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Safety study of sibling cord blood cell infusion to children with cerebral palsy: study protocol and rationale

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Abstract

Introduction: Cerebral palsy (CP) is the most common physical disability of childhood but has no cure. Stem cells have the potential to improve brain injury and are proposed as a therapy for CP. However, many questions remain unanswered about the most appropriate cell type, timing of infusions, dose required and associated risks. Therefore, human safety and efficacy trials are necessary to progress knowledge in the field.

Methods and Analysis: This is a single group study with sample size N=12 to investigate safety of single dose intravenous 12/12 HLA matched sibling cord blood cell infusion to children with CP aged 1-16 years without immune suppression. The study is similar to a 3+3 design, where the first two groups of participants have severe CP, and the final 6 participants include children with all motor severities. Children will be monitored for adverse events and the duration that donor cells are detected. Assessments at baseline, 3 and 12 months will investigate safety and preliminary evidence of change in gross motor, fine motor, cognitive and quality of life outcomes.

Ethics and dissemination: Full human research ethics approval was obtained, and a clinical trial notification was accepted by Australia's Therapeutic Goods Administration. Participant guardian informed consent will be obtained before any study procedures. The main results of this study will be submitted for publication in a peer-reviewed journal.

Trial registration number: ACTRN12616000403437, NCT03087110

Keywords: Cerebral palsy, cord blood, stem cell, safety, protocol

Word count: 4605

Article Summary

Strengths and limitations of this study

- This is a rigorous safety study of a potential stem cell intervention for children with CP
- An advantage of the study is the investigation to determine cell persistence in immune-competent patients' circulation, which is relevant to many patient groups.
- However, as this is a safety study, the sample size is small, using a heterogeneous participant population.

Introduction

Cerebral palsy

Cerebral palsy (CP) describes a group of permanent non-progressive motor and postural disorders arising from damage to the developing brain while *in utero*, during birth or in the first years of life [1 2], and affects around 2 per 1000 live births across the world. Depending on the location and severity of brain damage, different regions of the body may be affected. The main types of motor disorder found in CP include spasticity (stiffness of muscles accounting for around 80% of all diagnoses), dyskinesia (abnormal involuntary movements) and ataxia (unsteadiness) which result from lack of normal nervous control of muscles.

CP may be classified by the distribution of impairment: hemiplegia indicates that one side of the body is affected, diplegia that the legs greater than arms are affected and quadriplegia involves all four limbs and often the trunk. The degree of motor impairment is often defined using the Gross Motor Function Classification System (GMFCS), with GMFCS I describing a mildly impaired child able to walk independently, increasing in severity to GMFCS V indicating limited motor function and wheelchair use with poor head control. CP is often associated with epilepsy, difficulties in speech, sight, hearing, sensation, perception, behaviour or cognition. There is currently no cure for CP.

Cord blood for CP

Recent interest in stem cell therapy for intractable neurological disorders has led to a large number of preclinical studies of brain injuries related to CP that show evidence of therapeutic potential. Human umbilical cord blood was used as the source of stem cells as it is less ethically complex than other sources. Umbilical cord blood has been shown to be therapeutically useful and contains a variety of multipotent stem cells and other active cell types. The stem cells in UCB do not lead to cancers and present a lower risk of graft-versus-host disease (GvHD) than bone marrow stem cells [3]. Transplantation of UCB cells in acute animal models of CP such as excitotoxic white matter injury [4] and neonatal hypoxia-ischaemia [5-10] have shown significant neurofunctional improvement, as have models of adult stroke [11-16], spinal cord injury [17-21] and traumatic brain injury [22]. While some studies involve transplanting UCBCs directly to the injured area of the brain, there is evidence that the minimally invasive intravenous infusion to the periphery is equally as effective [4 23]. Because peripherally administered human (xenogeneic) stem cells do not engraft to replace lost brain cells in immune-suppressed animal models, such stem cell treatment is conceptualised best as a transfusion, not a transplant.

Investigations into the mechanism of action of UCBC infusion reveal (a) decreased astrogliosis and neuronal apoptosis [24 25]; (b) increased white matter injury repair [6 26 27]; (c) angiogenesis [10 28]; and (d) enhancement of endogenous neural stem cell proliferation [29 30]. CP is a heterogeneous condition with varied brain pathology, and stem cell infusion may act through different mechanisms for different children [29 31 32]. Preclinical work has focussed mainly on acute brain injury, which involves

inflammation, primary and secondary cell death and chemical signalling, and it is unknown if these transfusion mechanisms will operate in the same way in the chronic phase of disease.

Safety considerations

Autologous blood transfusions are immunologically safe, while allogeneic cell infusions introduce the risk of an immune response. The first use of allogeneic UCBC infusion was a transplant in 1989 [33], and after optimising the technique in immune-depleted conditions for 25 years, there is still a risk of mortality from GvHD, whereby the donor cells attack the immune-suppressed recipient. This risk is at its lowest when using fully matched related donors [3].

The preclinical data behind stem cell therapy as a possible treatment for CP demonstrates that donor UCBCs may not need to persist or engraft to mediate functional benefit. Given the risks and side effects, and little expected benefit, this protocol does not use a conditioning regimen or immune suppression. Without immune suppression, the recipient's immune system is expected to easily reject infused cells, further reducing the risk of GvHD.

There is a risk when a cryopreservant such as dimethyl sulfoxide (DMSO) is required which will be mitigated by 'washing' the cord blood unit before infusion. There is also a risk as with any intravenous (i.v.) cell infusion that pulmonary capillaries may temporarily become blocked [34]. These adverse events are considered temporary and treatable.

Rationale for phase I study

Despite the lack of conclusive evidence, UCBC infusion for CP is already in use in some parts of the world. Moreover, Australian children with CP are travelling to different parts of the world to undergo UCBC therapy in an unregulated environment and at a great financial cost [35]. Therefore, well-designed and properly administrated trials evaluating the safety and efficacy of UCBCs in CP are necessary to guide clinicians and to inform patients and their families; and if successful, to develop treatment programs in Australia. Such treatments would ideally involve cells that are available to any child with CP, yet this must be balanced against the increasing risk profile of cells taken from unrelated donors when there is as yet little evidence of benefit. For the same reasons, the method of administration must be designed to reduce risk wherever possible. A recent systematic review and meta-analysis of stem cells used for children with CP indicated an acceptable risk-benefit ratio of 3% adverse events in CP stem cell recipients and 2% adverse events in controls [36]. This study aims to investigate safety in cryopreserved washed 12/12 HLA matched sibling UCBCs, i.v. infused without immune suppression.

Methods

Aims and objectives

Primary objective

The primary objective of this study is to gain preliminary information on the safety of 12/12 HLA matched sibling UCBC infusion in children with CP.

Secondary objectives

The secondary objectives of this study are:

A) to gain preliminary information on the treatment effect of 12/12 HLA matched UCBC infusion relative to baseline
B) to better understand the length of time that infused matched sibling UCBCs remain within recipients
C) to gather information and samples for future studies into the mechanistic activity of UCBCs

Study design

Multisite single group investigator-initiated safety study conducted in tertiary hospitals. Rather than dose escalation, a 3+3 type design, with independent safety review by an independent Data Safety Monitoring Board (DSMB) comprising transplant, paediatric, rehabilitation, biostatistical and clinical trials expertise between each group of 3 to assess the ongoing ethical acceptability of the study. After

the first 3+3 participants with severe CP, the DSMB will decide whether the study can include a reduced burden of disease and continue with the final six participants having CP of any severity (see Table 1). Any indication of Graft-versus-Host Disease (GvHD) severe enough to require intervention will stop the study.

Table 1: Participant cohorts within 3+3 type design

Cohort	No. of participants	Burden of disease
1	3	Severe CP
2	3	Severe CP
3	6	CP of any severity

Subject/study population

Inclusion Criteria

To be eligible for this study, the following criteria must be fulfilled:

- Aged older than 1 year and younger than 16 years at the time of enrolment
- Diagnosis of CP
- 12/12 HLA matched sibling CBU in storage at a TGA licenced private cord blood bank
- Ability to travel to one of the trial centres and participate in assessments
- Informed consent by parent/guardian and an indication of willingness/compliance by children

Exclusion Criteria

Patients will be unable to participate in the trial if they:

- Show presence of progressive neurological disease
- Have a known genetic disorder
- Have a known brain dysplasia
- Have ever been diagnosed with an immune system disorder or immune deficiency syndrome
- Have infectious disease markers showing up on the virology screen
- The intended cord blood unit shows evidence of contamination or has fewer than 10^7 nucleated cells per kg of body mass
- Require ventilator support
- Are unwell, or if the participant's medical condition does not allow safe travel
- Have previously undertaken any form of cell therapy
- Have had, or are scheduled for, treatment with Botulinum toxin A within three months before or after infusion
- Have had, or are scheduled for, surgery within three months before or after infusion
- Cannot obtain parental or guardian consent

Enrolment and Screening

The study will be advertised through private Australian cord blood banks, clinical trial registries, CP professional and community organisations and institutional websites. When families of children with CP approach the study team with evidence of sibling cord blood unit in storage, they are provided with full information and invited to an informed consent discussion. Once written parent/guardian consent is obtained, and optional consent for extended use of biological samples is considered, screening for HLA match is undertaken. A 75% screen fail rate is expected due to HLA mismatch, and no other eligibility screening is undertaken until this result is available.

Schedule of assessments

Study phase	*Screening*	*Baseline*	*Infusion*	*Follow up*					
Timing	*> 8 wks prior to infusion*	*28 days prior to infusion*	*0*	*1 day*	*1 wk*	*1 mo*	*3 mo*	*6 mo*	*12 mo*
Informed consent	X								

Medical history, CP assessment		X							
Medical examination, adverse events		X	X	X	X	X	X	X	X
Motor function assessment		X					X		X
Upper limbs assessment		X					X		X
Quality of life assessment		X					X		X
Cognition assessment		X							X
Infusion of UCBCs			X						
Blood collection	X	X	2X	X	X	X	X		

Intervention

The intervention will take place as a day procedure within a tertiary hospital paediatric haemopoietic stem cell transplant ward to ensure appropriate expertise. After peripheral venous cannulation (PVC), the patient will receive i.v. normal saline for 2 hours along with hydrocortisone, antihistamine, paracetamol and ondansetron to reduce risk of adverse infusion reactions.

Cryopreserved UCBCs are pilot-thawed by the storage facility before shipment, checked on arrival at the Cell Therapy Laboratory, and washed and resuspended in dextran/albumin to a volume of 100ml. Infusion must be completed within 1 hour of thaw: infusion by gravity for 5 minutes, then paused to assess immediate safety before continuing. Minimum cell dose of 10^7 total nucleated cells/kg is based on pilot thaw cell counts. Normal saline is provided for an additional 4 hours after infusion, and intramuscular rhesus D immunoglobulin provided if donor/recipient is a rhesus mismatch. Vital signs and adverse events will be monitored, and the patient discharged if medically stable.

Treatment discontinuation

Treatment administration is a single dose; therefore, interruption or discontinuation will only occur in response to immediate infusion reactions. Infusion will initially be interrupted, and continued if safe, but discontinued if reactions cannot easily be treated.

Endpoints

Safety

The primary safety endpoint will be assessed through the number of adverse events (AEs) possibly related to UCBCs or infusion procedure. AEs will be elicited during observation, study visit medical reviews, laboratory tests, and between-visit reports from families. Relationship of AEs to study intervention will be assessed based on expectedness, timing relative to infusion, ongoing presence of donor DNA in the circulation, the patient's clinical state and environment.

Preliminary efficacy

Motor function will be assessed using the gold standard for CP, the Gross Motor Function Measure (GMFM-66) which is valid, reliable and responsive to change [37] and has population norms available. Upper limb movement will be assessed with the Quality of Upper Extremity Skills Test (QUEST), which measures each upper limb separately, then combines limb scores for each of four domains: Disassociated movements, Grasp, Weight-bearing and Protective extension. The QUEST is limited by measuring impairment reduction rather than functional activity but is one of the few bimanual assessment tools for CP with appropriate psychometric properties [38].

Cognitive assessment for CP is known to be challenging due to the motor requirements, yet there is anecdotal evidence of improvements in attention and learning following stem cell transplants. The direct cognitive assessments will be age appropriate (Bayley Scales of Infant Development, second edition, for 1-2 year old children, Wechsler Preschool Primary Scale of Intelligence, fourth edition, for

2-6 year old children and Wechsler Intelligence Scale for Children, fifth edition, for 6-16 year old children). Additionally, the Beery-Buktenica Developmental Test of Visual-Motor Integration will be used, along with parent report versions of the Vineland Adaptive Behaviour Scales second edition, Behaviour Rating Inventory of Executive Function, and the Strengths and Difficulties Questionnaire.

Donor cell persistence

Because there is no direct evidence of the longevity of matched sibling cord blood cells after infusion to an immune-competent recipient, donor cell persistence will be examined using a highly sensitive surrogate chimerism analysis of donor DNA. Donor and recipient will be genotyped to detect copy number deletions; then digital droplet PCR will be used to quantify the fraction of donor DNA, sensitive to 20 genome equivalents/mL [39].

Statistical analysis

As the primary aim of this study is to assess safety, the sample size of 12 participants was selected to allow sequential groups of three participants. We will compare group characteristics with population data from the Australian Cerebral Palsy Register to assess the generalisability of the results obtained. Given the pilot nature of this trial, the results from this study will be presented descriptively. Safety data will be summarised as the proportion of participants who have an SAE and an AE within either of the three safety periods: within 36 hours, within three months or within the 12-month study period. The change in lab results at each time point will be presented relative to baseline. Change in motor and cognitive function will be presented relative to baseline. Donor cell persistence data will be categorised as 'immediate rejection' to indicate return to baseline fraction of donor DNA within 24 hours; 'rejection' to indicate a return to baseline fraction of donor DNA by 1 month; 'slow rejection' to indicate the presence of between 200 donor genome equivalent/ml and engraftment at 3 months, and 'engraftment'.

Data management and administrative aspects

Study data will be collected and managed using REDCap electronic data capture tools hosted at MCRI. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. Hard copy documents will be stored in locked files, and electronic files will be password protected and accessible by the study team only. Final data collection is predicted to occur mid-2020. Records will be securely stored until the youngest participant turns 25 years of age, although records of biobanked samples and their consent conditions may be retained longer.

Neuroscience Trials Australia will independently verify source data and adherence to Good Clinical Practise. The study may be audited or inspected by representatives of regulatory organisations.

Data statement: The de-identified data set collected for this analysis of the SCUBI-CP trial will be available six months after publication of the primary outcome. The study protocol, analysis plan and consent forms will also be available. The data may be obtained from the Murdoch Children's Research Institute. Prior to releasing any data the following are required: a data access agreement must be signed between relevant parties, the SCUBI-CP Trial Steering Committee must see and approve the analysis plan describing how the data will be analysed, there must be an agreement around appropriate acknowledgement and any additional costs involved must be covered. Should the Trial Steering Committee be unavailable, this role is delegated to the Murdoch Children's Research Institute. Data will only be shared with a recognised research institution which has approved the proposed analysis plan.

Ethics and dissemination

This study received initial approval from The Royal Children's Hospital Human Research Ethics Committee (HREC) in late 2015, as have all changes to participant documents and protocol amendments. The current protocol is version 10, approved on 6 March 2017. A clinical trial notification was submitted to the Therapeutic Goods Administration, Australia, in March 2016. The study is registered on both the Australian and New Zealand Clinical Trials Registry and

Clinicaltrials.gov with all items from the World Health Organisation Trial Registration Data Set and regularly updated. Publication in a peer-reviewed journal is planned regardless of the outcome. The decision of what to publish and when, along with authorship according to Vancouver guidelines, will be made by the trial Steering Committee. No participant will be identifiable from the data reported.

Patient and Public Involvement

A Delphi study of research priorities for CP found that stem cell research was the third highest research priority [40] for the community. The CP Quest community reference group will be consulted before communication of study outcomes to ensure the messages and distribution are appropriate. No attempt was made to assess the burden of the intervention by patients themselves.

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Declaration of Interests

Cell Care Australia is a private cord blood bank with a representative on the Trial Steering Committee. There is, therefore, a potential conflict of interest which has been declared to HREC and Steering Committee and is well recognised. No one affiliated with Cell Care Australia will be involved in data analysis or interpretation.

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Author Contributions

All authors provided substantial contribution to design and drafting. KC: coordination of the study. FM, NE, IN: content expertise; KL: biostatistical study design; DR, MF, NB, EW, PC, FM, IN, KL, PE and KC: members of the Steering Committee; DR: study lead at coordinating centre (The Royal Children's Hospital), PE: study lead at sub site (Brisbane Children's Hospital).

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	6
Protocol version	#3	Date and version identifier	6
Funding	#4	Sources and types of financial, material, and other support	6
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	7
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	6, 1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	6
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team,	3, 7

		and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2, 3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	NA (no comparator)
Objectives	#7	Specific objectives or hypotheses	3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	3
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data	3

		will be collected. Reference to where list of study sites can be obtained	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	5
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	NA (intervention is single dose)
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	4
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical	5

		relevance of chosen efficacy and harm outcomes is strongly recommended	
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	4
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	3
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	4
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	NA (single group study)

Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	NA (single group study)
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA (single group study)
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA (single group study)
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA (single group study)
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and	6

		validity, if known. Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	6
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	6
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	5
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	NA (none planned)
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	5
Methods: Monitoring			

Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	3
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	3
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	5
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	6
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	6

Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	6
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	4
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	4
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	7
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	6
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA

Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	6
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	7
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	6
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Uploaded as separate file
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Available upon request

BMJ Open

Single group multisite safety trial of sibling cord blood cell infusion to children with cerebral palsy: study protocol and rationale

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Single group multisite safety trial of sibling cord blood cell infusion to children with cerebral palsy: study protocol and rationale

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Abstract

Introduction: Cerebral palsy (CP) is the most common physical disability of childhood but has no cure. Stem cells have the potential to improve brain injury and are proposed as a therapy for CP. However, many questions remain unanswered about the most appropriate cell type, timing of infusions, dose required and associated risks. Therefore, human safety and efficacy trials are necessary to progress knowledge in the field.

Methods and Analysis: This is a single group study with sample size N=12 to investigate safety of single dose intravenous 12/12 HLA matched sibling cord blood cell infusion to children with CP aged 1-16 years without immune suppression. The study is similar to a 3+3 design, where the first two groups of participants have severe CP, and the final 6 participants include children with all motor severities. Children will be monitored for adverse events and the duration that donor cells are detected. Assessments at baseline, 3 and 12 months will investigate safety and preliminary evidence of change in gross motor, fine motor, cognitive and quality of life outcomes.

Ethics and dissemination: Full approval was obtained from the Royal Children's Hospital Human Research Ethics Committee, and a clinical trial notification was accepted by Australia's Therapeutic Goods Administration. Participant guardian informed consent will be obtained before any study procedures. The main results of this study will be submitted for publication in a peer-reviewed journal.

Trial registration number: ACTRN12616000403437, NCT03087110

Keywords: Cerebral palsy, cord blood, stem cell, safety, protocol

Word count: 4605

Article Summary

Strengths and limitations of this study

- This is a rigorous safety study of a potential stem cell intervention for children with CP
- An advantage of the study is the investigation to determine cell persistence in immune-competent patients' circulation, which is relevant to many patient groups.
- However, as this is a safety study, the sample size is small, using a heterogeneous participant population.

Introduction

Cerebral palsy

Cerebral palsy (CP) describes a group of permanent non-progressive motor and postural disorders arising from damage to the developing brain while *in utero*, during birth or in the first years of life [1 2], and affects around 2 per 1000 live births across the world [3]. Depending on the location and severity of brain damage, different regions of the body may be affected. The main types of motor disorder found in CP include spasticity (stiffness of muscles accounting for around 80% of all diagnoses), dyskinesia (abnormal involuntary movements) and ataxia (unsteadiness) which result from lack of normal nervous control of muscles [1].

CP may be classified by the distribution of impairment: hemiplegia indicates that one side of the body is affected, diplegia that the legs greater than arms are affected and quadriplegia involves all four limbs and often the trunk. The degree of motor impairment is often defined using the Gross Motor Function Classification System (GMFCS), with GMFCS I describing a mildly impaired child able to walk independently, increasing in severity to GMFCS V indicating limited motor function and wheelchair use with poor head control [4]. CP is often associated with epilepsy, difficulties in speech, sight, hearing, sensation, perception, behaviour or cognition. There is currently no cure for CP.

Cord blood for CP

Recent interest in stem cell therapy for intractable neurological disorders has led to a large number of preclinical studies of brain injuries related to CP that show evidence of therapeutic potential. Human umbilical cord blood was used as the source of stem cells as it is less ethically complex than other sources. Umbilical cord blood has been shown to be therapeutically useful and contains a variety of multipotent stem cells and other active cell types. The stem cells in UCB do not lead to cancers and present a lower risk of graft-versus-host disease (GvHD) than bone marrow stem cells [5]. Transplantation of UCB cells in acute animal models of CP such as excitotoxic white matter injury [6] and neonatal hypoxia-ischaemia [7-12] have shown significant neurofunctional improvement, as have models of adult stroke [13-18], spinal cord injury [19-23] and traumatic brain injury [24]. While some studies involve transplanting UCBCs directly to the injured area of the brain, there is evidence that the minimally invasive intravenous infusion to the periphery is equally as effective [6 25]. Because peripherally administered human (xenogeneic) stem cells do not engraft to replace lost brain cells in immune-suppressed animal models, such stem cell treatment is conceptualised best as a transfusion, not a transplant.

Investigations into the mechanism of action of UCBC infusion reveal (a) decreased astrogliosis and neuronal apoptosis [26 27]; (b) increased white matter injury repair [8 28 29]; (c) angiogenesis [12 30]; and (d) enhancement of endogenous neural stem cell proliferation [31 32]. CP is a heterogeneous condition with varied brain pathology, and stem cell infusion may act through different mechanisms for different children [31 33 34]. Preclinical work has focussed mainly on acute brain injury, which involves

inflammation, primary and secondary cell death and chemical signalling, and it is unknown if these transfusion mechanisms will operate in the same way in the chronic phase of disease.

Safety considerations

Autologous blood transfusions are immunologically safe, while allogeneic cell infusions introduce the risk of an immune response. The first use of allogeneic UCBC infusion was a transplant in 1989 [35], and after optimising the technique in immune-depleted conditions for 25 years, there is still a risk of mortality from GvHD, whereby the donor cells attack the immune-suppressed recipient. This risk is at its lowest when using fully human leucocyte antigen (HLA) matched related donors [5]. Generic HLA matching examines six HLA genes and requires a minimum 4/6 HLA match depending on clinical context, however technology allows examination of additional HLA genes.

The preclinical data behind stem cell therapy as a possible treatment for CP demonstrates that donor UCBCs may not need to persist or engraft to mediate functional benefit [36]. Given the risks and side effects, and little expected benefit, this protocol does not use a conditioning regimen or immune suppression. Without immune suppression, the recipient's immune system is expected to easily reject infused cells, further reducing the risk of GvHD.

There is a risk of nausea, anaphylaxis and cardiovascular side effects when a cryopreservant such as dimethyl sulfoxide (DMSO) is required which will be mitigated by 'washing' the cord blood unit before infusion [37]. There is also a risk as with any intravenous (i.v.) cell infusion that pulmonary capillaries may temporarily become blocked [38], although this is less likely with cord blood or bone marrow mononuclear cells than larger types of stem cell [39]. These adverse events are considered temporary and treatable [37 38].

Rationale for phase I study

Despite the lack of conclusive evidence, UCBC infusion for CP is already in use in some parts of the world. Moreover, Australian children with CP are travelling to different parts of the world to undergo UCBC therapy in an unregulated environment and at a great financial cost [40]. Therefore, well-designed and properly administrated trials evaluating the safety and efficacy of UCBCs in CP are necessary to guide clinicians and to inform patients and their families; and if successful, to develop treatment programs in Australia. Such treatments would ideally involve cells that are available to any child with CP, yet this must be balanced against the increasing risk profile of cells taken from unrelated donors when there is as yet little evidence of benefit. For the same reasons, the method of administration must be designed to reduce risk wherever possible. A recent systematic review and meta-analysis of controlled trials of stem cells used for children with CP found five trials that met criteria, studying four different types of stem cells (fetal- and bone marrow-derived neural stem cells, olfactory ensheathing cells and allogenic UCBCs; all cryopreserved) at doses ranging from $2x10^6$ cells in total to $\geq 3x10^7$ cells/kg. The analysis indicated an acceptable risk-benefit ratio of 3% adverse events in CP stem cell recipients and 2% adverse events in controls and a small intervention effect on gross motor skills [41]. This study aims to investigate safety in cryopreserved washed 12/12 HLA matched sibling UCBCs, i.v. infused without immune suppression.

Methods

Aims and objectives

Primary objective

The primary objective of this study is to gain preliminary information on the safety of 12/12 HLA matched sibling UCBC infusion in children with CP.

Secondary objectives

The secondary objectives of this study are:

A) to gain preliminary information on the treatment effect of 12/12 HLA matched UCBC infusion relative to baseline
B) to better understand the length of time that infused matched sibling UCBCs remain within recipients
C) to gather information and samples for future studies into the mechanistic activity of UCBCs

Study design

Multisite single group investigator-initiated safety study conducted in tertiary hospitals. Rather than dose escalation, a 3+3 type design, with independent safety review by an independent Data Safety Monitoring Board (DSMB) between each group of 3 to assess the ongoing ethical acceptability of the study. After the first 3+3 participants with severe CP, the DSMB will decide whether the study can include a reduced burden of disease and continue with the final six participants having CP of any severity (see Table 1). Any indication of Graft-versus-Host Disease (GvHD) severe enough to require intervention will stop the study.

Table 1: Participant cohorts within 3+3 type design

Cohort	No. of participants	Burden of disease
1	3	Severe CP
2	3	Severe CP
3	6	CP of any severity

Safety

The role of the DSMB is to safeguard the interests of trial participants by monitoring safety throughout the trial, trial feasibility, and together, advise Trial Steering Committee and HREC on continuing ethical acceptability. The five-member DSMB will comprise transplant, paediatric, rehabilitation, biostatical and clinical trials expertise and will require a minimum of three members to make decisions according to the trial DSMB Charter.

Adverse events (AEs) will be recorded from the time of infusion until the last visit (12 months post infusion) regardless of their association with the study. The study team will estimate the likelihood that the AE was the result of the study intervention as unrelated, possible, probable or definite, according to the timing of the AE relative to the cell infusion, whether the AE is a known response to infusion, or could have occurred as part of the participant's clinical status or environment.

Serious adverse events (SAEs) will be reported to the DSMB within 72 hours of notification regardless of relatedness. The DSMB will provide independent advice on relatedness and evaluate the study team's response to the SAE (designation as Suspected Unexpected Serious Adverse Reaction or Significant Safety Issue, or requirement of Urgent Safety Measure, all of which will be reported to the local HREC within 72 hours). The DSMB has the power to suspend or cease the trial, and detection of GvHD of a severity that requires treatment will automatically stop the trial.

Subject/study population

Inclusion Criteria

To be eligible for this study, the following criteria must be fulfilled:

- Aged older than 1 year and younger than 16 years at the time of enrolment
- Diagnosis of CP as confirmed by paediatrician and physiotherapist study team members
- 12/12 HLA matched sibling CBU in storage at a TGA licenced private cord blood bank
- Ability to travel to one of the trial centres and participate in assessments
- Informed consent by parent/guardian and an indication of willingness/compliance by children

Exclusion Criteria

Patients will be unable to participate in the trial if they:

- Show presence of progressive neurological disease
- Have a known genetic disorder
- Have a known brain dysplasia
- Have ever been diagnosed with an immune system disorder or immune deficiency syndrome
- Have infectious disease markers on virology screen (HIV 1 and 2 antibody and nucleic acid testing (NAT), hepatitis B core antibody, surface antigen and NAT, hepatitis C antibody and NAT, human T-cell lymphotropic 1 and 2 antibody, cytomegalovirus, syphilis)
- The intended cord blood unit shows evidence of contamination or has fewer than 10^7 nucleated cells per kg of body mass
- Require ventilator support

- Are unwell, or if the participant's medical condition does not allow safe travel
- Have previously undertaken any form of cell therapy
- Have had, or are scheduled for, treatment with Botulinum toxin A within three months before or after infusion
- Have had, or are scheduled for, surgery within three months before or after infusion
- Cannot obtain parental or guardian consent

Enrolment and Screening

The study will be advertised through private Australian cord blood banks, clinical trial registries, CP professional and community organisations and institutional websites. When families of children with CP approach the study team with evidence of sibling cord blood unit in storage, they are provided with full information and invited to an informed consent discussion. Once written parent/guardian consent is obtained, and optional consent for extended use of biological samples is considered (sample consent form in Supplementary material), screening for HLA match is undertaken. A 75% screen fail rate is expected due to HLA mismatch, and no other eligibility screening is undertaken until this result is available (see Table 2).

Table 2: Schedule of assessments

Study phase	*Screening*	*Baseline*	*Infusion*	*Follow up*					
Timing	*> 8 wks prior to infusion*	*28 days prior to infusion*	*0*	*1 day*	*1 wk*	*1 mo*	*3 mo*	*6 mo*	*12 mo*
Informed consent	X								
Medical history, CP assessment		X							
Medical examination, adverse events		X	X	X	X	X	X	X	X
Motor function assessment		X					X		X
Upper limbs assessment		X					X		X
Quality of life assessment		X					X		X
Cognition assessment		X							X
Infusion of UCBCs			X						
Peripheral blood collection	X	X	2X	X	X	X	X		

Intervention

The intervention will take place as a day procedure within a tertiary hospital paediatric haemopoietic stem cell transplant ward to ensure appropriate expertise. After peripheral venous cannulation (PVC), the patient will receive i.v. normal saline for 2 hours along with hydrocortisone, antihistamine, paracetamol and ondansetron to reduce risk of adverse infusion reactions.

Cryopreserved UCBCs previously collected, tested for standard infectious disease markers (HIV, Hep B, C, HTLV, CMV, syphilis), aerobic and anaerobic microbiology contamination/sterility and cell count, and stored in the gaseous phase of liquid nitrogen by a licensed cord blood bank are pilot-thawed by the storage facility before shipment, checked on arrival at the Cell Therapy Laboratory, and washed and resuspended in dextran/albumin to a volume of 100ml. Cell viability, characterisation of CD34+ and CD45+ fraction and sterility are assessed on both pilot-thaw and the final product. Infusion must be completed within 1 hour of thaw: infusion by gravity for 5 minutes, then paused to assess immediate safety before continuing. Minimum cell dose of 10^7 total nucleated cells/kg is based on pilot thaw cell counts and was selected based on preclinical data and international trials at the time of

ethics submission. Normal saline is provided for an additional 4 hours after infusion, and intramuscular rhesus D immunoglobulin provided if donor/recipient is a rhesus mismatch. Vital signs and adverse events will be monitored, and the patient discharged if medically stable.

Treatment discontinuation

Treatment administration is a single dose; therefore, interruption or discontinuation will only occur in response to immediate infusion reactions. Infusion will initially be interrupted, and continued if safe, but discontinued if reactions cannot easily be treated.

Endpoints

Safety

The primary safety endpoint will be assessed through the number of adverse events (AEs) possibly related to UCBCs or infusion procedure by 36 hours, 3 months and 12 months post-infusion. AEs will be elicited during observation, study visit medical reviews with transplant specialist and developmental paediatrician, laboratory tests (full blood examination, liver function tests, inflammatory markers), and between-visit reports from families. Relationship of AEs to study intervention will be assessed based on expectedness, timing relative to infusion, ongoing presence of donor DNA in the circulation, the patient's clinical state and environment.

Preliminary efficacy

Motor function will be assessed using the gold standard for CP, the Gross Motor Function Measure (GMFM-66) which is valid, reliable and responsive to change [42] and has population norms available. Upper limb movement will be assessed with the Quality of Upper Extremity Skills Test (QUEST), which measures each upper limb separately, then combines limb scores for each of four domains: Disassociated movements, Grasp, Weight-bearing and Protective extension. The QUEST is limited by measuring impairment reduction rather than functional activity but is one of the few bimanual assessment tools for CP with appropriate psychometric properties [43]. See Table 2 for the schedule of assessments.

Cognitive assessment for CP is known to be challenging due to the motor requirements, yet there is anecdotal evidence of improvements in attention and learning following stem cell transplants. The direct cognitive assessments will be age appropriate (Bayley Scales of Infant Development, second edition, for 1-2 year old children, Wechsler Preschool Primary Scale of Intelligence, fourth edition, for 2-6 year old children and Wechsler Intelligence Scale for Children, fifth edition, for 6-16 year old children). Additionally, the Beery-Buktenica Developmental Test of Visual-Motor Integration will be used, along with parent report versions of the Vineland Adaptive Behaviour Scales second edition, Behaviour Rating Inventory of Executive Function, and the Strengths and Difficulties Questionnaire.

Donor cell persistence

Because there is no direct evidence of the longevity of matched sibling cord blood cells after infusion to an immune-competent recipient, donor cell persistence will be examined using a highly sensitive surrogate chimerism analysis of donor DNA. Donor and recipient will be genotyped to detect copy number deletions; then digital droplet PCR will be used to quantify the fraction of donor DNA, sensitive to 20 genome equivalents/mL [44].

Patient and Public Involvement

A Delphi study of research priorities for CP found that stem cell research was the third highest research priority [45] for the community. The CP Quest community reference group will be consulted before communication of study outcomes to ensure the messages and distribution are appropriate. No attempt was made to assess the burden of the intervention by patients themselves.

Statistical analysis

As the primary aim of this study is to assess safety, the sample size of 12 participants was selected to allow sequential groups of three participants. We will compare group characteristics with population data from the Australian Cerebral Palsy Register to assess the generalisability of the results obtained. Given the pilot nature of this trial, the results from this study will be presented descriptively. Safety data will be summarised as the proportion of participants who have an SAE and an AE within either of the three safety periods: within 36 hours, within three months or within the 12-month study period.

The change in lab results at each time point will be presented relative to baseline on an individual participant basis, with comparison to published minimal clinically important difference of the tool [46 47]. Change in motor and cognitive function will be presented relative to baseline. Donor cell persistence data will be categorised as 'immediate rejection' to indicate return to baseline fraction of donor DNA within 24 hours; 'rejection' to indicate a return to baseline fraction of donor DNA by 1 month; 'slow rejection' to indicate the presence of between 200 donor genome equivalent/ml and engraftment at 3 months, and 'engraftment'.

Data management and administrative aspects

Study data will be collected and managed using REDCap electronic data capture tools hosted at MCRI. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. Hard copy documents will be stored in locked files, and electronic files will be password protected and accessible by the study team only. Final data collection is predicted to occur mid-2020. Records will be securely stored until the youngest participant turns 25 years of age, although records of biobanked samples and their consent conditions may be retained longer.

Neuroscience Trials Australia will independently verify source data and adherence to Good Clinical Practise. The study may be audited or inspected by representatives of regulatory organisations.

Data statement: The de-identified data set collected for this analysis of the SCUBI-CP trial will be available six months after publication of the primary outcome. The study protocol, analysis plan and consent forms will also be available. The data may be obtained from the Murdoch Children's Research Institute. Prior to releasing any data the following are required: a data access agreement must be signed between relevant parties, the SCUBI-CP Trial Steering Committee must see and approve the analysis plan describing how the data will be analysed, there must be an agreement around appropriate acknowledgement and any additional costs involved must be covered. Should the Trial Steering Committee be unavailable, this role is delegated to the Murdoch Children's Research Institute. Data will only be shared with a recognised research institution which has approved the proposed analysis plan.

Ethics and dissemination

This study received initial approval from The Royal Children's Hospital Human Research Ethics Committee (HREC) in late 2015, as have all changes to participant documents and protocol amendments. The current protocol is version 10, approved on 6 March 2017. A clinical trial notification was submitted to the Therapeutic Goods Administration, Australia, in March 2016. The study is registered on both the Australian and New Zealand Clinical Trials Registry and Clinicaltrials.gov with all items from the World Health Organisation Trial Registration Data Set and regularly updated. Recruitment is complete. Publication in a peer-reviewed journal is planned regardless of the outcome. The decision of what to publish and when, along with authorship according to Vancouver guidelines, will be made by the trial Steering Committee. No participant will be identifiable from the data reported.

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Declaration of Interests

Cell Care Australia is a private cord blood bank with a representative on the Trial Steering Committee. There is, therefore, a potential conflict of interest which has been declared to HREC and Steering

Committee and is well recognised. No one affiliated with Cell Care Australia will be involved in data analysis or interpretation.

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Author Contributions

All authors provided substantial contribution to design and drafting. KC: coordination of the study. FM, NE, IN: content expertise; KL: biostatistical study design; DR, MF, NB, EW, PC, FM, IN, KL, PE and KC: members of the Steering Committee; DR: study lead at coordinating centre (The Royal Children's Hospital), PE: study lead at sub site (Brisbane Children's Hospital).

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Participant Information Sheet/Consent Form – Parent/Guardian

Title	*Safety study of sibling cord blood cell infusion to children with cerebral palsy*
Short Title	*Stem Cells in Umbilical Blood Infusion for CP (SCUBI-CP)*
HREC ID	*HREC/14/RCHM/38*
Principal Investigator	*Prof Dinah Reddihough*
Location	*The Royal Children's Hospital Melbourne*

1 Introduction

This is an invitation for your child to take part in this research project because he or she has cerebral palsy (CP). The research project is testing a possible new treatment for cerebral palsy. The new treatment is called sibling cord blood cell infusion.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want your child to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not your child can take part, you might want to talk about it with a relative, friend or your child's local doctor.

Participation in this research is voluntary. If you do not wish your child to take part, they do not have to. Your child will receive the best possible care whether or not they take part.

If you decide you want your child to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:
• Understand what you have read
• Consent to your child taking part in the research project
• Consent for your child to have the tests and treatments that are described
• Consent to the use of the cord blood you have in storage from a brother or sister to your child who has cerebral palsy
• Consent to the use of your child's personal and health information as described.

You will be given a copy of this Participant Information Sheet and Consent Form to keep.

2 What is the purpose of this research?

Cord blood is the blood collected from the umbilical cord when a child is born. It contains different types of cells, including a small number of stem cells.

Cord blood cell infusion is approved in Australia to treat disorders (conditions) that affect the blood. However, it is not approved as a treatment for cerebral palsy. Therefore, it is an experimental treatment for cerebral palsy. This means that it must be tested to see if it is safe for children with cerebral palsy.

This research study is the first step in a long process of finding out if cord blood cell infusion into a vein can help children with cerebral palsy (CP). We aim to find out if the cord blood cell infusion is safe. Depending on the results of this small safety study, we will need further studies to test the infusion on more people to find out if it does help children with CP.

This safety trial will include infusion with cord blood cells from your child's brother or sister if they match with your child's blood.

3 What does participation in this research involve?

Study length

If you consent to your child participating in this study, there will be about 9 visits with the study team. These visits will mostly be at the hospital, although some may be at your local doctor's clinic if you choose.

Before you consent, you may want to think about whether you and your family are able and willing to commit to the time and travel this study will take.

From the time that you consent, the study will take 14 months or more of your family's involvement.

Screening

We will not start your child in this study until you have signed the consent form and we think that your child is eligible for the study. To find out if your child is eligible, we first need to know if your child has cerebral palsy, whether your child has any disorders of the immune system, and whether any of your children have cord blood currently in storage.

Although your child may be eligible to take part in the study, they may not be able to participate if the study doctor does not think that the cord blood cell infusion is appropriate for your child. For example, this might happen if your child is unhealthy or becomes unwell.

If your child has sibling cord blood in storage, we will find out whether or not the sibling cord blood matches your child with cerebral palsy. Only 1 out of 4 siblings have matching blood. This means that 3 out of 4 children *cannot use* their sibling's blood. If the blood matches and is usable, your child will receive the cord blood cells in an infusion. Once the trial is full, your child will not be able to take part in the study. If the blood does not match, your child is unable to have those cord blood cells in their body. It is much more likely that your child will have to leave the study than to receive cord blood cells.

If your child is not able to take part in the study because the study is full, the study doctor will phone you to tell you whether the cord blood matches or not.

Visits and Procedures

The table below details the visits that are needed as part of this project and what will happen at each visit.

	Visit 1 (Screening)	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
Visit time (hours):	1	5	9	1	1	1	2	1	4
Where:	Hospital	Hospital	Hospital	Hospital	Hospital	Hospital	Hospital	Hospital, community	Hospital
Sign consent form	✓								
Blood samples	✓	✓	✓	✓	✓	✓	✓		
Sibling blood sample		*							
Physical examination		✓		✓		✓	✓	✓	✓
CP assessment		✓							
Gross motor function assessment		✓					✓		✓
Upper limb assessment		✓					✓		✓
Intelligence assessment		✓							✓
Quality of Life questionnaire		✓					✓		✓
Parent questionnaire		✓							✓
Cord blood infusion			✓						
Medical assessment			✓	✓	✓	✓	✓	✓	

Visits 1-4 and 6, 7 and 9 must take place at the hospital. Visit 5 can be completed by the assessment team in your home, and visit 8 can be conducted by your local paediatrician if it is difficult for you to come to the hospital.

Visit 2 can be quite tiring, so we will make sure your child takes regular breaks. If necessary we can split this visit over two days.

Blood samples

Blood will be collected at most visits. Section 10 below describes how much blood will be taken at each visit, what it will be tested for, where it is tested and what happens to the samples after testing.

* If your child has sibling cord blood in storage, we will try to find out not only whether the cells match, but also whether the blood groups match. If we cannot get all the information we need from the cord blood that is in storage, we may need to ask the sibling to give a blood sample. We will tell you if it is necessary to bring the sibling for study visit 2, and what would be involved.

Physical examination

This will involve listening to your child's heart and lungs, feeling the abdomen, taking your child's pulse and respiratory rates, confirming neurological signs including assessing muscle tone and reflexes, and checking your child's skin. The doctor will take a photo of your child's skin to compare with the skin's appearance after the infusion, to help the doctor know whether your child's skin changes during the study.

CP assessment

We will assess your child's CP using some standard tests including the Gross Motor Function Classification Scheme (GMFCS), Australian Spasticity Assessment Scale (ASAS) and the Manual Assessment Classification Scheme (MACS).

Medical assessment

This is to check your child for any reactions following the infusion. It includes questions about your child's general health and may be conducted in person or by phone. If the doctor needs to see your child in person after these questions, we may need to arrange an extra visit for your child to come to the hospital.

Gross Motor Function assessment

We will document your child's motor abilities. A digital video recording of your child will be made to help with the assessment.

Upper Limb assessment

We will look at how your child's arm functions.

Intelligence assessment
We will assess your child's visual construction skills and general intelligence.

Child questionnaires
We will ask your child to complete the CP Quality of Life questionnaire for children. It looks at social wellbeing, feelings about functioning, participation, emotional wellbeing and self-esteem, access to services, pain and impact of disability, and family health.

Parent questionnaires
We will ask you, depending on the age of your child, to complete questionnaires that focus on your child's behaviour.

- The Strengths and Difficulties Questionnaire (SDQ) looks at emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems and prosocial behaviour.
- The Behaviour Rating Inventory of Executive Function (BRIEF) looks at your child's ability to regulate their behaviour, such as to control impulses, to tolerate change and to regulate emotional responses appropriately. The BRIEF also looks at how your child's mind works, such as problem-solving strategies, working memory, ability to plan and organise, and to keep track of their behaviour.
- The Vineland Adaptive Behaviour Scales looks at your child's personal and social skills in everyday life.

Study Intervention

Infusion

Your child will need to come to the hospital for Visit 3 for the study treatment infusion.

During this visit the following procedures will occur:

- A nurse will use a numbing cream and insert an intravenous catheter (IV catheter, a needle) into a vein in your child's arm, hand or foot. This catheter will stay in your child's vein until they are ready to leave the hospital.

- Your child will be given medication to prepare them for the infusion. Some of the medication will go through the IV catheter, some can be by mouth (swallowed). The medications are:
    - To reduce the chance of allergic reaction
        a) Hydrocortisone - IV
        b) Antihistamine (Phenergan or Zyrtec) - IV or by mouth
    - To reduce pain
        a) a) Paracetamol – by mouth
    - To reduce nausea
        a) Ondansetron – by mouth

- If your child is blood group rhesus negative (Rh^-, for example AB^- or O^-), and receiving cord blood cells from a sibling who is blood group rhesus positive (Rh^+), your child may need an injection of anti-rhesus D immunoglobulin (also known as Anti-D) so that your child's blood doesn't build up antibodies that could cause problems in the future. This injection will be through the IV catheter.
- A nurse will take a blood sample from your child.
- Your child will be given intravenous fluids through the catheter (sometimes called a 'drip'). The fluid keeps your child hydrated and helps your child's body to cope with the infusion. It will make them urinate more which gets rid of toxins in the body. The fluid will stay attached to your child's arm for 2 hours before the cord blood cell infusion. Your child will be able to move around during this time.

- When your child is ready and the cord blood cells arrive from the laboratory, your child will receive the product intravenously, through the catheter into a vein. The infusion will take around half an hour. The nurse will continue to give your child extra fluids through the catheter for 4 hours afterwards to look after your child, and will watch him/her carefully and call the doctor if needed.
- The nurse will take another blood sample 4 hours after the infusion to compare with the blood taken just beforehand.
- When your child is ready and the nurse has taken out the catheter, your child will be able to go home. Your child will not need to stay at the hospital overnight unless they have had an unusually bad reaction to the infusion.

Informing your GP

It is desirable that your child's local doctor be advised of your decision for your child to participate in this research project. If your child has a local doctor, we strongly recommend that you inform them of your child's participation in this research project.

1) Optional consent

We would like to provide information about the safety of cord blood cell infusions to an international registry called the Center for International Bone Marrow Transplant Research (CIBMTR) and to a local registry called the Australasian Bone Marrow Transplant Recipient Registry (ABMTRR). The registries collect information about all bone marrow transplants and cord blood cell infusions from the hospitals involved in this study. Data from large numbers of patients receiving similar treatments in different hospitals is valuable because it can be analysed with more meaningful results than just looking at small numbers of patients from a single hospital or single clinical trial.

The CIBMTR is located at the Medical College of Wisconsin, Milwaukee, USA. This centre has been collecting information on worldwide allogeneic transplants and infusions since the early 1970s. The ABMTRR is located in St Vincent's Hospital Sydney, Australia and has collected data since 1992. Your child's name would not be on any information sent to the registries. The information will be coded with a unique identification number. A master file linking the identification number with your child's name will be stored in a password-protected file in the infusion hospital's transplant centre. The registries would collect information about your child's gender, date of birth and medical condition. We would also give information about the infusion, including the drugs used before, during and after, whether the infused cells engraft or are rejected by your child's body, any illness, infections or side-effects developed after the infusion begins and information about the cord blood unit itself. This information is already collected as part of the trial, but you can choose whether we send all the information to the CIBMTR and ABMTRR.

2) Optional Consent

We would like you to consider allowing us to send you information about new research projects related to this project. The information we send will give you full details about the project. It is your choice whether you agree to let your child take part in any future project or not.

4 Your responsibilities to the study

- Your child and a parent/guardian needs to be able to attend the infusion hospital for at least 7 visits and another two visits either at the hospital or in your community.
- Your child needs to be able to accept various needles for blood tests, cord blood cell infusion and hydration.
- Your child must be healthy to participate in this research study. The study doctor will examine your child and your child's blood to look for viruses or other signs of ill health. The study doctor will refer your child to appropriate health professionals if the examinations find anything that might indicate your child is not healthy, so that your child can receive professional advice and treatment if it is needed.

5 Other relevant information about the research project

There will be up to 12 children from around Australia taking part in this research study. Cord blood cell infusions may take place at two hospitals:

1. The Royal Children's Hospital Melbourne;
2. Lady Cilento Children's Hospital, Brisbane.

Other trial activities may take place at The Children's Hospital at Westmead, NSW, and at Monash Medical Centre in Melbourne.

6 Does the child have to take part in this research project?

Participation in any research project is voluntary. If you do not wish for your child to take part, they do not have to. If you decide that they can take part and later change your mind, you are free to withdraw your child from the project at any stage.

You do not need to tell us the reason why you or your child want to stop being in the project. However, please tell us if your child plans to leave the research study so that we can let you know if there are any health risks or special requirements linked to withdrawing. If your child leaves the study, we will use any information or samples already collected unless you tell us not to.

If you withdraw your child from the study after your child's cord blood has been transported from the cord blood bank where it is stored, the cord blood bank may not allow the cord blood to be returned to storage.

If you do decide that your child can take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision that your child can or cannot take part, or that they can take part and then be withdrawn, will not affect their routine treatment, relationship with those treating them, or their relationship with The Royal Children's Hospital Melbourne.

7 What are the alternatives to participation?

Your child does not have to take part in this research project to receive treatment at this hospital. The study doctor will discuss with you if other options are available.

8 What are the possible benefits of taking part?

We do not know whether there will be any benefit to your child if your child receives cord blood cells. We expect the main benefits of this study to be for others in the future. We hope the information we get will allow us and other researchers around the world to eventually determine the safety and effectiveness of stem cell infusion for children with cerebral palsy.

9 What are the possible risks and disadvantages of taking part?

Many participants in this study will not be able to continue with participation because 3 out of 4 siblings do not have matching blood.

Medical treatments often cause side effects. Your child may have none, some or all of the effects listed below, and they may be mild, moderate or severe. If your child has any of these side effects, or you are worried about them, talk with the study doctor. The study doctor will also be looking out for side effects.

There may be side effects that the researchers do not expect or do not know about and that may be serious. Tell the study doctor immediately about any new or unusual symptoms that your child gets.

Many side effects go away shortly after treatment ends. However, sometimes side effects can be serious, long lasting or permanent. If a severe side effect or reaction occurs, the study doctor may need to stop your child's treatment. Your child's study doctor will discuss the best way of managing any side effects with you.

Side Effect	How often is it likely to occur?	How severe might it be?	When might it happen?	How long might it last?
Anaphylaxis (allergic reaction)	Unlikely	Life-threatening	Soon after infusion	Temporary with treatment
Pain where the needle goes in	Likely	Mild	When the needle goes in	Temporary
Pain in the chest or back	Not known	Severe	During infusion	Temporary with treatment
Heart not beating in normal rhythm	Not known	Severe	Soon after infusion	Not known
Chills and/or Fever	Not known	Severe	Soon after infusion Days after infusion	Temporary with treatment
Headache	A mild reaction is moderately likely, severe is unlikely	Severe	Soon after infusion Days after infusion	Temporarily with treatment
Rash		Severe	Soon after infusion	Not known
Blood pressure rises or drops	A mild reaction is likely, severe is unlikely	Severe	Soon after infusion Days after infusion	Temporary with treatment
Nausea or vomiting	A mild reaction is likely, severe is unlikely	Severe	Soon after infusion	Temporary
Shortness of breath, cough	Not known	Moderate	Soon after infusion	Temporary with treatment
Not enough oxygen in blood	A mild reaction is likely, severe is unlikely	Severe	Soon after infusion	Temporary
Rigors (shaking chills)	A mild reaction is likely, severe is unlikely	Moderate	Soon after infusion	Temporary
Haemoglobin in urine	Not known	Moderate	Soon after infusion Days after infusion	Temporary
Infection in blood	Not known	Moderate	Days after infusion	Temporary with treatment
Graft-versus-Host disease	Very unlikely	Life-threatening	Within 3 months of infusion	It may be treatable and last only a short time, or it may last the rest of your child's life.
Developing antibodies to the sibling blood cells	Moderately likely	If your child needs a blood transfusion in the future, the antibodies might attack it If your child becomes pregnant in the future, the antibodies might attack the baby	Soon after infusion	Permanently

It is unlikely but possible that the cord blood cell infusion will change your child's functioning to the degree that your child may need different mobility aids after the infusion compared to the aids they are already using. The research study will not pay for these costs. Your family may have to pay for any new aids that are needed.

The following medications are given before the infusion to reduce the risk of allergic reaction and pain. These medications are available over the counter and their side effects are listed in Appendix 1.

- Antihistamime eg Phenergan or Zyrtec
- Hydrocortisone
- Paracetamol
- Ondansetron

If your child participates in this trial and receives cord blood cells, we will use all of his/her sibling's stored cord blood. The sibling donor will be unable to receive an infusion of his/her own cord blood cells for possible life saving treatment in the future. Your children would be dependent on finding matched cord blood through a public bank, should the need arise. If your child is unable to take part in the study and does not receive a cord blood cell infusion, his/her sibling's cord blood will remain in storage.

It is possible that this research study may uncover information about your child's movement disorder or general health that you were not aware of. We will also screen your child's blood for viruses and other signs of ill health that may prevent them participating in this study, and this test may find out information that you were not aware of. If your child needs medical care after these tests, we can refer your child to a doctor.

If you or your child becomes upset or distressed as a result of participation in the research questionnaires (e.g. CP QOL-Child), the study doctor will be able to arrange for counselling or other appropriate support. Any counselling or support will be provided by qualified staff who are not members of the research project team. This counselling will be provided free of charge.

Having a drug injected or blood taken may cause some discomfort, bruising, minor infection or bleeding. If this happens, it can be easily treated.

10 What will happen to your child's test samples?

The amount of blood collected at each visit is detailed below: please note 5 ml is equal to 1 teaspoon.

Blood collection	Blood volume needed	When is it taken?	What is it for?	Where does it go?	What happens to it afterwards?
1	10 ml	Visit 1	• To match your child with the cord blood	Red Cross Transplantation Services	Transported and destroyed after matching
Sibling sample	2.7 ml	Visit 2	• To find out the sibling's blood group*	RCH Melbourne pathology labs	Destroyed after matching
Maternal sample	2.7 mL	Visit 2	• To assess risk of contamination of cord blood*	RCH Melbourne pathology labs	Transported and destroyed
2	19 ml	Visit 2	• To confirm the cord blood matches with your child • To check that your child is healthy • Pregnancy test if required	• Red Cross Transplantation Services • RCH Melbourne pathology labs	Transported and destroyed after matching Destroyed

3	11 ml	Visit 3 (before infusion)	• To compare with the blood sample taken afterwards	• RCH Melbourne pathology labs • Research labs	Destroyed Frozen, transported
4	8.2 ml	Visit 3 (after infusion)	• To compare with your child's blood before the therapy	• Cyto-molecular diagnostics lab • Research labs	Frozen, transported and stored
5	8.2 ml	Visit 4	• To check for infection • To check the cell types in your child's blood	• RCH Melbourne pathology labs Cyto-molecular diagnostics lab • Research labs	Destroyed Frozen, transported
7	8.2 ml	Visit 5	• To look for inflammation • To check the cell types in your child's blood	• RCH Melbourne pathology labs Cyto-molecular diagnostics lab • Research labs	Destroyed Frozen, transported
8	7.2 ml	Visit 6	• To look for inflammation • To check the cell types in your child's blood	• RCH Melbourne pathology labs Cyto-molecular diagnostics lab • Research labs	Destroyed Frozen, transported
9	7.2 ml	Visit 7	• To look for inflammation • To check the cell types in your child's blood	• RCH Melbourne pathology labs Cyto-molecular diagnostics lab • Research labs	Destroyed Frozen, transported

* We may not need these samples, we hope to test the cord blood instead but if more testing is needed the study coordinator will contact you as soon as possible.

Samples of your child's blood obtained for the purpose of this research project will be transferred to the Cyto-molecular diagnostics research group at the Murdoch Childrens Research Institute (MCRI) for testing.

The proposed blood tests include a screening test for HIV (also called the 'AIDS' virus) and Hepatitis. This is because the study doctors need to know that your child is healthy enough to receive cord blood cell infusion. You and your child will receive information and counselling before the test. If a test shows your child has HIV or Hepatitis, follow-up counselling and medical advice will be provided. If the test results are positive, the study doctors are required by law to notify government health authorities. Signing the consent form means that you agree to your child having this testing; it will not be done without your consent.

Pregnancy test

If your child is a girl who has reached puberty and is able to have children, she will have a blood pregnancy test.

Girls must have a negative pregnancy test to be able to take part in this project.

3) Optional Consent

We would like to store samples of your child's blood from before and after the infusion, for future ethically-approved research studies related to stem cell treatment of cerebral palsy. **This would need a further 5 ml (a teaspoonful) of your child's blood at each blood collection.** We hope that when more information is known about stem cell treatment for cerebral palsy, we or other researchers in Australia will be able to test your child's samples in the future. If you consent, we will store your child's samples at the Biobanking Laboratory in the Murdoch Childrens Research Institute for an indefinite period of time. The samples will be stored using a special ID number. Your child's name will not be attached to the samples. We do not plan to

contact you or your child if the samples are used in future research, however you will be able to withdraw your child's samples at any time in the future if you choose. Your child's samples will not be sold by the Monash Medical Centre, however they may charge study doctors a fee to recover some of the costs of storing and administering the tissue samples.

Once your child's blood samples are transferred to the Murdoch Childrens Research Institute, The Royal Children's Hospital Melbourne will not be able to control whether the Murdoch Childrens Research Institute transfers the samples at some future date, however the Murdoch Childrens Research Institute will not knowingly transfer your child's samples to anyone who has expressed intent to sell the samples.

11 What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, the study doctor will tell you about it and discuss with you whether you want the participant to continue in the research project. If you decide to withdraw the participant, their study doctor will make arrangements for their regular health care to continue. If you decide that the participant can continue in the research project, you will be asked to sign an updated consent form.

Also, on receiving new information, the study doctor might consider it to be in the participant's best interests to withdraw them from the research project. If this happens, the doctor will explain the reasons and arrange for the participant's regular health care to continue.

12 Can your child have other treatments during this research project?

Whilst your child is participating in this research project, they may not be able to have treatments for their condition or for other reasons. It is important to tell the study doctor and the study staff about any treatments or medications the participant may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell the study doctor about any changes to these during your child's participation in the research project. The study doctor should also explain to you which treatments or medications need to be stopped for the time your child is involved in the research project.

It may also be necessary for the participant to take medication during or after the research project to address side effects or symptoms that they may have. You will not need to pay for these medications during this study.

It is also important to tell us about any CP surgery your child has had, and to tell us about any other cell therapy your child has received.

Your child will not be assessed or receive the infusion within three months of having surgery or Botulinum toxin A injection. After the infusion, they will not be able to have Botulinum toxin A injection or surgery for 3 months. However, we do not want any participants to delay having a treatment that they need, so please discuss this with the study doctor.

Please fully disclose all relevant information.

13 What if I withdraw my child from this research project?

If you decide to withdraw your child from the project, please notify a member of the research team before you withdraw them. This notice will allow that person or the research supervisor to further discuss any health risks or special requirements linked to withdrawing.

If you do withdraw the participant during the research project, the study doctor and relevant study staff will not collect additional personal information, although personal information already collected will be kept to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected up to the time of

withdrawal will form part of the research project results. If you do not want this to happen, you must tell the study doctor before your child joins the research project.

14 Could this research project be stopped unexpectedly?

This research may be stopped for a variety of reasons. We may need to stop the cord blood cell infusion or total participation for your child for the following reasons:

- if we believe that it is in their best interest
- if your child has side effects from the infusion that are considered too severe
- if the research group needs to stop the study unexpectedly
- decisions made by local regulatory/health authorities

New information may become available that might affect your decision to let your child stay in the study. If we learn any new information, we will talk to you about it.

15 What happens when the research project ends?

After the research study is finished and all the information has been examined, the study team will send you a summary of the results from the whole trial. We can also send you a copy of your child's personal assessment results.

16 What will happen to information about your child?

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal information about your child for the research project. Any information obtained in connection with this research project that can identify your child will remain confidential. It will be disclosed only with your permission, or as required by law. Their information will be coded with a unique study identification number. All electronic and paper documents will be securely stored at the Murdoch Childrens Research Institute or at The Royal Children's Hospital Melbourne. Your child's information will only be used for the purpose of this research project.

Information about your child may be obtained from their health records held at this and other health services, for the purpose of this research. By signing the consent form, you agree to the study team accessing health records if they are relevant to your child's participation in this research project.

Information about your child's participation in this research project may be recorded in their health records.

Your child's health records and any information obtained during the research project are subject to inspection (for the purpose of verifying the procedures and the data) by the relevant authorities, the institution relevant to this Participant Information Sheet, The Royal Children's Hospital Melbourne, or as required by law. By signing the Consent Form, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

As the participants in this project are under 18 years old, we must keep information until the youngest participant turns 25 years old. The research information may be destroyed or kept indefinitely in secure storage after this time.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that your child cannot be identified, except with your permission.

Information about your child's involvement in this trial will be used in the future to help us plan other clinical trials of cord blood cell infusion for cerebral palsy. Any information used in this way will not identify your child.

In accordance with relevant Australian and/or Victorian privacy and other relevant laws, you have the right to request access to the participant's information collected and stored by the study team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access the participant's information.

17 Compensation

If your child suffers any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment for your child. If your child is eligible for Medicare, they can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

By signing this consent form, you are not giving up any legal rights to seek to obtain compensation for injury.

18 Who is organising and funding the research?

This research has been initiated by the Murdoch Childrens Research Institute, Cerebral Palsy Alliance, The Royal Children's Hospital Melbourne, Monash Health, Hudson Institute of Medical Research, The Children's Hospital at Westmead, Lady Cilento Children's Hospital Brisbane, and The University of Queensland.

The research is primarily funded by Cell Care Australia and the Cerebral Palsy Alliance. Whilst these organisations are funding this study, they are also part of the research team, and we have research agreements in place to manage this arrangement.

No member of the research team will receive a personal financial benefit from your child's involvement in this research project (other than their ordinary wages).

There are no additional costs associated with participation in this research project, nor will you or your child be paid. All medication, tests and medical care required as part of the research project will be provided to your child free of charge.

You will be assisted with the expenses for any travel, accommodation, parking, meals and other expenses associated with the research project visits.

19 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of The Royal Children's Hospital, Melbourne.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

20 Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if your child has any medical problems which may be related to their involvement in the project (for example, any side effects), you can contact the principal study doctor, Professor Dinah Reddihough, on (03) 9345 5898 or any of the following people:

Clinical contact person

Name	Dr Francoise Mechinaud
Position	BMT Transplant Doctor
Telephone	(03) 9345 5522
Email	francoise.mechinaud@rch.org.au

For matters relating to research at the site at which your child is participating, the details of the local site complaints person are:

Complaints contact person

Position	Director
HREC name	Research Ethics & Governance, The Royal Children's Hospital Melbourne
Telephone	(03) 9345 5044
Email	Rch.ethics@rch.org.au

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC approving this research and HREC Executive Officer details

Reviewing HREC Name	The Royal Children's Hospital HREC
HREC position	Director
Telephone	(03) 9345 5044
Email	Rch.ethics@rch.org.au

Consent Form – Parent/Guardian

Title	*Safety study of sibling cord blood cell infusion to children with cerebral palsy*
Short Title	*Stem Cells in Umbilical Blood Infusion for CP (SCUBI-CP)*
HREC ID	*HREC/14/RCHM/38*
Principal Investigator	*Prof Dinah Reddihough*
Location	*The Royal Children's Hospital Melbourne*

Declaration by Parent/Guardian

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I give permission for the child's doctors, other health professionals, hospitals or laboratories outside this hospital to release information to The Royal Children's Hospital Melbourne concerning the child's disease and treatment for the purposes of this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to the child participating in this research project as described and understand that I am free to withdraw them at any time during the research project without affecting their future health care.

I freely agree to the full use of my child's cord blood for this research project as described and understand that I am free to withdraw my agreement at any time before the cord blood has been used.

I understand that I will be given a signed copy of this document to keep.

☐ I do	☐ I do not	consent to the transfer of information about my child's cord blood cell infusion to the Center for International Bone Marrow Transplant Research in the USA and to the Australasian Bone Marrow Transplant Recipient Registry
☐ I do	☐ I do not	consent to be contacted about future research projects that are related to this project
☐ I do	☐ I do not	consent to the collection of an extra 5 mls of blood (one teaspoonful) of my child's blood each time blood is collected. This will be stored at the Biobanking Laboratory in the Murdoch Childrens Research Institute for an indefinite period and used for future ethically approved research into cord blood cells for cerebral palsy

Name of Child (please print) _____

Name of Parent/Guardian _____

Signature of Parent/Guardian _____ Date_____

Name of Witness* to
Parent/Guardian's Signature (please print) _____

Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the parent/guardian has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Appendix 1: Risks and side effects of over-the-counter medications used in this study
In large doses or with long term use:

Risks and side effects of Phenergan		
Common	**Serious**	**Very Serious**
• dry mouth, nose & throat • stomach upset • loss of appetite • nausea or vomiting • diarrhoea or constipation • tiredness or sleepiness • restlessness • dizziness • blurred vision	• fever • difficulty breathing • irregular heart beat • jaundice - yellow tinge to skin or eyes • tremors or convulsions • tinnitus - buzzing, hissing, ringing or other persistent noise in the ears • seizures (fits) • hallucinations • nervousness and irritability • anxiety • twitching or jerking muscles	• wheezing or difficulty breathing • swelling of the face, lips, tongue or other parts of the body • skin rashes
• **Risks and side effects of Zyrtec**		
• **Common**	• **Serious**	• **Very Serious**
• dry mouth, nose & throat • stomach upset • loss of appetite • nausea • diarrhoea or constipation • tiredness or sleepiness • restlessness • dizziness • blurred vision • nosebleed	• difficulty breathing • irregular heart beat • hepatitis or liver problems • seizures (fits) • nervousness and irritability • problems with eyesight • twitching or jerking muscles	• wheezing or difficulty breathing • swelling of the face, lips, tongue or other parts of the body • allergic reaction

Risks and side effects of Paracetamol		
Common	**Serious**	**Very Serious**
• Nausea and vomiting • Stomach pain • Indigestion • Sweating	• Skin rashes • Painful red areas with blisters and peeling layers of skin which may be accompanied by fever and/or chills • Severe blisters and bleeding in the lips, eyes, mouth, nose and genitals • Hepatitis (symptoms include loss of appetite, itching, yellowing of the skin and eyes, light coloured bowel motions, dark coloured urine)	• shortness of breath • wheezing or difficulty breathing • swelling of the face, lips, tongue or other parts of the body • rash, itching or hives on the skin

Risks and side effects of Hydrocortisone		
Common	**Serious**	**Very Serious**
• fluid retention (causes an increase in weight) • increased sweating • headache or dizziness • effects on your menstrual periods • mood changes e.g. over-excitement, depression, suicidal thoughts, hallucinations, anxiety • itchy skin • thin fragile skin, bruising or change in skin colour • facial redness • excessive thirst, the passing of an increased amount of urine, increase in appetite with a loss of weight, feeling tired, drowsy, weak, depressed, irritable and generally unwell	• Problems with your growth. • muscle weakness or loss of muscle mass	• Allergic reactions, e.g. skin rash, itching, difficulty breathing, wheezing or coughing • bone fractures or muscle pain • severe stomach pain, nausea and vomiting • vomiting blood or material that looks like coffee grounds, bleeding from the back passage, black sticky bowel motions (stools) or bloody diarrhoea • convulsions or fits • blurred or distorted vision or loss of vision, eye infections • red, purple or brown patches on your skin • problems with your back, including pain or weakness • loss of sensation or problems with your reflexes (slow or too fast) • bouts of anxiety and headaches, sweating, palpitations, dizziness, a feeling of weakness, nausea, vomiting, diarrhoea, dilated pupils and blurring vision, stomach pains, and raised blood pressure. These could be symptoms of a rare tumour of the adrenal gland, which sits near the kidney.

Risks and side effects of Ondansetron		
Common	**Serious**	**Very Serious**
• anxiety • difficulty having a bowel movement • dry mouth • general feeling of discomfort or illness • hyperventilation • irritability • restlessness • shaking • trouble sleeping	• confusion • dizziness • fast heartbeat • fever • headache • shortness of breath • weakness	

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	6
Protocol version	#3	Date and version identifier	6
Funding	#4	Sources and types of financial, material, and other support	6
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	7
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	6, 1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	6
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team,	3, 7

		and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2, 3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	NA (no comparator)
Objectives	#7	Specific objectives or hypotheses	3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	3
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data	3

		will be collected. Reference to where list of study sites can be obtained	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	5
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	NA (intervention is single dose)
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	4
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical	5

		relevance of chosen efficacy and harm outcomes is strongly recommended	
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	4
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	3
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	4
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	NA (single group study)

Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	NA (single group study)
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA (single group study)
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA (single group study)
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA (single group study)
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and	6

		validity, if known. Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	6
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	6
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	5
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	NA (none planned)
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	5
Methods: Monitoring			

Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	3
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	3
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	5
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	6
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	6

Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	6
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	4
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	4
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	7
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	6
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA

Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	6
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	7
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	6
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Uploaded as separate file
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Available upon request