re-operation 12-months following decompressive surgery [sub-set of patients undergoing decompressive surgery]	Rates of complications and need for further operations following decompressive surgery	12-months following decompressive surgery
[3] To determine the natural history of patients with CM1 treated conservatively without decompressive surgery	HRQoL*	Baseline and 12-months following baseline
[4] To determine the radiological correlates of presenting symptoms, signs and outcomes	Measure of cerebellar tonsillar herniation vs. baseline symptoms, baseline HRQoL* and follow up HRQoL*.	Baseline, 12-months and 12-months after decompressive surgery
Exploratory Objectives To determine the scope and	Comparison of:	Baseline, 12-months and 12-

[1] Health related quality of life (HRQoL) will be measured in adults (16 years and above) using the 36-Item Short Form Health Survey (SF-36; UK version). HRQoL will be measured in children (2 – 15 years) using the Age-appropriate parent-reported Pediatric Quality of Life Inventory™ (PedsQL™; UK version). Children less than two years of age will be recruited into the study, but not included in the HRQoL analyses.

variation within UK practice in referral patterns, patient pathways, investigations and surgical decisions	• Referral pathway • Investigations • Management strategy	months after decompressive surgery

7. STUDY DESIGN

The *UK Chiari 1 Study* will be a prospective, multi-centre cohort study and will be complete after three years. The study is purely observational and will not alter patient care in any way.

The study will collect both patient- or parent- reported (hereafter referred to as patient-reported) and surgeon-reported data. The study design allows for remote, online data collection and therefore does not require further visits to the hospital or any other facility. Participants will be required to provide patient-reported data at baseline and 12-months following baseline. Additionally, if the patient undergoes a decompressive surgery, then they will be asked to provide patient-reported data 12-months after their surgery. The maximum duration of follow up following baseline, therefore, will be 12-months for patients who do not undergo decompressive surgery and 24-months for patients who do undergo decompressive surgery.

8. PARTICIPANT IDENTIFICATION

8.1. Study Participants

Participants will be patients with a new diagnosis of CM1 presenting to neurosurgical clinic for the first time. Participants will be eligible from the age of 0 days and there is no upper age limit.

8.2. Inclusion Criteria

The participant may enter the study if both of the following apply:

- Patients of 0 days of age and above who are referred to a neurosurgeon with CM1. A diagnostic threshold based on millimetres of herniation below the foramen magnum is not specified (as there is no evidence-based threshold and may introduce bias and inappropriately eliminate cases). Further analysis of clinical features and outcomes with the severity of herniation may be conducted.
- Patients seen for the first time in a neurosurgical outpatient clinic within the study recruitment period.

8.3. Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Patients considered to have an alternative Chiari malformation (type 2, 3 or 4).
- Patients with a history of spinal dysraphism.
- Patients who have already undergone neurosurgical intervention for Chiari malformation or an alternate neurological diagnosis.

9. PROTOCOL PROCEDURES

Procedures	Timepoint
Recruitment	Baseline
Outcome data collection [all patients]	12-months following baseline
Outcome data collection after decompressive surgery [sub-set of patients undergoing decompressive surgery]	12-months following decompressive surgery

9.1. Recruitment

The study will follow the BNTRC model for multi-centre, trainee-led collaboration (Chari *et al.*, 2018) and each participating UK neurosurgical unit (NSU) will be required to commit both a Consultant Principal investigator (PI) and a Trainee co-PI. Whilst as many possible interested consultants are welcome to participate as collaborator, we will be particularly interested in the input of consultant neurosurgeons frequently seeing patients with CM1 to participate in order to detect as many patients as possible. Considering the length of the study, trainee investigators may have to handover to trainee co-PI role to another trainee during the study course, but this will not interfere with the study design. All UK NSUs will be invited to participate.

Participating sites may commence their own 12-month recruitment period with a start date between 8th October 2020 to 7th April 2021.

9.2. Screening and Eligibility Assessment

Patients will be identified by participating neurosurgical consultants and trainees. The neurosurgical team will ask permission for the patient to be contacted by the study team (i.e. the researchers working on the study at that particular hospital / neurosurgical unit) via telephone.

Eligible patients may be enrolled at any point, but in order to be included in the primary outcome analysis (patient-reported), patients must be enrolled within 45 days of the first clinic appointment. Those enrolled after 45 days will have only their record-based data included in the secondary analyses.

Patients must satisfy all of the inclusion and exclusion criteria of the protocol. There will be no exceptions.

Neurosurgical units (NSU) that join the study after the overall study has commenced will be able to retrospectively recruit patients from the start of the overall study start date (8th October 2020), provided that the patients were seen in their first neurosurgical clinic within the last 45-days. Again, the neurosurgical team will make the first contact with the patient and ask the patient's permission for them to be contacted by the study team. This will be documented in the patient's notes. The study team will then contact the patient and continue with the consent process.

9.3. Informed Consent

After identification, patients will be contacted via telephone by a member of the study team who will explain the details of the study, its aims and what it involves for the participant. The person who obtained the consent must be suitably qualified and experienced and have been authorised to do so by the Chief Investigator (CI). The study will be explained and if the patient agrees then the patient will be sent an email that contains:

- a PDF version of the participant information sheet
- a hyperlink to the digital consent form

The digital consent form will be a submission form linked to our REDCap study database. Patients will explicitly be consented for their email address to be stored on the database. Patients will draw an electronic signature, type their name and type the date on the electronic consent form. A copy of the signed informed consent will be sent via email to the patient, a copy will be saved to the local study site and a copy will be saved at the Sponsor site.

If patients prefer or if they do not have an email address, they can choose to have these documents sent to them via post (including two copies of the consent form (both signed by the study team member taking consent) and participant information sheet). Patients will be given an addressed, stamped envelope so that they sign and return one copy of the consent form back to their local neurosurgical unit. The returned consent form will be filed in a local NSU filing system. Data collection would not start before the local NSU has received the signed consent form.

Patients will be given sufficient time to consider the study and patients will have the contact details of their local NSU investigators so that they may ask questions. Patients must be told that the study is completely voluntary. Patients may withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal. If a patient withdraws, identifiable data or tissue already collected with consent would be retained and used in the study. No further data would be collected or any other research procedures carried out on or in relation to the participant.

The parents or legal guardians will consent for children (<16 years) approached for the study and the parents' contact details will be used. If a child turns 16 years of age during the study period, then the patient will be reconsented to remain in the study. For patients who lose capacity during the process of the study will not be contacted again, but the previous information collected (as per their valid consent) will be retained.

The BNTRC Chiari 1 Study is currently limited to 12-month follow up. At the time of consent, an additional option will be for patients to consent to being contacted for future studies. A potential future study will be to collect outcome data at five and/or ten years, but these are considered separate and are not within the current study protocol.

Patients will be given the additional option on the consent form to be contacted following the completion of the study for the synopsis of the overall study results to be emailed to the email address they provided.

9.4. Blinding and code-breaking

This study will not use a blinding procedure.

9.5. Description of study intervention(s), comparators and study procedures (clinical)

This study is only observational.

9.5.1. Description of study procedure(s)

Data collection will have two sources:

The first source is **patient-reported data** and will be acquired at baseline, at 12-months. Additionally, if the patient undergoes decompressive surgery, patients will be asked to complete a survey 12-months after their operation. This patient-reported model of data collection has been piloted and shown to be feasible by the Understanding Cauda Equina Study (Woodfield et al., 2018). After completion of the consent form, patients will have a secure survey sent to them via our online database system called REDCap (explained section 12.3). Once patients have been added to the REDCap system, they will automatically be sent an email invitation when each follow up phase is due. If patients do not want to use the online-based system, then they will be given the option to give their data via post or telephone. If patients do not respond to the initial automated email invitation, local collaborators or the study steering group will contact them via phone to ensure that they have received the invitation.

For children enrolled in the study, it is the parents who will complete the survey, not the child.

The second source is **surgeon-reported data** and will require observational data collection from patient notes, imaging and surgical logs. This data input is performed by the local collaborating study team. We list the full list of data fields in Appendix 3.

9.6. Baseline Assessments

Patient-reported data at baseline will consist of an online questionnaire, including the baseline HRQoL assessment. For a patient's baseline HRQoL to be included in the analysis, the questionnaire must have been completed by 45-days after being seen in the neurosurgical clinic.

Surgeon-reported data at baseline will be by review of clinical records by the study team at the participating NSU.

9.7. Subsequent Assessments

All patients will be followed up at 12-months following first neurosurgical clinic attendance. Patients will be sent an email with a link to the online questionnaire. Either the local study team or steering committee may phone the patient if there is no response to the online questionnaire after seven days.

Surgeon-reported data based on clinical records will also be inputted to the database at the 12-month mark. At the time of this data review, the local investigators will identify a sub-group of the patients who have undergone decompressive surgery since enrolment in the study. For patients who have undergone decompressive surgery, an additional 12-month follow up questionnaire shall be scheduled. Similarly, this sub-group of patients will be sent an email with a link to their questionnaire 12-months after their

operation and the study team or steering group may follow up with a phone call, if necessary, after seven days.

For each follow up timepoint, patient-reported data (i.e. questionnaires) must be completed within 45-days from the target date to be included in the analysis).

9.8. Early Discontinuation/Withdrawal of Participants

During the course of the study a participant may choose to withdraw early from the study treatment at any time. This may happen for several reasons, including but not limited to:

- Inability to comply with study procedures
- Participant decision

If a participant chooses to stop study assessments then all of their identifiable data will be destroyed, but all prior collected data assigned to the non-identifiable study ID will be retained. The participant will not be further contacted by the study team.

In addition, the Investigator may discontinue a participant from the study treatment at any time if the Investigator considers it necessary for any reason including, but not limited to:

- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Significant protocol deviation

9.9. Definition of End of Study

The end of study is the point at which all the study data has been entered and queries resolved.

10. SAFETY REPORTING

Considering that this is purely an observational study, there are no foreseeable potential serious adverse events.

11. STATISTICS AND ANALYSIS

11.1. Statistical Analysis Plan (SAP)

The plan for the statistical analysis of the study are outlined below. There is not a separate SAP document in use for the study.

11.2. Description of the Statistical Methods

For the primary outcome, the baseline and 12-month HRQoL assessments will be used for analysis. For all patients, comparison will be made between baseline and 12-months, but both will also be compared against the UK normative datasets.

For the secondary outcome pertaining to the sub-group undergoing decompressive surgery, HRQoL data will be similarly be compared to baseline and to UK normative datasets. Further comparisons of outcome data will be made between specific surgical techniques used, baseline symptoms and radiological findings.

Descriptive statistics will be used to report the data from the exploratory objective, regarding referral pathways, investigations and management strategies for CM1 in UK neurosurgical practice.

11.3. Sample Size Determination

A pilot retrospective data review from two neurosurgical units (Birmingham and Oxford) showed that, in one month, one unit saw eleven and the other saw four patients that met the inclusion criteria aforementioned. Assuming a 50% recruitment rate, we would recruit around 90 patients in one year in these two units. Although we hope that more than 30 NSUs take part, if 12 similar sized units took part, we could potentially recruit >500 patients. These pessimistic estimates will account for some NSUs not taking part and also for patient withdrawals.

11.4. Analysis populations

Adult and paediatric HRQoL will be analysed separately since the measurement tools are different. Health related quality of life (HRQoL) will be measured in adults (16 years and above) using the 36-Item Short Form Health Survey (SF-36; UK version). HRQoL will be measured in children (2 – 15 years) using the Age-appropriate parent-reported Pediatric Quality of Life Inventory™ (PedsQL™; UK version). Children less than two years of age will be recruited into the study, but not included in the HRQoL analyses.

11.5. Decision points

Following the last possible date of patient recruitment (6th April 2022), a review of the number of recruited patients will be performed.

11.6. The Level of Statistical Significance

Statistical significance will be set at $p < 0.05$.

11.7. Procedure for Accounting for Missing, Unused, and Spurious Data.

For surgeon-reported data, the database entry system with standardised fields will prevent spurious or duplicate data input. If missing data is noted by the principal investigators, the local study team will be contacted and asked to provide the data.

For patient-reported data, if any duplicate questionnaires are filed, the first submitted questionnaire will be used. Patients may be contacted up to 45-days after the relevant past due assessment by the study team if there is a missing questionnaire.

11.8. Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Deviations from the original statistical plan will be described and justified in protocol and/or in the final report, as appropriate).

12. DATA MANAGEMENT

The plan for the data management of the study are outlined below. There is not a separate Data Management document in use for the study.

12.1. Source Data

As described in 9.6.1, source data falls under two categories:

1. Patient-reported data (questionnaires)
2. Surgeon-reported data (medical records, theatre records and radiology)

All source data and documents will be stored securely on the REDCap database. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by identifiable information.

12.2. Access to Data

Direct access will be granted to authorised representatives from the Sponsor and host institution for monitoring and/or audit of the study to ensure compliance with regulations.

12.3. Data Recording and Record Keeping

Data will be entered onto a secure, online database platform called REDCap (https://projectredcap.org/) [13]. REDCap has been used extensively in clinical studies by the NHS and UK universities, including the recent DISCOVER study by the STARSurg collaborative [14]. Online data capture has been used successfully by previous BNTRC studies, such as the Understanding Cauda Equina Study [15].

All information will be kept strictly confidential and the study will comply with the Data Protection Act 1998 and the EU General Data Protection Regulation (GDPR).

Every member of the local study teams will be given personal log-in details in order to input and access data to and from the database. Local study team members will have full access to their local data, but not the data of other participating NSUs. The lead/Sponsor site (Oxford) will have full access to all of the data (from every NSU) to allow multicentre data analysis, ensure ongoing validity of the study or to follow up with patients. The REDCap system also allows the lead/Sponsor site full visibility of the electronic audit trail that tracks all user activity on the database, allowing full accountability of its usage and to ensure standard operating procedures are maintained.

Once a patient electronically signs the consent form, the REDCap system will automatically assign the patient a unique UK Chiari 1 Study ID number. Each NSU will keep a log of the corresponding local ID number or NHS number on their local secure NHS system. With their consent, each patient's email address and phone number will be securely stored on the database and is hidden behind access controls

so that only the local collaborator and principal investigators can see them. Other than on the consent form, the name and any other identifying detail will not be included in any study data electronic file.

Following completion of the study, all data recorded on the database will be downloaded by the sponsor site and retained within the secure electronic NHS system for at a maximum of 10 years following completion of the study. Data, including the separately stored consent forms, will be retained further if patients have been consented to being contacted for future studies.

13. QUALITY ASSURANCE PROCEDURES

Quality assurance procedures will be conducted by the Sponsor site. The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

13.1. Study Committees

The *UK Chiari 1 Study* will be overseen by the *UK Chiari 1 Study* steering committee, who will meet at least six-monthly to ensure ongoing validity of the study.

The *UK Chiari 1 Study* was selected for support by the BNTRC following an open, national call for projects in 2018. It has been reviewed by the BNTRC committee, the Society of British Neurological Surgeons (SBNS) Academic Committee, and the British Syringomyelia Chiari Group (BSCG).

14. PROTOCOL DEVIATIONS

A study related deviation is a departure from the ethically approved study protocol, other study document or process or from Good Clinical Practice (GCP) requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file.

A standard operating procedure should be in place describing the procedure for identifying non-compliances, escalation to the central team and assessment of whether a non-compliance /deviation may be a potential Serious Breach.

15. SERIOUS BREACHES

A “serious breach” is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the study subjects; or

(b) the scientific value of the research.

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and the relevant NHS host organisation within seven calendar days.

16. ETHICAL AND REGULATORY CONSIDERATIONS

16.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

16.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice. Whilst it is not an absolute requirement, we would encourage all collaborators to complete their Good Clinical Practice (GCP) training prior to the start of their involvement in the study.

16.3. Approvals

Following Sponsor approval, the protocol, informed consent form and participant information sheet will be submitted to an appropriate Research Ethics Committee (REC), and HRA (where required) and host institutions for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

16.4. Other Ethical Considerations

Patients under the age of 16 will be enrolled into the study by their parents or legal guardians. If a patient turns 16 years of age during the duration of the study, then the patient will be asked to consent for themselves using the same procedures as mentioned in section 9.3. Those who are unable to consent to the study themselves may be enrolled by their next of kin.

16.5. Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, HRA (where required) host organisation, Sponsor and funder (where required). In addition, an End of Study notification and final report will be submitted to the same parties.

16.6. Transparency in Research

Not applicable.

16.7. Participant Confidentiality

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s), with the exception of the consent form where the patient must type their name and sign the form. All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

16.8. Expenses and Benefits

There are no additional visits required of patients and no foreseeable expenses for patients.

17. FINANCE AND INSURANCE

17.1. Funding

This study is kindly supported by the Ann Conroy Trust, primarily a support group for those affected by Chiari malformations, syringomyelia and associated conditions (www.annconroytrust.org). The Ann Conroy Trust is providing £300.

Written permission was given by the Mapi Research Trust (www.mapi-trust.org) to use the PedsQL™ questionnaires free of charge.

17.2. Insurance

NHS bodies are legally liable for the negligent acts and omissions of their employees. If a patient is harmed whilst taking part in a clinical research study as a result of negligence on the part of a member of the study team this liability cover would apply.

17.3. Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

18. PUBLICATION POLICY

In publications of national data, as per the BNTRC model (Chari et al., 2018), all participating trainees and consultants will be named as PubMed-citable collaborators. The REDCap database allows visibility of data input and will ensure that named collaborators have contributed towards the study. Authorship will be decided in accordance with the *International Committee of Medical Journal Editors* (ICMJE). Authors thus far will include the steering group of the UK Chiari 1 Study (Rory J. Piper, Fardad T. Afshari, Wai C. Soon, Angelos Kolias, Rodney Laing, William B. Lo & Jayaratnam Jayamohan), the BSCG and the BNTRC. As per the BNTRC constitution, the senior author will be the BNTRC (https://www.bntrc.org.uk/about-us).

The steering committee and BNTRC will retain ownership of the entire national dataset and the right to publish the data. Local data, however, will be available to the local investigators to facilitate local audit. Local outputs must acknowledge the *UK Chiari 1 Study*.

We plan to submit the following reports for both presentation at national/international meetings and peer-reviewed publication:

- The study protocol, as exampled by the *BNTRC UK Cranioplasty Registry* (Kolias *et al.*, 2014) and the *Understanding Cauda Equina Study* (Woodfield *et al.*, 2018)
- *UK Chiari 1 Study* outcomes

This study is intended as a research study in order to inform further research and perhaps future clinical practice. Variance in practice or the outcomes of individual NSU or neurosurgeon will be available for each NSU to review, but NSU or individual neurosurgeon identifying data will not be exposed publicly or to any other NSU.

19. ARCHIVING

All study documentation will be retained at the Sponsor site for a maximum of 10 years after competition of the study and will not be destroyed without permission from the sponsor. Only the steering committee site and sponsor will have access to the data. Paper documentation will be retained in appropriately secure NHS storage and electronic data will be stored on the sponsor NHS server.

20. REFERENCES

1. Cesmebasi A, Loukas M, Hogan E, et al (2015) The Chiari malformations: a review with emphasis on anatomical traits. Clin Anat 28:184–94 . doi: 10.1002/ca.22442

2. Meadows J, Kraut M, Guarnieri M, et al (2000) Asymptomatic Chiari Type I malformations identified on magnetic resonance imaging. J Neurosurg 92:920–6 . doi: 10.3171/jns.2000.92.6.0920

3. Piper RJ, Pike M, Harrington R, Magdum SA (2019) Chiari malformations: principles of diagnosis and management. BMJ 365:l1159 . doi: 10.1136/bmj.l1159

4. Piper RJ, Magdum SA (2019) Chiari 1 malformation and raised intracranial pressure. Child's Nerv Syst 35:1719–1725 . doi: 10.1007/s00381-019-04232-x

5. Chiari H (1891) Ueber Veränderungen des Kleinhirns infolge von Hydrocephalie des Grosshirns 1). Dtsch Medizinische Wochenschrift 17:1172–1175 . doi: 10.1055/s-0029-1206803

6. Mediratta S, Haden N (2018) Surgeons singing from the same hymn sheet: a proposal for the pre-operative investigation of patients with Chiari malformation. In: Syringomyelia-Chiari 2018 International Symposium

7. Schijman E, Steinbok P (2004) International survey on the management of Chiari I malformation and syringomyelia. Child's Nerv Syst 20:341–8 . doi: 10.1007/s00381-003-0882-2

8. Shweikeh F, Sunjaya D, Nuno M, et al (2015) National trends, complications, and hospital charges in pediatric patients with Chiari malformation type I treated with posterior fossa decompression with and without duraplasty. Pediatr Neurosurg 50:31–7 . doi: 10.1159/000371659

9. Dyson EW, Chari A, Stevens AR, et al (2015) Intracranial pressure guided management of patients with Chiari malformations presenting with headache: a paradigm shift? Fluids Barriers CNS 12:O29 . doi: 10.1186/2045-8118-12-S1-O29

10. Gallo P, Sokol D, Kaliaperumal C, Kandasamy J (2017) Comparison of Three Different Cranio-Cervical Decompression Procedures in Children with Chiari Malformation Type I: Does the Surgical Technique Matter? Pediatr Neurosurg 52:289–297 . doi: 10.1159/000479327

11. Kurzbuch AR, Jayamohan J, Magdum S (2019) Decompressive surgery for Chiari I malformation in children without dural repair: a still effective and safe procedure? Child's Nerv Syst. doi:

10.1007/s00381-019-04241-w

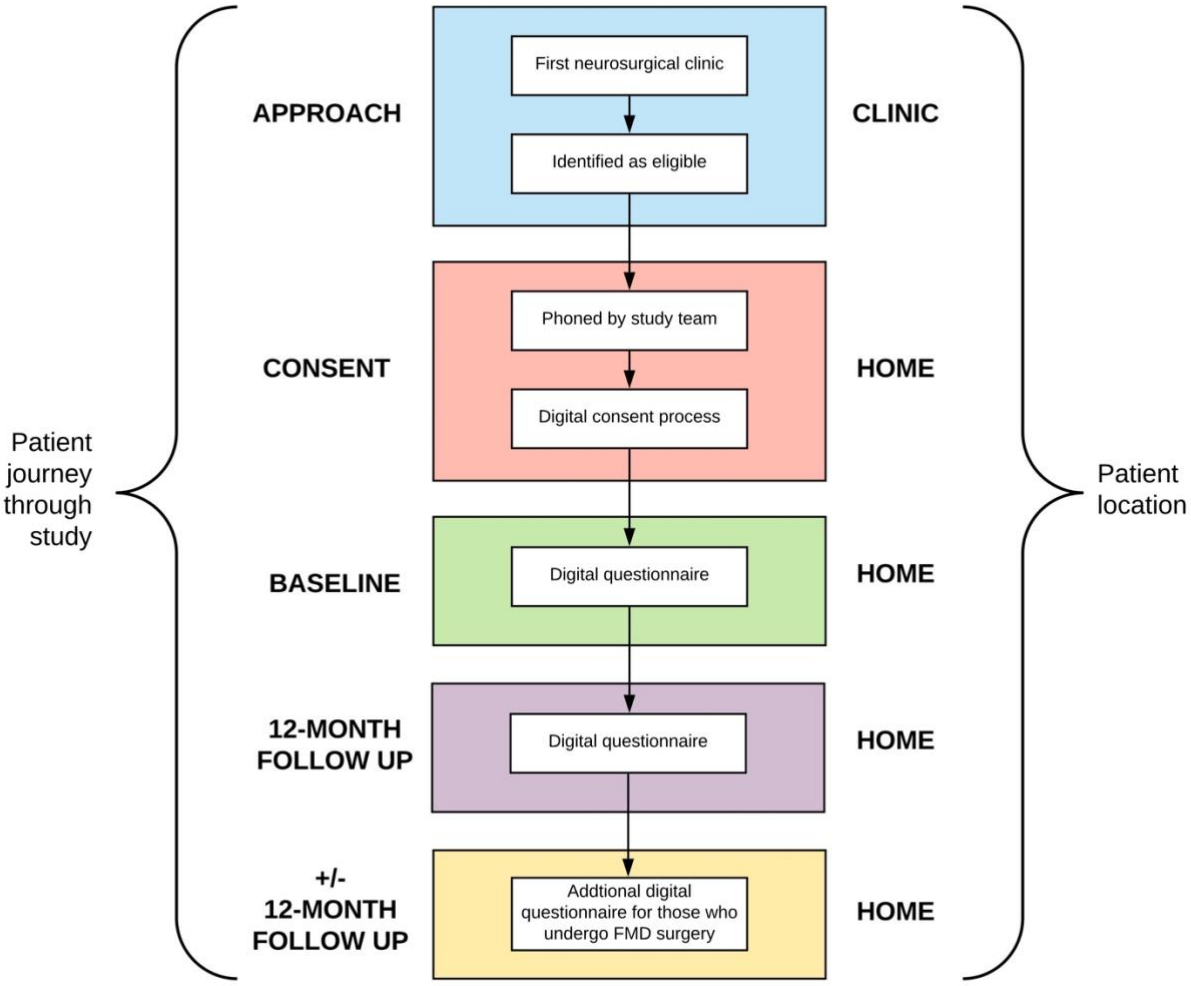
12. McGirt MJ, Attenello FJ, Datoo G, et al (2008) Intraoperative ultrasonography as a guide to patient selection for duraplasty after suboccipital decompression in children with Chiari malformation Type I. J Neurosurg Pediatr 2:52–7 . doi: 10.3171/PED/2008/2/7/052

13. Harris PA, Taylor R, Thielke R, et al (2009) Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 42:377–81 . doi: 10.1016/j.jbi.2008.08.010

14. Nepogodiev D, Chapman SJ, Glasbey J, et al (2015) Determining Surgical Complications in the Overweight (DISCOVER): a multicentre observational cohort study to evaluate the role of obesity as a risk factor for postoperative complications in general surgery. BMJ Open 5:e008811 . doi: 10.1136/bmjopen-2015-008811

15. Woodfield J, Hoeritzauer I, Jamjoom AAB, et al (2018) Understanding cauda equina syndrome: protocol for a UK multicentre prospective observational cohort study. BMJ Open 8:e025230 . doi: 10.1136/bmjopen-2018-025230

21. APPENDIX A: STUDY FLOW CHART



22. APPENDIX B: SCHEDULE OF STUDY PROCEDURES

Procedures	**Day 0**	**Day 0***	**12-months***	**12-months after date of decompressive surgery***
Baseline	x			
First neurosurgical clinic	x			
Identified as eligible	x			
Approached for study		x		
Consented for study		x		
12-month patient-reported data			x	
12-month surgeon-reported data			x	
Additional 12-month **patient-reported data** (for decompressive surgery group)				x
Additional 12-month **surgeon-reported data** (for decompressive surgery group)				X
*45 days are allowed for patients to complete the questionnaire.				

23. APPENDIX C: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	2.0	13.10.20	Rory Piper	• Study start date changed to 8.10.20 • Study end date changed to 7.3.24 • 3-year study timeline is site-dependent and begins on the opening of the study at each site