MissionEB

Mesenchymal Stem Cells in Epidermolysis Bullosa

Call: 18/129 Mesenchymal Intravenous Stromal cell Infusions in children with recessive dystrophic Epidermolysis Bullosa

This document describes a clinical trial,and provides information about procedures for entering participants. The protocol is not intended for use as a guide to the treatment of other patients. Amendments may be necessary; these will be circulated to known participants in the trial.

RESEARCH PROTOCOL
Version 8.0, 14Nov2022

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[1] **EudraCT Number:** It is mandatory that any CTIMP is registered on the EU Clinical Trial Register (EudraCT) and details must be recorded on the Protocol. *http://www.ct-toolkit.ac.uk/routemap/eudract-number/*

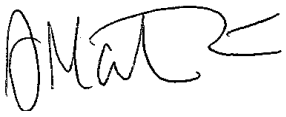
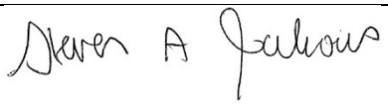
Authorisation Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, GOSH, CTRU (and/or any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

Protocol authorised by:

Name, Role and Organisation	**Signature**	**Date**
Dr Anna Martinez, Chief Investigator, Great Ormond Street Hospital	 Email approval attached	19/12/2022
Subarna Sriskantharajah, Sponsor Representative	Email approval attached	21/12/2022
Steven Julious, Statistician, University of Sheffield	 Email approval attached	18/11/2022

Contents

Abbreviations

Definition of terms

AE	Adverse Event
AR	Adverse Reaction
ATMP	Advanced therapy medicinal product
BCH	Birmingham Children's Hospital
BM-MSCs	Bone marrow-derived MSCs
CA	Competent Authority
CCC	Confirmation of Capacity and Capability
CHU-9D	Child Health Utility 9D
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
CTRU	Clinical Trials Research Unit
DEB	Dystrophic Epidermolysis Bullosa
DEJ	Dermoepidermal junction
DLT	Dose Limiting Toxicity
DMEC	Data Monitoring and Ethics Committee
DMP	Data Management Plan
DMSO	Dimethyl sulfoxide
DSUR	Development Safety Update Report
EB	Epidermolysis Bullosa
EBDASI	Epidermolysis Bullosa Disease Activity and Scarring Index
EC	European Commission
ELISA	Enzyme-Linked Immunosorbent Assay
EMEA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GvHD	Graft versus host disease
GMP	Good Manufacturing Practice
GOSH	Great Ormond street hospital
HLA	Human leukocyte antigens
HRA	Health Research Authority
HSCT	Haematopoietic stem cell transplantation
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IFN-γ	Interferon gamma
IL-2	Interleukin-2
iscorEB	Instrument for scoring clinical outcomes of research for Epidermolysis Bullosa
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier

ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials Number
LPLV	Last Patient Last Visit
MSC	Mesenchymal Stem Cells
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
MS	Member State
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHS	National Health Service
NICE	National Institute of Clinical Excellence
NIHR	National Institute of Health Research
NIMP	Non-Investigational Medicinal Product
NSCLC	Non-Small Cell Lung Cancer
PET-CT	Positron emission tomography-computed tomography
PE	Pulmonary Emboli
PI	Principal Investigator
PIS	Participant Information Sheet
PSS	Personal Social Services
QA	Quality Assurance
QALYs	Quality-adjusted life years
QC	Quality Control
QP	Qualified Person
RCT	Randomised Control Trial
REC	Research Ethics Committee
RDEB	Recessive Dystrophic Epidermolysis Bullosa
SAEs	Serious Adverse Events
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SCC	Squamous cell carcinoma
SDV	Source Data Verification
SLE	Systemic lupus erythematosus
SMP	Site Monitoring Plan
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TNF	Tumour Necrosis Factor
TRAIL	TNF-Related Apoptosis Inducing Ligand
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
UC-MSCs	Umbilical Cord Derived Mesenchymal Stem Cells
UCT	Umbilical cord tissue
VAS	Visual Analogue Scale

1. General information

1.1 Investigator details

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1.7 Role of the Funder

NHS England/National Institute for Health Research

The funder has reviewed the research protocol but will have no role in data collection, analysis, data interpretation, report writing or in the decision to submit the report for publication. The funder has approved the selection of members for oversight committees. No conflicts of interest to declare.

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1.10 Protocol amendments

Protocol Version No.	Date issued	Details of Changes made
1.0	11Dec2020	N/A
2.0	08Feb2021	• Updated these sections in response to MHRA GNA. • Section 4.1, 4.5.2, 8.1.1 of the protocol have been amended to clarify the procedures for the phase I trial. • Table 4 has been amended to clarify phase I study procedures. • Section 4.3 of the protocol updated to clarify the criteria required for beginning the open label trial. • Section 5.7 of the protocol amended to define true abstinence. • Section 8.1.1 of the protocol updated to clarify that the duration of follow-up for any participant receiving IMP will be 15 years. • Figure 4 has been updated to clarify that the duration of follow-up for any participant receiving IMP will be 15 years. • Section 8.6 of the protocol has been amended to clarify that participants will be invited to enter a long-term follow up trial of 15 years. • The definition of 'end of trial' has been updated in Section 8.12 of the protocol and in the study summary

		• Section 9.5 and 9.6 of the protocol amended to clarify that AEs will be recorded until the last visit of the participant. • Section 9.6 of the protocol updated to clarify that an amendment would be required to continue the trial in the event of a treatment-related death.
3.0	10Mar2021	• This version contains changes in response to REC initial submission and includes the changes made for MHRA submission. • Section 5.5 updated to include the consenting procedure for participants who turn 16.
4.0	02Jun2021	• Table 4 (study procedures) and Section 8.5.4 updated to outline the assessment of changes in amount of analgesia/itch medications. Analgesia use and itch medication will be monitored with concomitant medications at every visit. • Figure 3 amended to include assessment of changes to analgesia/itch meds. • Figure 5 (AE/SAE decision tree) updated to correct errors. • Trial summary and Section 4.5.2 of the protocol updated to clarify that an age appropriate by proxy version of the CHU-9D will be used for children 3-6 years old. • Section 4.6 of the protocol updated to include an independent unblinded research nurse from another team within the CRF who will prepare and administer the IMP/placebo. This will ensure that the study research team remains blinded. • Section 5.5 duplicated sentence removed, updated to clarify that participant approach will be recorded in patient notes. • Section 5.8 added to outline procedures for patient withdrawal from follow-up • Section 6.2.1, updates made to the infusion process. It will be administered as a slow bolus. Paracetamol will be given to all patients prior to the infusion according to local procedure. • Section 8.1 updated to include guidance on timeframe between randomisation and Day 0. • Section 8.5.2 Updated to correct error. Leuven itch scale will not be completed by parents/guardians but by participants over 14 years of age only. • Section 8.9 updated to clarify procedures for blood sample collection and storage. • Section 8.10 patient withdrawals procedures amended to state that long-term safety data and follow up of any SAEs will continue if a patient withdraws from follow-up, unless the patient explicitly states they do not consent to the collection of this data .
5.0	30July21	• Table 2 composition of the IMP updated to $3x10^6$/ml.

		• Table 4 Study Procedures updated to include 48 hour logs of the pain and itch medications taken by participants in the 48 hours prior to study visits. • Section 4.6 and 4.7.1 of the protocol updated to clarify that pharmacy will be unblinded to allow them to perform QP certification checks upon delivery of the IMP . • Section 6.1 updated to align with IMPD. IMP will be presented in 50ml CryoMACS bags with a fill volume of 10ml or 15ml cell suspension per bag and a minimum concentration of $3x10^6$ CORDStrom per ml. • Section 6.3 and section 7 local storage of IMP will be for 21 days. • Section 7 and 7.3 updated to outline that pharmacy will be unblinded and have access to the treatment allocation. • Section 8.1 updated to outline that from randomisation to Day 0, sites must allow at least 5 working days for IMP order and delivery. • Section 8.5.4 updated process for how data will be collected to assess changes in analgesia and itch medication use. • Section 10.2.2 sentence on outcome analysis amended for clarity.
V6.0	19Jan2022	• Section 4.1 Clarification that dose de-escalation or expansion decisions will be based on 3 participants randomised to UC-MSCs in each cohort receiving at least one infusion. • Section 4.5.2: - Addition of 'change in EBDASI' at 6 months post infusion - Clarified timeframes for outcome measures - Clarified that the assessment of analgesia and itch medications will be based on the participants use in the last 48 hours and assessed by clinicians - Corrected to clarify that outcome measures will look for 'change' not only improvement • Section 5.2 – exclusion criteria update with budesonide as an exemption. • Section 7.1 Amended to clarify that DMEC decisions will be based on 3 participants in each cohort receiving at least one infusion of active substance. • Section 6.6 and Table 4 The allowed windows of time to complete the follow up visits have been corrected to be consistent across the trial.
V7.0	Mar2022	• Section 5.4 addition of recruitment procedures for qualitative interviews. • Section 8.8 Changes to the number of children being interviewed and the interview schedule • Section 8.8 and Section 12 Removal of the Sekhon acceptability framework to reduce unnecessary participant burden. The aim of the interviews is to find out about the impact of treatment on the child and

		rather than around acceptability as relation to implementation. • Table 4 non-mandatory bloods for iscorEB added at month 3 and 12 (primary outcome follow-up) and month 12 in the open label. • Section 8.5.1 updated to outline the blood results that should be used for scoring iscorEB, and the details of using 'standard of care' bloods. • Section 5.2 exclusion criteria amended to add inhaled fluticasone as an exemption. • Section 4.2 amended to clarify qualitative interview timepoints. • Section 4.5.2 amended to clarify timepoints of secondary outcome measures and non-mandatory iscorEB bloods. • Section 5.5 amended to clarify separate consent for the qualitative interview. • Figure 3 updated to include non-mandatory iscorEB bloods. • Section 11 amended to clarify information used for cost estimation. • Section 14 clarification on when a screening ID is assigned to participants.
V7.1	07Sept2022	• Minor amendment to the text in Section 5.5 around consent for the interview. Consent will be taken after the participant's first infusion and prior to the interview. • Minor amendment to correct an error Section 6.2.2 and Section 6.2.3. These sections have been corrected to be in line with Section 6.2.1.
V8.0	14Nov2022	• Section 1.8 Ben Weil was added as an IMP supplier contact. • Section 5.2 exclusion criterion 6 updated to clarify the timeframe. • Section 5.7.1 and Section 9.8 updated to give details on pregnancy follow up and reporting. • Section 6.6 has been updated to amend the allowed windows for IMP dosing. • Section 8.3 updated to clarify how the follow-up visits are calculated. • Table 4 amended to clarify follow-up visits.

Trial Summary

Study title	Mesenchymal Stem Cells in Epidermolysis Bullosa**CalI:** 18/129 **M**esenchymal **I**ntravenous **S**tromal cell Infu**sion**s in children with recessive dystrophic **E**pidermolysis **B**ullosa
EudraCT	2020-005049-18
Sponsor	Great Ormond Street Hospital
Funder	NHS England/National Institute for Health Research
ISRCTN	ISRCTN14409785
Project start date	1st August 2020 Recruitment start: August 2021
Project end date	December 2024 OR May 2025 in the case of dose de-escalation
Aim	The overall aim of this study is to assess if repeated infusions of umbilical cord-derived mesenchymal stem cells (UC-MSCs) are safe and can benefit children with RDEB.
Primary objective	**For the phase 1 de-escalation study:** To assess the safety of third party intravenous UC-MSCs in improving disease severity in children with RDEB **For the crossover study**: To assess the efficacy of third party intravenous UC-MSCs in improving disease severity in children with RDEB.
Secondary Objectives	**For the crossover study** • To assess the safety of repeated UC-MSCs in children with RDEB. • To assess the efficacy of repeated UC-MSCs in improving quality of life and symptoms (e.g., pain, itch) in children with RDEB. • To undertake a health economic analysis to assess the costs and consequences of treatment with UC-MSCs versus usual care • To explore patients and parents' views in relation to treatment effectiveness and acceptability.
Study design	Prospective, double-blind, randomised, placebo controlled crossover trial with an internal dose de-escalation trial (for safety) and a further 12 month continued treatment follow-on study.
Setting	Participants will be recruited from 2 sites that are National Centres for treating children with RDEB - Great Ormond Street Hospital and Birmingham Children's Hospital.
Sample size	4 + 5 cohort of children with RDEB for the dose de-escalation study (with potential for an additional 4 + 5 cohort depending on observed toxicity levels)

	Total of 36 children with RDEB for the crossover trial with further follow-up (children in dose de-escalation study will be recycled)
Participants	**Inclusion criteria** • Patients who have a diagnosis of RDEB characterised by partial or complete C7 deficiency including generalised severe and generalised intermediate subtypes. • Patients who are over 6 months and before their 16th birthday at time of enrolment. • Patients whose responsible parent/guardian has voluntarily signed and dated an Informed Consent Form (ICF) prior to receiving the intervention. Whenever the minor child is able to give consent, the minor's assent will be obtained in addition to the signed consent of the minor's legal guardian. **Exclusion criteria** • Patients with other subtypes of epidermolysis bullosa (EB) such as EB simplex, EB junctional, dominant dystrophic EB and Kindler EB. • Subjects who have received oral or topical corticosteroids for more than 7 consecutive days within 30 days of enrolment into this study, **with the exception of** the following steroids with non-systemic effects and intended to relieve oesophageal symptoms: oral viscous budesonide and inhaled fluticasone. Patients with a known allergy to any of the constituents of the investigational product. • Patients with signs of active infection that requires treatment with oral or intravenous antibiotics within 7 days of screening. • Patients with a medical history or evidence of active malignancy, including cutaneous squamous cell carcinoma. • Patients with both a) positive C7 ELISA and b) a positive indirect immunofluorescence (IIF) with binding to the base of salt split skin at screening. • Patients who are pregnant or of child-bearing potential who are not abstinent or practicing an acceptable means of contraception, as determined by the Investigator, for the duration of the treatment phase. • Patients having received MSCs from any source in the last 9 months. • Simultaneous or previous participation in any interventional trial within 3 months

	before entering this trial but participation in simultaneous registry, and diagnostic trials during the trial is allowed.
Investigational medicinal product and dosage	Third party umbilical cord-derived mesenchymal stromal cells, 2-3 million cells/kg. This will be adjusted to 1-1.5 million cells/kg if necessary, based on observed toxicity data during the internal dose de-escalation phase.
Active comparator product(s)	Placebo
Route(s) of administration	Intravenous
Maximum duration of treatment of a subject	24 months
Procedures: Screening & enrolment	• Assessment of patient's eligibility according to inclusion/exclusion criteria. • Written informed consent • Documentation of demographics (age, weight, height, ethnicity). • Medical history review. • Concomitant medication review including amount of analgesia. • Physical examination and vital signs. • Skin biopsy for immunofluorescence (only if not already available). • Obtain routine blood samples, bloods for storage (research bloods) and bloods for DNA mutation analysis (the latter will only be done if not already available). • Bloods for serum C7 antibodies and indirect immunofluorescence. • Disease severity (iscorEB and EBDASI) • Body wound photography.
Baseline/Pre-dose assessments	Baseline for outcome measures will be taken prior to dosing after randomisation on Day 0 (visit 2). Other baseline data will be taken at screening.
Treatment Period	***Internal phase 1 de-escalation trial*** • 2-3 million/kg UC-MSCs, adjusted to 1-1.5 million/kg, if necessary, according to observed toxicity data • UC-MSCs (day 0) + UC-MSCs (day 14) OR • Placebo (day 0) + placebo (day 14) ***Main crossover trial*** • UC-MSCs (day 0) + UC-MSCs (day 14) followed by placebo (9 months) + placebo (9 months & 2 weeks) • Placebo (day 0) + placebo (day 14) followed by UC-MSCs (9 months) + UC-MSCs (9 months & 2 weeks)

	Follow-on open-label non-randomised study • 2-3 million/kg UC-MSCs, adjusted to 1-1.5 million/kg, if necessary according to toxicity data • Day 0 – UC-MSCs infusion • Day 0 + 2 weeks – UC-MSCS infusion • 4 months – UC-MSCs infusion • 4 months + 2 weeks – UC-MSCs infusion • 8 months – UC-MSCs infusion • 8 months + 2 weeks – UC-MSCs infusion
Primary outcome(s)	**Internal phase I de-escalation trial**: Toxicity as defined by a patient experiencing a SUSAR (see Section 9 for definition) within 48 hours of a patient receiving an infusion. **Main crossover trial:** The primary outcome will be change in disease severity as measured by Epidermolysis Bullosa Disease Activity and Scarring Index (EBDASI) at 3 months post-infusion of UC-MSCs (from day 0). The timing of the primary outcome is based on the EBSTEM study (Petrof *et al*, 2015) where the maximum effect of the MSCs was seen at Day 100. Disease severity is related to the total score across all 5 domains of the EBDASI. **Open-label non-randomised study**: same as for the main crossover trial but assessed at 4, 8, and 12 months from day zero.
Secondary outcome(s)	• Change in disease severity as measured by EBDASI at 6 months post infusion (from day 0). • Change in disease severity measured by iscorEB (Bruckner *et al*, 2018) at 3- and 6-months post infusion (from day 0). The iscorEB consists of 2 parts – clinician and patient scores. In the first part, the clinician will score skin, mucosal and internal organs involvement, laboratory abnormalities and complications. In the second part, the patient or caregiver will need to give scores to each domain which consists of pain, itch, essential functions, sleeping, daily activates, mood and impact. These subscores will be combined into a total iscorEB score. • Non-mandatory iscorEB bloods at 3 months post infusion (from day 0, period baseline) where appropriate (see section 8.5.1 Disease Severity).

	• Change of general clinical appearance of skin disease as assessed by clinical photography at 3 and 6 months post infusion (from day 0). • Change in pain and itch as assessed by the FACES Pain scale (Wong *et al*., 1988) and Leuven itch scale (Haest *et al*, 2011) scores at 3 and 6 months post infusion (from day 0). • For pain and itch, changes in amount of analgesia and itch medications required as assessed by whether the amount recorded within 48 hours has increased, reduced or remained unchanged will be recorded at 3 months post infusion (from day 0). • Change in quality of life according to the validated Child Health Utility 9D (CHU-9D) scoring system (Furber and Segal, 2015) at 3 and 6 months post infusion. The CHU-9D is a sensitive and validated nine item child health-related quality of life assessment scale developed specifically with and for children and will be used in children aged 7 years and over. Age appropriate by proxy versions will be used for children aged 3 – 6. • To undertake a health economic analysis to assess the costs and consequences of treatment with UC-MSCs versus usual care. • AEs and SAEs (see Section 5.11.4 for definitions) both during the trial and long-term adverse events after the trial. • Safety bloods (Routine blood tests and C7 antibodies) • Research bloods (will be stored for further analysis in a separate research application) ○ Serum for cytokines, IL-10, IL-13, IL-22, TNF-alpha at screening, day 0, day 14, month 9 and 2 weeks later in the crossover trial and all visits for the open label study, except the final 12 month visit.
Definition of end of trial	The end of the trial is defined as last patient last visit (LPLV).

2. Introduction

2.1 Background

Epidermolysis bullosa (EB) is a heterogeneous group of inherited disorders characterised by skin blisters and mucosal fragility. EB affects approximately 1 in 17,000 live births and affects approximately 1400 people in the UK and half a million worldwide. One of the most severe forms of EB is dystrophic epidermolysis bullosa (DEB), caused by loss of function mutations in the type VII collagen gene (*COL7A1*) leading to reduced or absent type VII collagen (C7). Recessive dystrophic epidermolysis bullosa (RDEB) is the most severe subtype resulting in extensive skin blistering following minor mechanical trauma (Fine *et al*, 2008). Wound healing is often slow, leading to chronic erosions, secondary infection and progressing to extensive, mutilating scars and contractures (Fine *et al*, 2005). RDEB is sub classified to severe (absent C7) and intermediate (decreased C7) (Has *et al*, 2020).

The care of children with severe EB has been supportive with no active treatment being available. Over the last 50 years, haematopoietic stem cell transplantation (HSCT) has emerged as a stem cell therapy with a wide range of clinical indications, initially for haematological malignancies in the late 1960s, but subsequently in the 1980s for non-malignant disorders such as the mucopolysaccharidoses and other inherited enzymopathies (Sands *et al*, 1997, Krivit *et al*, 1984 and Hobbs *et al*, 1981). Over the past decade there has been evidence that HSCT influences the natural phenotype (natural course) of RDEB significantly. Reported clinical trials of cell-based therapies for RDEB comprise intradermal allogeneic fibroblasts (Petrof *et al*, 2013; Venugopal *et al*., 2013), bone marrow transplantation (Wagner *et a*l, 2010), intradermal mesenchymal stromal cells (MSCs) (Conget *et al*, 2010), and intravenous MSCs in children with RDEB (El-Darouti *et al*, 2016; Petrof *et al*, 2015) and adults with RDEB (Rashidghamat *et al*, 2019). In 2014, members of the MissionEB trial team (including the Chief Investigator) conducted the EBSTEM trial, an uncontrolled open-label trial of allogeneic intravenous bone marrow-derived MSCs (BM-MSCs) in 10 children with RDEB (Petrof *et al*, 2015). The study suggested that intravenous MSCs are safe in RDEB and indicated early evidence of disease amelioration by improving the appearance of the wounds, reducing pain and itch and improving quality of life for the children and their families. There is a need for a robust study to validate these findings and add to the evidence base using UC-MSCs, which are potentially more effective than bone marrow-derived MSCs (BM-MSC)s.

2.1.1 Existing Research

2.1.1.1 Data from non-clinical studies

The immunomodulatory function of UC-MSCs has been demonstrated *in vitro* by measuring the inhibition of mitogen-induced T cell proliferation (Table 1).

Table 1: MSC suppression of PBMC proliferation *in vitro*

UC-MSC batch	Mean percentage change in the T cell division fraction following MSC addition	Mean percentage change in the non-dividing PBMC fraction following MSC addition
UC-MSC Batch 1	-34.99%	17.16%
UC-MSC Batch 2	-41.42%	28.79%
UC-MSC Batch 3	-46.25%	50.68%

UC-MSC inhibit activated T cell proliferation via indoleamine 2,3-dioxygensae and cyclooxygenase-2 pathways and also suppress secretion of pro-inflammatory cytokines with downregulation of interferon gamma (IFN-g), interleukin-2 (IL-2), IL2RA, CXCL9 and CCND3 (Vellasamy *et al*, 2016).

In the manufacturer's *in vivo* preclinical studies in newborn piglets, they have injected two doses of 30 million UC-MSC intravenously or administered intra-nasally over two days. None of the piglets showed adverse effects with either route of administration. Moreover, in a model of hypoxic-ischaemic encephalopathy in the same piglets, the intranasal administration of human UC-MSC led to significantly reduced inflammation, improved brain energy metabolism and a neuroprotective effect in the white matter compared to placebo controls (manufacturer data).

2.1.1.2 Clinical data

The first human bone marrow transplant in RDEB patients was performed by Wagner *et al* in 2010.[15] Seven children with RDEB were selected. Of those, six proceeded with allogeneic stem cell transplant following immunomyeloablative chemotherapy. Engraftment was successful as evidenced by high levels of donor chimerism detectable in both skin and blood. All children had improved wound healing and five out of six showed increased levels of C7 at the dermoepidermal junction (DEJ). Notably, one patient died due to cardiomyopathy before transplantation and one developed severe regimen related cutaneous toxicity.

Non-tissue matched BM-MSCs were given by intradermal injections in two individuals with severe RDEB with complete absence of C7 in 2009, age 13 and 25 years (Conget *et al*, 2009). Allogeneic MSCs were intradermally injected around chronic wounds; placebo injections lacking MSCs were also given. At week 12, the wounds treated with MSCs had almost healed compared to the sites treated with placebo. The beneficial effects on wound healing lasted for 4 months before the skin started to become fragile again and re-ulcerate. Importantly, no adverse effects at the sites of injection, or systemically, were noted.

Based on these studies, in 2015, ten children with severe RDEB each received three intravenous infusions of allogeneic BM-MSCs over 28 days with no human leukocyte antigen (HLA)-matching or preconditioning (Petrof *et al*, 2015). No serious adverse events (SAEs) were observed and the reported adverse events related to the infusions were the odour from the cell preservative, known as dimethyl sulfoxide (DMSO). There were two episodes of nausea, one mild headache and one abdominal pain which resolved spontaneously. Laboratory assessments did not reveal any adverse impact of the MSCs on liver, kidney or bone marrow function. Nine children received two further infusions after the trial completion (five in total). Four and a half years after the last infusions the children remain under clinical follow up and have no unexpected complications not related to their disease's natural course. The clinical benefits of the MSCs infusions have tailed off since the last infusion 4.5 years ago. A further clinical trial published in 2016, used a single dose of intravenous allogeneic BM-MSCs in 13 children and one adult (age 20), with half receiving cyclosporine for preconditioning with variable clinical improvement and no SAEs (El-Darouti *et al*, 2016).

In 2019, a study of 10 adults with RDEB was completed with patients receiving two intravenous infusions, two weeks apart of unrelated BM-MSCs (Rashidghamat *et al*, 2019). There was a reduction in blister numbers and pruritus. Two participants developed squamous cell carcinoma (SCC) during the study period (6 and 7 months after MSCs infusion). Individuals with RDEB are 70% more likely to develop SCC, and thus far, more than 700 clinical trials have been performed using MSCs from various sources and for a variety of diseases with malignancy not being reported (Rashidghamat *et al*, 2019). RDEB patients are routinely monitored for SCCs from the age of 10 and this will continue throughout the study and in long-term follow up. There is currently an ongoing commercial open label trial including children and adults with severe RDEB using three intravenous infusions of ABCB5-positive skin-derived MSCs (2x10^6 cells/kg) (NCT03529877).

For this study, we propose using UC-MSCs, which have been shown to be safe and potentially more effective than BM-MSCs. The proposed UC-MSCs have been genetically modified to express the TNF-Related Apoptosis-inducing Ligand (TRAIL) for an MRC-funded clinical trial in non-small cell lung cancer (NSCLC) called TACTICAL (Targeted Stromal Cells Expressing TRAIL as a Therapy for Lung Cancer) (NCT03298763). The trial opened at the end of 2019 and, to date, two patients have been treated with 3 doses of 400 million UC-MSC (TRAIL) while a third received 2 doses. Two patients showed a reduction in tumour mass by positron emission tomography-computed tomography (PET-CT) and the third showed stabilisation. The first two patients showed evidence of micro pulmonary emboli (PE) by PET-CT but without any clinical sequelae. It is unknown whether the micro-PE were pre-existing as is common in NSCLC patients but, the protocol has been amended to reduce the dose to 200 million x3 and to include a pre-treatment PET-CT scan.

UC-MSC are being tested in a second clinical trial (MSC-SLE) (NCT03562065) but without the TRAIL gene insertion. The trial is underway in Paris at Hospital St Louis and will treat 10 patients with systemic lupus erythematosus (SLE) where the mode of action is modulation of the autoreactive T cells by direct immunosuppression. This is a dose escalation trial ranging from 1 million to 3 million MSC per kg. The French regulatory agency, ANSM, approved the investigational medicinal product dossier (IMPD) and clinical trial protocol. So far three patients have been treated at the lowest dose with no AEs and early evidence of clinical improvements. Three patients have been treated compassionately (under Specials legislation) with UC-MSC; two for Graft vs Host Disease (GvHD) and a third for myocardial ischaemia. The GvHD dose was 3 million /kg x2 over two weeks. Neither showed evidence of adverse effects but neither

showed clinical improvement. Most recently, a neonatal patient received a single, intramyocardial injection of 10 million UC-MSC to treat myocardial ischaemia as a bridge to transplant. The patient remains alive and well at 5 weeks post injection with no reports of adverse events (data from Investigation Medicinal Product (IMP) manufacturer).

In two separate open label studies investigating autism, a total of 32 children aged 4-16 years old received between 1-4 infusions of allogeneic UC-MSC (Riordan *et al*, 2019; Sun *et al*, 2020). They were followed up for 1 year and no treatment-related SAEs were observed during the course of both trials.

2.2 Rationale for the current study

The study will be conducted in accordance with the protocol, Good Clinical Practise (GCP) and the Medicines for Human Use (Clinical Trials) Regulations 2004.There are several considerations that influenced the overall design of this trial. First, there is a need for some safety gatekeeping of UC-MSC treatment to ensure that the selected dosage has an acceptable toxicity profile. Secondly, the RDEB study sample size is very limited so there was a need for a study design to generate robust evidence in restricted populations and also to utilise the available sample size efficiently. Finally, most (if not all) previous related studies were either open-label, uncontrolled or not randomised limiting the quality of evidence gathered.

The internal phase 1 dose de-escalation trial is for safety gatekeeping of the proposed dose, with the option of halving the dose if recommended by the data monitoring and ethics committee (DMEC). The assessment of efficacy in the trial is through a two period, crossover study where patients will be randomised to receive either placebo followed by the active intervention or the active intervention followed by placebo. When used appropriately, crossover studies are an efficient study design which allows an assessment of efficacy for a fraction of the sample size compared to a parallel group trial as each patient acts as their own control and all patients receive both study treatments.

2.2.1 Rationale for dose regimen selection

The dose we propose is two infusions of 2-3 million MSCs per kg two weeks apart (at Day 0 and Day 14). At 9 months, the participants who initially received MSCs will be crossed over and receive two infusions of placebo. Similarly, the participants originally allocated placebo in the first treatment period of the crossover study will receive two infusions of 2-3 million MSCs per kg two weeks apart at 6 months. See Figure 3 for the study timeline (section 8) for details. The cell dose in this study has been chosen based on the safety and efficacy data from EBSTEM (Petrof *et al*, 2015) and previous clinical trials with intravenous BM-MSCs, predominantly for steroid resistant GvHD (Le Blanc *et al*, 2008, Le Blanc *et al*, 2003). In recent years, UC-MSCs have emerged as a source of MSCs with many advantages over BM-MSCs (Nagamura-Inoue and He, 2014). In a recent review of MSCs (BM and UC-derived) for GvHD the dose of infused MSCs ranged from 3.4×10^5 to 7.2×10^6 per kilogram (Zhao *et al*, 2019).

The dosing regimen used in the EBSTEM trial (Petrof *et al,* 2015) and previously approved by the Medicines and Healthcare Regulatory Agency (MHRA), was 1-3

million cells/kg with no safety concerns. The dose for EBSTEM was based on the treatment regimen used at the University Medical Center Utrecht as part of the protocol: 'Treatment of steroid resistant grade II to IV acute GvHD by infusion of mesenchymal stem cells expanded with human plasma and platelet lysate; a phase I/II study (NL13729.000.07). The dose of 1-3 x 10^6 cells/kg per infusion was reviewed by the EBSTEM external advisory board who felt that this regimen would be the most appropriate with a view to testing higher doses in future studies. The dose of 2-3 million cells for this proposed study has been agreed by senior Haematology clinicians, including co-applicant Prof Dazzi, experienced in delivering MSCs for GvHD. The serial dosing has been chosen based on the EBSTEM results where children saw positive effects after the second dose and these effects lasted for 4-6 months.

MSCs (BM and UC-derived) have been administered in varying doses and regimens ranging from 1-9 x 10^6 cells/kg in either single or repeated infusions (Zhao *et al*, 2019). Safety data has been published for third party MSCs (Prochymal, Osiris Therapeutics) at doses of 0.5, 1.6 and 5 x 10^6 cells/kg in acute myocardial infarction (Hare *et al*. 2009). No toxicity was evident at the higher dose. Le Blanc *et al* (2008) have safely treated 55 patients with acute GvHD using third party or haploidentical donors in multicentre phase II clinical trial using doses of 0.4-9 x 10^6 cells/kg, with half of the study group receiving multiple infusions. Significantly higher dose regimens have been used in children with acute GvHD with no untoward effect. Prasad *et al* (2011) administered 8 x 10^6 cells/kg of MSCs (Prochymal) twice a week for four weeks in 2 patients and 2 x 10^6 cells/kg in the remaining 10 children. There is no evidence from these and studies in other conditions that higher numbers of cells have added benefit. The dose was also chosen for feasibility reasons to ensure that sufficient numbers of cells are available for the whole study, after discussions with the cell manufacturer.

2.2.2 Rationale for choice of comparator drug

The EBSTEM trial administered 3 infusions (Petrof *et al*, 2015) and 9 children received two further infusions on a compassionate basis (total of 5 infusions). Currently, MSCs are not approved as treatment for RDEB and there is no high-quality published evidence of repeated infusions in this disease population. The study by El-Darouti *et al* (2016) had serious design flaws; notably half of the children were given immunosuppression with cyclosporine and the effects of that were difficult to assess in the trial. ADSTEM (Rashidghamat *et al*, 2019) and a current commercial study (NCT03529877) are both open-label studies with no trial where systemic MSCs infusions have been compared with placebo. The comparison is necessary to generate the best quality evidence to inform commissioning decisions about the use of MSCs as part of routine National Health Service (NHS) care (as discussed with NHS England).

Previous trials investigating the use of MSCs in RDEB have not incorporated a comparator arm or placebo. NHS England requires the most robust evidence possible to make a commissioning decision for the use of MSCs in RDEB and thus a placebo-controlled trial design is required. This design will eliminate response bias and the placebo effect. There are no other active treatments available for this condition that can be used as a comparator.

The placebo product contains DMSO which is the preservative used in the MSCs suspension which has a characteristic odour and taste. Therefore, to maintain the blinding, DMSO must be incorporated. DMSO is also known to have an anti-

inflammatory effect (Elisia *et al*, 2016) and its use as comparator is also necessary to prove that it is the cells that have a true effect on inflammation in the context of RDEB.

There are no known AEs relating to the use of DMSO which has been used extensively in clinical trials involving MSCs, except for transient and self-limiting adverse events such as mild headache, nausea and abdominal pain. The incident of all of these side effects in the EBSTEM trial was 2.2% (Petrof *et al,* 2015). The delivery of both IMP and placebo are intravenously through a peripheral line. This is appropriate because of the systemic nature of the disease and systemic rather than localised treatments are required.

2.2.3 Risk and benefits

Currently, there is no effective treatment for RDEB and the management is supportive. RDEB has a significant medical, physical, emotional and socio-economic impact for the patients and their families (Bruckner *et al*, 2020). Best practice treatment involves a multidisciplinary team of healthcare workers, with daily dressings often taking 1-4 hours to perform (Grocott *et al*, 2012). RDEB also has a major health economic burden (Angelis *et al*, 2016). Wound dressings alone for a 10-year-old child can cost up to £500 per day (Kirkorian *et al*, 2014), which equates to approximately £192,000 annually.

Current skin management of children with RDEB is regular foam absorbent dressings and topical and systemic antimicrobials for skin infections (Denyer *et al*, 2017). They also require regular and breakthrough analgesics, including opioids, many times at high and unlicensed doses (Goldschneider *et al*, 2014). The care of these children is multidisciplinary involving dermatologists, specialist nurses, dieticians, dentists, ophthalmologists, occupational therapists, physiotherapists, interventional radiologists, paediatricians, gastroenterologists, plastic surgeons and podiatrists. RDEB is a multi-system disease and therefore systemic treatments are required and should be prioritised (Completed EB Clinical Practice Guidelines, last accessed 25th September 2020, available at: https://www.eb-clinet.org/clinical-guidelines/completed-eb-guidelines/).

Worldwide, MSCs have been administered in a variety of conditions. There are currently over 300 active trials registered using either autologous or allogeneic MSCs populations (source www.clinicaltrials.gov, last accessed 24th September 2020). Because of the marked immunomodulatory effects of MSCs, most trial activity has focused on the use of MSCs in the treatment or prevention of GvHD following allogeneic HSCT. Up until August 2020, no significant adverse events (AEs) have been reported in any of the clinical trials involving MSC products as sole therapy, either autologous or allogeneic.

The investigational medicinal product (IMP) for this study, UC-MSCs, has a relatively unknown safety profile in children with RDEB. However, reporting of AEs in previous trials suggest that BM-MSCs were well tolerated. There is a risk of RDEB patients developing SCC but there is no evidence linking the use of MSCs to SCC in over 700 clinical trials (Rashidghamat *et al,* 2019). It has been suggested that, UC-MSCs have a higher survival rate in the tissue and show more anti-inflammatory and angiogenic effects compared to BM-MSCs, and therefore are expected to have higher efficacy in injury healing and symptom relief (Yousefifard *et al*, 2016). Overall, the benefit of the

treatment to the patient's disease state and quality of life is anticipated to largely outweigh any risk associated with receiving UC-MSC infusions.

3. Aims and objectives

3.1 Hypothesis

The hypothesis being tested is that repeated intravenous infusions of allogeneic (unrelated) UC-MSCs are safe and can benefit children with RDEB.

3.2 Aims

The overall aim of this study is to assess if repeated infusions of UC-MSCs are safe and can benefit children with RDEB.

3.3 Objectives

Primary objective

1. Internal phase 1 dose de-escalation study: To assess the safety of third party intravenous UC-MSCs in children with RDEB.
2. Main study (crossover and open-label): To assess the efficacy of third party intravenous UC-MSCs in improving disease severity in children with RDEB.

Secondary objectives (main study):

1. To assess the safety of repeated UC-MSCs in children with RDEB.
2. To assess the efficacy of repeated UC-MSCs in improving quality of life and symptoms (e.g., pain, itch) in children with RDEB.
3. To undertake a health economic analysis to assess the costs and consequences of treatment with UC-MSCs versus usual care.
4. To explore patients and parents 'views in relation to treatment effectiveness and acceptability.

4. Trial Design

This is a randomised, placebo controlled, double blinded crossover trial with an internal phase 1 dose de-escalation trial in the first 3 months and a 12 month continued treatment follow-on open-label study following review of the data. The trial will be conducted at two sites, Great Ormond Street Hospital (GOSH) and Birmingham Children's Hospital (BCH), that both specialise in paediatric dermatology and are Nationally Commissioned centres for paediatric EB.

4.1 Internal phase 1 dose de-escalation trial

An internal phase 1 study will be conducted on the first 9 participants in GOSH in two cohorts, see Figure 1. Each child will undergo an initial screening including physical examination, assessment of vital signs and disease severity assessment. Using an overall 2:1 (UC-MSCs:placebo) randomisation ratio, we will recruit 4 participants (each receiving the full treatment of two infusions before the next participant begins treatment and randomise them 3:1 (UC-MSCs:placebo). Outcome measures will be taken at screening, both infusion visits and then at the three month follow-up. This data will be reviewed by the DMEC and if toxicities (the primary safety outcome) are found in one (or fewer) patients receiving the active treatment, we will confirm this dose with a further 5 patients which will be randomised 3:2 (UC-MSCs:placebo). If no further toxicities, we will progress to the main two period crossover study. Of note, dose de-escalation or expansion decisions will be based on 3 participants randomised to UC-MSCs in each cohort receiving at least one infusion.

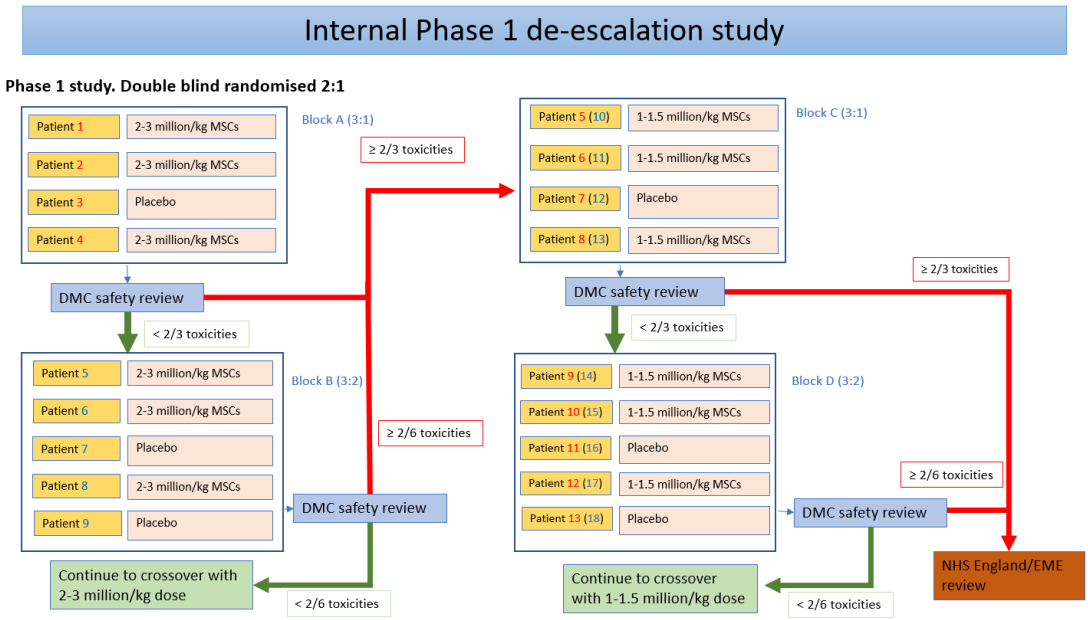

Figure 1: Internal dose de-escalation phase

In the event that no de-escalation is required, 9 patients will take part in phase I. If there is a dose de-escalation, new patients will begin the phase I at half dose i.e., patients will not be required to re-enter the phase I trial. The patient numbers in brackets reflect the numbers if dose de-escalation occurs within the second cohort (block B). It should be noted that treatments shown in Figure 1 can be viewed as first period treatments of the crossover trial to enable seamless transition into the main crossover trial after this internal phase when deemed appropriate.

4.2 Main crossover trial

Each child will undergo an initial screening including physical examination, assessment of vital signs and disease severity assessment. All study participants will be randomised to receive two consecutive intravenous MSCs or placebo infusions at day 0 and day 14. See study timeline (Figure 3) in section 8 for details. After outcome assessment at 9 months, all children will be crossed over and receive either placebo or UC-MSCs at 9 months and 14 days later. The placebo effect, if any, is expected to tail off by 3 months. In EBSTEM, the maximum benefit of the UC-MSCs was seen at 3 months, and in one patient the beneficial effects lasted for up to 6 months (Petrof, *et al,* 2015). This was the primary reason behind the 9 month wash-out period.

Outcome measures will be taken at 0, 3, 6, 9, 12 and 15 months. All children will be followed up every 3 months as part of their clinical care for the first year following the first infusion.

An evaluation of costs associated with treatment will also be undertaken.

We will explore the impact of the treatment on participants' by conducting interviews with children and parents (n=10 dyads or individuals) in both arms at the 3 month and 12 month follow-up time points.

4.3 Open-label non-randomised study

The open-label study will go ahead if the treatment is found to be effective without safety concerns by the National Institute of Health Research (NIHR) and NHS England. MissionEB is not an adequately powered study for feasibility reasons and as such, the judgement on efficacy of UC-MSCs will be based on totality of evidence from all clinical (primary and secondary) outcomes. The criteria for starting the open-label trial are based on the absence of any SUSARs which the DMEC consider of clinical concern. In addition, as this is a naturally progressive disease, the study will continue if there is an improvement in any of the primary or secondary outcomes for patients (improvement in disease severity, pain and itch and quality of life). The DMEC and TSC will review and consider whether the data indicate evidence of improvement. Participants of the crossover trial will be invited to the open-label study and be given 6 infusions in total (two infusions at 4 monthly intervals, at day 0, month 4 and month 8) and followed up at month 12, and outcome measures taken at each visit. No placebo will be administered in the open-label study.

The design of this study has been proposed by the leading clinicians that successfully conducted the EBSTEM trial of 10 children with RDEB. Experts in EB have been consulted as well as the parents of children with RDEB who have previously received MSCs and the patient advocacy group. Input from the Young People's Advisory Group at GOSH has also been sought. Methodological experts in trial design, medical statistics and health economics have collaborated with the clinical team to develop this application. NIHR and NHS England had also input into the trial design.

4.4 Washout period and rationale

Crossover studies require the participant to return to 'baseline' prior to crossing-over to the next treatment where the 'baseline" is defined here as the response they would be at that time had they not been in the clinical trial in period 1.

In this study we propose the period of time elapsing between starting one treatment (active or placebo) and crossing-over to the other treatments is 9 months. We know from the EBSTEM trial (Petrof *et al*, 2015), that the maximum effect from MSCs was 3 months (hence our choice of timing for the primary outcome), with the majority continuing to receive benefit at 4-6 months. A very small number of children may have longer-lasting benefits beyond 6 months and up to 9 months; however, this is based on very limited data.

4.5 Outcome measures/ study endpoints

Details concerning the timing of outcome measures and how they will be assessed are in Section 9.

4.5.1 Primary outcome/endpoint

Internal phase I dose de-escalation trial: Toxicity as defined by a patient experiencing a Suspected Unexpected Serious Adverse Reaction (SUSAR) (see section 9 for definition) within 48 hours of a patient receiving an infusion.

Main crossover trial: The primary outcome will be change in disease severity as measured by the Epidermolysis Bullosa Disease Activity and Scarring Index (EBDASI) at 3 months post-infusion of UC-MSCs (from day 0, period baseline). Disease severity is related to the total score across all 5 domains of the EBDASI (Jain *et al.*, 2017).

Open-label non-randomised study: the primary outcome will be the same as for the main crossover trial but assessed at 4, 8 and 12 months from day 0 (of the open-label study).

NB MissionEB is not an adequately powered study for feasibility reasons and as such, the judgement on efficacy of UC-MSCs will be based on totality of evidence from all clinical (primary and secondary) outcomes.

4.5.2 Secondary outcomes/ endpoints

The secondary outcomes/endpoints are applicable for the internal phase 1 dose de-escalation and crossover parts of the study.

- Change in EBDASI total score (as described in Section 4.5.1) at 6 months post infusion (from day 0, period baseline).
- Change in disease severity measured by iscorEB at 3 and 6 months post infusion (from day 0, period baseline) (Bruckner *et al.*, 2018). The iscorEB consists of 2 parts – clinician and patient scores. In the first part, the clinician will score skin, mucosal and internal organs involvement, laboratory abnormalities and complications. In the second part, the patient or caregiver will need to give scores

to each domain which consists of pain, itch, essential functions, sleeping, daily activates, mood and impact. These subscores will be combined into a total iscorEB score.

- Change in general clinical appearance of skin disease as assessed by clinical photography at 3 and 6 months post infusion (from day 0, period baseline) as detailed in Section 8.5.3
- Change to pain and itch as assessed by the Wong-Baker FACES Pain scale for children over 6 years old (Wong *et al*., 1988) and Leuven itch scale scores (Haest *et al*, 2011) at 3 and 6 months post infusion (from day 0, period baseline).
- Additionally, for pain and itch, changes to the amount of analgesia and itch medications required will be assessed. Participants or their guardians will be asked to detail what pain and itch medication the participant has taken in the last 48 hours, including dose and frequency. At 3 months post infusion, clinicians blinded to treatment allocation will compare whether this is unchanged, increased or decreased since baseline (day 0, period baseline).
- Change in quality of life according to validated Child Health Utility 9D (CHUD-9D) scoring system (Furber *et al*., 2015) at 3 and 6 months post infusion. Quality of life assessment will be conducted using CHU-9D. The CHU-9D is a sensitive and validated nine item child health-related quality of life assessment scale developed specifically with and for children and will be used in children aged 7 years and over. An age appropriate by proxy version will be used for children aged 3 – 6.
- To undertake a health economic analysis to assess the costs and consequences of treatment with UC-MSCs versus usual care.
- AEs and SAEs (see Section 9 for definitions) both during the trial and long-term adverse events after the trial.
- Safety bloods (Routine blood tests and C7 antibodies)
- Research bloods (will be stored for further analysis following a separate research application)
    - Serum for cytokines, IL-10, IL-13, IL-22, TNF-alpha at screening, day 0, day 14, month 9 and 2 weeks later in the crossover trial and all visits for the open label study, except the final 12 month visit.

The outcomes above are also applicable for the open label for month 4, 8 and 12.

4.6 Blinding

This is a double-blinded study so all participants and the research team will be unaware of the treatment allocation. This includes trial clinicians and research staff, the trial manager at CTRU, and trial statisticians. Trial pharmacists will be unblinded to allow them to perform QP certification checks upon delivery of the IMP. There will be an independent, research nurse from another team within the Clinical Research Facility who will prepare the IMP/placebo and perform the drug administration. This is necessary to avoid potential unblinding of study staff due to the differing appearance of the placebo and the IMP. This member of staff will be independent from the trial. A screen will be provided to shield the infusion procedure and ensure the patients and carers remain blinded. The blinded clinicians and nurses will be outside the room while the infusion is administered. Intended unblinding will only occur after the crossover trial during the extended open-label study. To facilitate unblinding which may occur due to unforeseeable circumstances (such as safety) and manufacturing and packaging of the study treatments, a Sheffield Clinical Trials Research Unit (CTRU) statistician who is independent of the conduct of the trial and the manufacturer, INmune Bio, will have secure access to the treatment allocation via the Sheffield CTRU validated, web-based randomisation system, SCRAM. INmune Bio will have internal systems to ensure that

the treatment allocations are correct. The randomisation schedule will be generated as detailed in Section 7.

4.7 Unblinding

The randomisation sequence will be held within the Sheffield CTRU web-based randomisation system. All participants will be unblinded at the end of the crossover trial when the statistical analysis plan has been agreed and signed. Participants will be provided with the treatments they were previously allocated to.

Since blinding is critical to the integrity of this study, the research team will ensure that participant's study treatment or order of treatment allocation remain masked during until the end of the crossover trial unless there is a medical emergency required to unblind treatment allocation and alter clinical management of the patient. Any cases of unblinding during the trial will be reported with an explanation. Procedures for unblinding are outlined in the MissionEB unblinding Standard Operating Procedure (SOP).

4.7.1 Accidental Unblinding

To avoid accidental unblinding only the delegated statistician independent of the conduct of this trial, the manufacturer and the pharmacy will have access to the treatment allocation. Site staff and research team will not have access. In the event that a patient is accidentally unblinded, this will be reported to the Sheffield CTRU using the Unblinding form, as detailed in MissionEB Unblinding SOP.

4.7.2 Emergency unblinding

Unblinding will generally only be considered in the event of a medical emergency where knowledge of the participant's treatment allocation would change clinical management. Where unblinding is being considered during work hours (Mon – Fri, 09:00 – 17:00 UK time), the case will normally be discussed with the CTRU and the sponsor first. However, the investigator may unblind the treatment allocation immediately if deemed medically necessary. Out of hours, the investigator (or assigned deputy) will have determined that the information is necessary i.e., that it will alter the participant's immediate management. Where it is deemed necessary, a site investigator or delegated member of site staff will be responsible for unblinding the treatment allocation out of hours using the online system, SCRAM. This will be performed according to the MissionEB Unblinding SOP. Unblinding for any purpose other than a medical emergency is generally not permitted but individual cases will be discussed with the CTRU if it is believed to be necessary for the medical care of the participant.

For any treatment code unblinding, the reason for the decision to unblind and the parties involved will be documented on the unblinding CRF. Treatment identification information will be kept confidential and will be disseminated only to those individuals that must be informed for medical management of the participant. Wherever possible, the study teams involved in the day-to-day running of the study will remain blinded. When unblinding for Safety Reporting, a member of staff at CTRU will unblind the treatment allocation and will be responsible for reporting any SUSARs as appropriate.

Treatment identification information will be kept confidential and will be disseminated only to those individuals that must be informed.

5. Selection and withdrawal of participants

These inclusion/exclusion criteria will be used for the crossover study (including the phase 1) and the open label study.

5.1 Inclusion criteria

1. Patients who have a diagnosis of RDEB characterised by partial or complete C7 deficiency including generalised severe and generalised intermediate subtypes.
2. Patients who are over 6 months and before their 16th birthday at time of consent.*
3. Patients whose responsible parent/guardian has voluntarily signed and dated an Informed Consent Form (ICF) prior to the first study intervention. Whenever the minor child is able to give consent, the minor's assent will be obtained in addition to the signed consent of the minor's legal guardian.

5.2 Exclusion criteria

1. Patients with other subtypes of EB such as EB simplex, dominant DEB, junctional EB and Kindler EB.
2. Subjects who have received oral or topical corticosteroids for more than 7 consecutive days within 30 days of enrolment into this study, **with the exception of** the following steroids with non-systemic effects and intended to relieve oesophageal symptoms: oral viscous budesonide and inhaled fluticasone.
3. Patients with a known allergy to any of the constituents of the investigational product.
4. Patients with signs of active infection that requires treatment with oral or intravenous antibiotics within 7 days of screening.
5. Patients with a medical history or evidence of active malignancy, including cutaneous squamous cell carcinoma.
6. Patients with BOTH a) positive C7 enzyme linked immunosorbent assay (ELISA) **and** b) a positive indirect immunofluorescence (IIF) with binding to the base of salt split skin at screening.
7. Patients who are pregnant or of child-bearing potential who are not abstinent or practicing an acceptable means of contraception, as determined by the Investigator, for the duration of the treatment phase.
8. Patients having received MSCs from any source in the last 9 months.
9. Simultaneous or previous participation in any interventional trial within 3 months before entering this trial but participation in simultaneous registry, and diagnostic trials during the trial is allowed.

* Participants must be recruited before their 16th birthday to the crossover trial as this will allow for completion of the whole trial (crossover and open-label) before they are 18 and transition to adult services. However, if there are delays to the study due to

dose de-escalation, all participants should be allowed the opportunity to partake in the open-label.

5.3 Participant identification

EB is a nationally commissioned service by NHS England. The children are looked after by the clinical teams at GOSH and BCH. This study has been designed for all children with a molecular diagnosis of RDEB and all eligible children and their parents/carers will be approached to take part. The total number of children with RDEB across both UK centres is 80. If we exclude children with too mild disease (i.e., less than 5 wounds, each smaller than 10cm^2) or who will be 16 years of age at the time of the study initiation the number of eligible children across both centres is 41. This number includes 19 children at BCH and 22 at GOSH. We estimate that up to a further 15% will not be eligible due to concurrent illness (for example on long term antibiotics) or will decline to participate in the study for other reasons (number of trial visits), leaving 37 patients. We estimate very few participants will drop-out during the study for reasons such as burden of visits or negative view of the treatment; however, we have assumed 1-2 dropouts during the study (approx. 5%). This will leave us with 36 evaluable participants.

There are no active EB interventional research studies at GOSH or Birmingham Children's hospital.

5.4 Recruitment and Setting

There will be two recruitment sites for the trial: GOSH and BCH. Both recruitment sites are Nationally Commissioned centres for children with RDEB. The children are regularly seen by the clinical teams, in the majority of cases, since birth until they transition to the adult EB service at age 16. The clinical teams have been in discussion with parents and patients about the study since its inception and are informed of the current design. A number of families experienced benefit during the EBSTEM trial and are keen to take part in this trial.

The number of eligible patients across both hospitals is 41 and all will be considered for the trial. Study information sheets will be provided and individuals interested will be invited for further consultation, assessed for eligibility and consented as necessary.

As RDEB is a rare condition, the sample size is based on feasibility of recruitment and not formal power considerations. Section 10.1 gives further details on the samples size for the study.

All participants aged 6 and over will be invited to interview following the decision to proceed to the main trial. Parents of all children in the trial will be invited to be interviewed. The qualitative lead will monitor the uptake and if necessary, liaise with the unblinded statistician to ensure a purposive sample of participants and parents across both arms, sites and all ages.

5.5 Informed consent process

Patients and guardians will be consented for the randomised crossover trial in the first instance. It will be made clear in the PIS and consent form that consenting to take part in the crossover trial will include consenting to potentially participate in the phase I de-escalation study. Once the crossover study is complete, and if the data review deems it appropriate, patients and guardians will be consented to take part in the open-label study. For both studies the following consenting procedures will be observed. Written informed consent will be obtained from the child's guardian/parent by a physician listed on the delegation of duties log before any study related procedures, including screening tests, are performed. Once the Investigator has determined the child's potential eligibility for the study, the background of the proposed study, as well as the benefits and risks of the procedures and study, will be explained to the potential study participant and caregiver. They will both be given an age-appropriate subject information sheet to read. They will be given adequate time (at least 24 hours) to review the information received and may take the information away to consider his/her participation in the study. The person obtaining consent will record in the patient notes when the patient information sheet (PIS) has been given to the patient. If the amount of time between the PIS being given and the date of consent is less than 24 hours, the PI will explain the rationale for this. Prior to screening, the guardian/parent must first sign the Independent Ethics Committee (IEC) approved informed consent form (ICF). Failure to provide informed consent renders the subject ineligible for the study. Study participants and their guardians/parents will be instructed that further information can be obtained at any time from the Investigator, and that they are free to withdraw their consent and to discontinue participation in the study at any time without prejudice. If new safety information results in significant changes in the risk/benefit assessment, the consent form will be reviewed and updated if necessary and subjects will be re-consented as appropriate.

When a subject deemed legally non-competent, such as a minor child, is able to give assent to decisions about participation in research, the investigator will obtain that assent in addition to the consent of the guardian/parent. In this context, "assent" will be understood to mean the expression of the minor's will to participate in a clinical trial. Assent will be sought from children aged 6 years and above. Separate information sheets for adults and children, and separate consent and assent forms will be used in order to provide age-appropriate information, in language and wording appropriate to age. If the child's assent is not obtained, this will be documented with justification in the consent form which is signed by the guardian/parent and investigator. The minor's assent will not be sufficient to allow participation in research unless supplemented by the informed consent of the guardian/parent.

If a participant turns 16 whilst enrolled in the trial, they are legally able to provide consent to continue with trial procedures. This will be explained to them, and they will be provided with a Patient Information Leaflet for participants. The clinical team will support the participant by answering any queries, and the participant will be allowed time to discuss the trial as necessary. If they consent to continuing on the trial, they will sign a participant consent form. If they wish not to continue on the trial, they will be withdrawn and no further data collected.

Separate consent for the interview will be sought after the first infusion and before the interview (around 3 months post-treatment). We will gain consent from the child and parent for the child interview, and from the parent for their own interview.

5.6 Co-enrolment guidelines

Participants will not be permitted to take part in any other interventional studies.

5.7 Contraception/ Lifestyle Guidelines

Females of childbearing potential and males must be willing to use a highly effective (effective contraceptive measures are only acceptable for IMP's with unlikely human teratogenicity / fetotoxicity in early pregnancy) method of contraception (hormonal or barrier method of birth control; abstinence) Contraceptive methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
    - oral
    - intravaginal
    - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation
- oral
- injectable
- implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomised partner
- Sexual abstinence

Sexual abstinence is acceptable only when it is true abstinence. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

5.7.1 Pregnancy testing

Female participants who are menstruating ***and*** sexually active will be required to have a urine pregnancy test at every visit.

Any pregnancies will be recorded on the 'Pregnancy Information' CRF and reported to the CTRU immediately. See Section 9.8 for reporting procedures. If a pregnancy occurs, the participant will be withdrawn from treatment but will be followed up as per protocol.

5.8 Patient withdrawal from follow-up

Excessive participant withdrawal from follow-up has a negative impact on a study. Centres will explain the importance of remaining on study follow-up to participants. Nevertheless, if participants do not wish to remain in the study their decision must be respected. If the participant explicitly states their wish not to remain in the study for follow up, this will be recorded on a Study Completion/Discontinuation form. However,

data up to the time of consent withdrawal will be included in the data reported for the study. This is made clear in the participant information sheet. The information sheet also informs participants that data collection for ongoing SAEs and long-term safety data will continue even if they withdraw from further follow up, unless they explicitly state that they do not wish this data to be collected. This data will be collected via a review of the medical records, i.e., a study visit will not be required, and this should be discussed with participants at the point of withdrawal to ensure their wishes are documented and respected.

6. Trial treatment

In relation to the event of a pandemic, sites must adhere to local Trust policies with regards to the operational management of patient treatment and follow-up. All efforts will be made to administer study treatment and assess outcomes where it is within safety guidelines (refer to NIHR guidance on trials during COVID-19). Where necessary visits can be conducted by telephone, video or as home visits.

6.1 IMP details

The investigational drug, “CordSTROM” is an advanced therapy medicinal product (ATMP) consisting of a suspension of allogeneic MSCs sourced from umbilical cord tissue (UCT) from between 4-10 pooled umbilical cord blood donors. UCT is supplied to INmuneBio from the UK National Anthony Nolan Cord Blood Bank from consenting donors who have been screened for cord blood donation. INmuneBio will manufacture the IMP with QP release by Royal Free London under their MIA (IMP) licence. Cord tissue is manually dissected, before enzymatic dissociation to release MSCs. MSCs are isolated by plastic adherence and expanded in xeno-free culture conditions in closed-system bioreactors for up to 30 population doublings to create the drug product.

After the culture, the cells are harvested and cryopreserved before being adequately packaged, labelled, stored in vapour phase nitrogen and shipped to the clinical unit when prescribed. All batches are tested at release for identity, sterility, viability and absence of detectable mycoplasma and endotoxin before certification. The drug product consists of a sterile, yellowish cell suspension cryopreserved in 50ml CryoMACS bags which are combined as necessary to make up the defined dose for the individual patients. The final cryopreserved product is supplied in clear and individually labelled overwrapped, 50ml CryoMACS bags with a fill volume of 10ml or 15ml cell suspension per bag and a minimum concentration of $3.0x10^6$ CORDStrom per ml. The cells in the drug product will have undergone a total of 4 cell passages (P4). Tables 2 and 3 detail the composition of the IMP and placebo, respectively.

Table 2: Composition of the IMP

Component	**Function**	**Quantity**	**Reference to standards**
Dulbecco’s Phosphate Buffered Saline		50%	Good Manufacturing Practise (GMP)-grade

ZENALB 4.5 (HAS)	Excipient	40%	Registered product for infusion
DMSO		10%	GMP-grade
CordSTROM (p4)	Active ingredient	$3.0x10^6$/ml	In-house testing described in IMPD

Table 3: Composition of the placebo control

Component	**Function**	**Quantity**	**Reference to standards**
Dulbecco's Phosphate Buffered Saline	Excipient	90%	GMP-grade
DMSO		10%	GMP-grade

6.1.1 Efficacy

UC-MSC have been shown to equal or exceed BM-MSC in their capacity for chondrogenic differentiation (Kern *et al*, 2006) and to be equivalent in their capacity for inhibition of activated-T cell proliferation (Kim *et al*, 2017). In our assays we have shown the ability of UC-MSC to inhibit activated T cell proliferation (Table 1) and to enhance wound healing *in vitro* via secretion of extracellular vesicles (Figure 2).

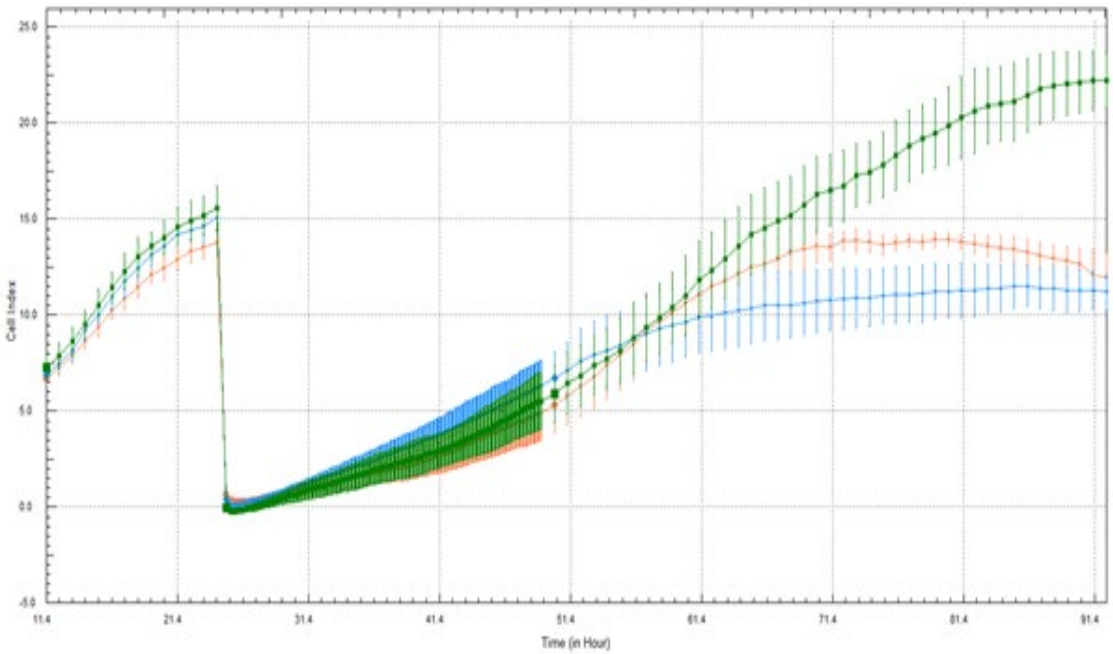

Figure 2: Fibroblast re-growth in a "scratch assay" Fibroblasts seeded onto Xcelligence cell replication growth plates in culture media supplemented with MSC-derived supernatants (blue), purified MSC-derived extracellular vesicles (green) or control culture medium (orange) and subjected to 50% cell removal by scratch at 24 hours. The regrowth of fibroblasts was significantly enhanced by treatment with UC-MSC-derived extracellular vesicles.

6.1.2 Pharmacology

The pharmacological effect of the MSCs is immune-modulation on different cellular components of innate and adaptive immunity. MSCs inhibit proliferation, cytokine secretion, and cytotoxic potential of natural killers and CD8+ T cells as well as the proliferation and antibody production of B cells. They also impair maturation, cytokine production, and T-cell stimulatory capacity of dendritic cells. Furthermore, MSCs inhibit the proliferation and cytokine secretion of subsets of CD4+ T lymphocytes and promote the expansion of regulatory T cells. The immune-modulating effects of MSCs are mediated by various cell membrane-associated and soluble molecules.

The understanding of MSC immunoregulatory properties was primarily focused on their ability to inhibit the proliferation of T lymphocytes. Since then, numerous studies have shown that the MSCs affect the function and the differentiation of several other types of immunocompetent cells. These biological data led to the first human clinical studies to evaluate the efficacy of MSC in treating graft-versus-host disease (Le Blanc et al 2004). MSC immunoregulatory and immunosuppressive properties also constitute an experimental rationale for the use of MSC to treat several autoimmune diseases.

There has been much discussion surrounding the proposed mechanism of action of MSC therapies. After Le Blanc's landmark paper in Lancet in 2004 (Le Blanc *et al* 2004) showed the curative potential of allogeneic MSC infusions in steroid-refractory GvHD, her group went on to show that the cells had an expected *in vivo* half-life of no more than 2 days which questioned the pharmacodynamics of any immunomodulatory effect. Hundreds of *in vitro* studies have reported multiple mechanisms of MSC medicated T cell inhibition and anti-inflammatory cytokine release but Dazzi *et al*, showed that apoptotic MSCs were at least as immunomodulatory and anti-

inflammatory as live cells and often more potent (Galleu *et al*, 2017). The mechanism is via phagocytic uptake of apoptotic MSCs and the production and release of indoleamine 2,3-dioxygenase which mediates the immunosuppressive and anti-inflammatory response.

6.2 Dosage schedules

6.2.1 Internal phase 1 dose de-escalation trial

Each participant will receive two intravenous infusions (Day 0 and Day 14), administered as a slow bolus. Participants will receive 2-3x10^6 cells per kg. For more details of the infusion procedure please refer to the MissionEB Infusion guidelines. No subject conditioning with chemotherapy or immunosuppression will be given. Chlorphenamine and Paracetamol will be given to each patient before the administration of the MSCs. The participant's usual acute pain relief, will be given where necessary prior to the cannula insertion. Vital signs will be documented before administration of the cells and thereafter every 15 minutes for two hours after the infusion and on discharge. Vital signs will include blood pressure, respiratory rate, heart rate, pulse oximetry and temperature, the results of which should be recorded on the CRF.

Section 6.6 details the dosing schedules in the event of toxicities. Criteria for dose de-escalation is outlined in Section 6.6 and Figure 1.

6.2.2 Main crossover trial

Each participant will receive a total of four intravenous infusions (Day 0 and D14, month 9 and 2 weeks later), administered as a slow bolus. For more details of the infusion procedure please refer to the MissionEB Infusion guidelines If it is not necessary to de-escalate the dose following phase 1, participants will receive 2-3x10^6 cells per kg. If a dose de-escalation is required, doing schedules will be reduced as outlined in Figure 1, and Section 6.6. The infusion procedure is detailed in the MissionEB Infusion guidelines.

6.2.3 Open-label study

Each study subject will receive a total of six intravenous infusions (Day 0 and D14, month 4 and 2 weeks later, month 8 and 2 weeks later). For more details of the infusion procedure please refer to the MissionEB Infusion guidelines. If it is not necessary to de-escalate the dose following phase 1, participants will receive 2-3x10^6 cells per kg. If a dose de-escalation is required, doing schedules will be reduced as outlined in Figure 1, and Section 6.6. The infusion procedure will be detailed in MissionEB Infusion guidelines.

6.3 Drug storage and supply

The working cell stock from which the drug is manufactured has a shelf life of three years with storage between -135°C and -196°C. The drug has long-term storage stability in vapour phase nitrogen (-196ºC) of 24 months and can be stored in a

mechanical freezer at or below -70°C for up to 26 days. For this trial, the drug product will be stored at or below -70°C in a monitored mechanical freezer within Pharmacy Department at the clinical site for a maximum of 21 days.

CordSTROM is being manufactured and supplied by INmune Bio International specifically for use in this trial. The technical agreement between Sponsor and drug manufacturer will be in place prior to opening for enrolment. INmune Bio International will also supply the placebo comparator under terms in the same Technical Agreement. For further details on IMP supply, handling and accountability please refer to MissionEB Pharmacy manual.

6.4 Accountability

There are no accountability issues with patients as all IMP is received within the hospital setting. The sponsor will undertake any accountability with the suppliers and pharmacies as appropriate, with procedures outlines in the MissionEB Pharmacy manual.

Procedures for drug distribution and accountability will be detailed in the MissionEB Pharmacy manual. This will involve site pharmacies, the manufacturer and the Qualifying Person responsible for releasing the investigational product in the respective production facility. Detailed records will be kept toallow for accurate accountability of the UC MSC cells. These records will include details of shipping, receipt, storage, prescribing, administration and destruction of the IMP if any. Transfer of cells from the facility to the hospital sites and administration of the cells to patients will be recorded.

6.5 Adherence

As the trial treatment is administered by clinical staff, there is no opportunity in this trial for patient-related non-adherence. Records will be maintained in the Clinical Research Facilities on each site and in the patient's medical notes to document that doses and regimens are correctly administered.

6.6 Dose Modification and interruptions

The definition of a dose limiting toxicity (DLT) for the phase 1 study is a suspected unexpected serious adverse reaction (SUSAR). Events will be assessed by the study clinicians as being caused by the study drug or not. These include immediate reactions such as severe allergic reactions, severe hypoxia, and severe shortness of breath and/or chest pain.

If 2 of the 6 patients receiving the proposed dose have a toxicity the phase 1 study will be repeated with up to 9 patients at half the dose using the same process as the starting dose. If no further toxicities are present this dose will be used for the main trial. If toxicities are present in more than one participant at this stage discussion will be required between the DMEC, sponsor and funder to determine the next steps (i.e., whether to de-escalate the dose further or stop the trial). Crossover studies require the participant to return to 'baseline' prior to crossing-over to the next treatment where the 'baseline" is defined here as the response they would be at that time had they not been in the clinical trial in period 1.

Outside of the phase 1 study, any dose modifications or interruptions of treatment will be discussed with the DMEC and TSC.

The allowed window for IMP delivery is +/- 5 days for the follow-up infusion (2 weeks later) (as indicated in Table 4) unless there are clinical reasons the dose cannot be administered in this timeframe (e.g., participant illness and difficulty cannulating). In these cases, the participant should be discussed with the central study team on an individual basis and treatment planned accordingly. The maximum time between the two infusions will be 4 weeks. Allowing adequate time for the 9 month washout (see Section 4.4) may need to be considered in cases where the time between the infusions has been extended beyond the usual allowed windows. Follow-up visits should allow for a minimum 8.5 months between ending one treatment period and beginning the next.

6.7 Concomitant therapy

The study subjects can continue to receive their regular medication(s). A complete listing of all concomitant medication received during the treatment phase will be recorded in the relevant case report form.

6.8 Post-trial treatment

The open-label study will only go ahead with the consent of NIHR and NHS England. The open-label study and the post-trial treatment will be decided based on the outcome of the current study. NHSE will make the final decision for ongoing funding of the excess cost of treatment. The aim and design of this study was designed with the aim to demonstrate the safety and efficacy of UC-MSCs in treating children with RDEB. Post-trial, participant's disease state will be reviewed and infusions administered on compassionate grounds may be made available by NHS England, providing no safety concerns have been raised during the trial.

7. Randomisation and enrolment

During both the internal phase I dose de-escalation trial and main crossover trial, the allocation sequence will be generated by the randomisation statistician using a validated web-based randomisation system within the Sheffield CTRU. This system offers restricted access to the members of the research team depending on their roles and responsibilities and details of the randomisation are retained within the system. The randomisation statistician will not have access to the allocation sequence even though they have generated the sequence.

Site research staff at GOSH and BCH will consent patients and enter their details on the randomisation system. They will remain blind to the treatment allocation. The randomisation email will be received by pharmacy and the IMP manufacturer, INmuneBio, who will make up the patient treatment as instructed (either placebo or active treatment) and label this with the patient ID. The treatment will be shipped to site pharmacy, where it can be stored at or below -70^{o}C for up to 21 days. Pharmacy will dispense the IMP or Placebo for site research staff to administer to each patient accordingly. Further details of the randomisation procedure are outlined in the MissionEB Randomisation SOP.

7.1 Randomisation during the internal dose de-escalation trial

Patients will be randomised in four cohorts and the choice of the cohort block depends on toxicity decisions made by the DMEC after each cohort (see Figure 1). The first 9 patients are divided into two cohorts all allocated using simple randomisation: the first 4 patients will be randomised (3: 1) to receive (UC-MSCs: placebo) and the second 5 patients will be randomised (3: 2) to receive (UC-MSCs: placebo). This gives an overall allocation (6: 3) for these 9 patients to receive (UC-MSCs: placebo). It should be noted that treatments stated here are technically for the first period of the crossover trial. These patients will only receive their second period treatments of the crossover if no concerning toxicity issues are found. For example, patients who received UC-MSCs in the first period will then receive a placebo in their second period after the washout period or vice versa. The reporting data to DMEC is based on 3 participants in each cohort receiving active treatment (at least one infusion). We will allow for flexibility in the randomisation process to address situations where a randomised participant may drop out before their first infusion. Further details will be covered in a study specific SOP on randomisation sequence generation.

7.2 Randomisation during the main crossover trial

Patients will be randomised (1:1) to either receive UC-MSCs (in period 1) followed by a placebo (in period 2) or placebo (in period 1) followed by UC-MSCs (in period 2) using simple blocked randomisation. We introduced blocking to ensure that the periods are balanced during the course of the trial which is key in an unpredictable COVID-19 pandemic. Only the randomisation statistician will have access to the block size during the trial. Of note, patients who have already received period 1 and 2 treatments on the correct UC-MSCs dose during the internal dose de-escalation trial will not be re-randomised again in the main crossover trial as they have contributed valid data for both periods. However, in the event that the dose needs to be de-escalated, patients who previously took part in the dose de-escalation study on a higher dose will washout for at least 9 months and be re-randomised to take part in the main crossover trial using the new, lower dose. Further details on when patients will be eligible for re-randomisation are outlined in the MissionEB Randomisation SOP.

7.3 Unblinding and access to the allocation sequence

This is a double-blinded study so all participants and the research team will be unaware of the treatment allocation. Intended unblinding will only occur after the crossover trial during the extended open-label study. To facilitate unblinding which may occur due to unforeseeable circumstances (such as safety) and manufacturing and packaging of the study treatments, a Sheffield CTRU statistician which is independent of the conduct of the trial and the manufacturer, will have access to the treatment allocation via the web-based randomisation system. Pharmacy will have access to the treatment allocation for QP release.

8. Assessments and procedures

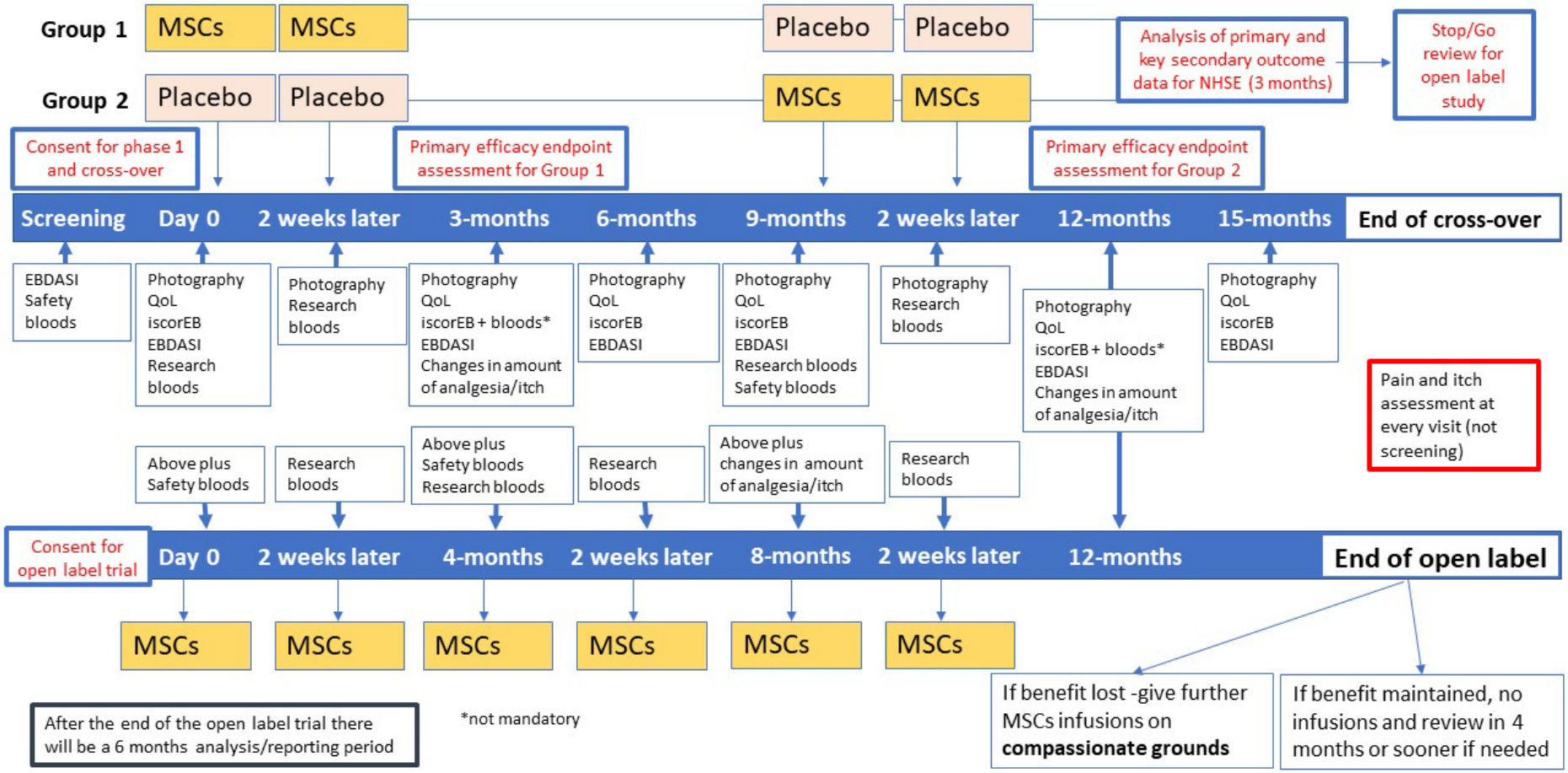

Figure 3: Overview of the crossover study and open-label study timelines

8.1 Study assessments schedule

8.1.1 Internal phase 1 dose de-escalation phase

The study assessment schedule below details the assessments required during the course of the study (Table 4). All participants will undergo these assessments regardless of which treatment arm they are randomised to, unless otherwise indicated. Participants will attend the trial site to be screened for eligibility as per the study assessment schedule table. If the results from the C7 antibody test confirm eligibility, and all other criteria are met, the participant should be randomised as soon as reasonably possible. Day 0, defined as the time point that the participant receives the first dose of intervention, should be attended as soon as possible (allowing a minimum of 5 working days for IMP order and delivery) but must be within four months of randomisation. If a participant develops a wound infection between the time of screening and attending the Day 0 visit, it is permitted for participants who are receiving a course of oral antibiotics to receive their Day 0 infusion, as long as they are clinically well. Any participants who are receiving IV antibiotics should have their Day 0 infusion delayed until recovered. Outcome measures will be completed pre-dose. The flow diagram below outlines the procedures for participants entering the phase I study (Figure 4). In the event of a dose de-escalation, all participants will be followed up until the three month time point, and safety data will be collected for this time period. Participants will be re-screened to re-enter the crossover study at the lower dose. Any patient that received IMP must have a washout period of at least 9 months before receiving the lower dose. Participants who receive an infusion but do not continue to enter the crossover trial will still be invited to join a long-term follow up trial for 15 years from the last dose of IMP, as per ATMP regulations (see Section 8.6 for more details).

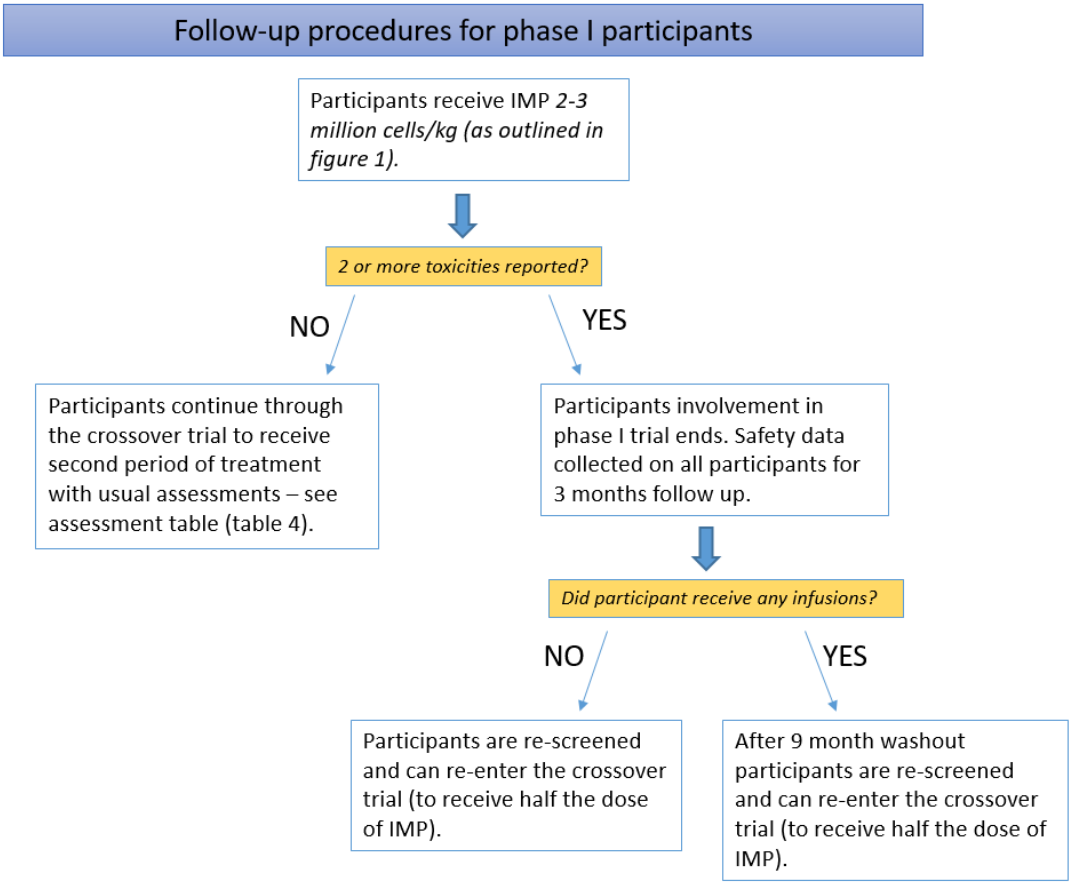

Figure 4: Phase I trial follow up

8.1.2 Crossover and open-label

The study assessment schedule below details the assessments required during the course of the study (table 4). All participants will undergo these assessments regardless of which treatment arm they are randomised to, unless otherwise indicated. Participants will attend the trial site to be screened for eligibility as per the study assessment schedule table. If the results from the C7 antibody test confirm eligibility, and all other criteria are met, the participant should be randomised as soon as reasonably possible. Period 1 Day 0, defined as the time point that the participant receives the first dose of intervention, should be attended as soon as possible but must be within four months of randomisation. If a participant develops a wound infection between the time of screening and attending the Day 0 visit, it is permitted for participants who are receiving a course of oral antibiotics to receive their Day 0 infusion, as long as they are clinically well. Any participants who are receiving IV antibiotics should have their Day 0 infusion delayed until recovered.

Crossover Trial	**Internal Phase 1, placebo-controlled randomised trial**								
		Period 1[1]				**Period 2[4]**			
				9m washout before Period 2[2]					
Visit #	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Purpose	Screening	1st infusion Day 0 Period 1*	2nd infusion Day 0 Period 1 + 14d (+/- 5 days)	Month 3 (+/- 7 days)	Month 6 (+/- 14 days)	3rd infusion / Month 9 Day 0 Period 2[3] (+ 8 weeks)*[¥]	4th infusion Day 0 Period 2 + 14d (+/- 5 days)	Month 12 (Period 2 Month 3) (+/- 7 days)	Month 15 (Period 2 Month 6) (+/- 14 days)
Patient information and informed consent	x								
Confirmation of consent	x	x	x	x	x	x	x	x	x
Inclusion/exclusion criteria review	x[‡]								
Skin biopsy**	x								
Pregnancy test***	x	x	x	x	x	x	x	x	x
Physical examination	x	x	x	x	x	x	x	x	x
Vital signs	x	x	x			x	x		
Blood DNA analysis (if not done)	x								
IMP/Placebo infusion		x	x			x	x		
iscorEB		x		x	x	x		x	x
EBDASI	x	x		x	x	x		x	x
Pain assessment		x	x	x	x	x	x	x	x
Itch assessment		x	x	x	x	x	x	x	x
Photography of wounds		x	x	x	x	x	x	x	x
Changes to analgesic/itch medication				x				x	
Quality of life assessment		x		x	x	x		x	x
Routine bloods (safety bloods)****	x			x[+]		x		x[+]	
C7 serum antibodies (safety bloods)	x					x			
Serum cytokines (research bloods)		x	x			x	x		
Adverse event assessment		x	x	x	x	x	x	x	x
Concomittant medication assessment (including analgesia and itch)	x	x	x	x	x	x	x	x	x
Pain and itch medication taken 48 hours prior to study visit		x		x		x		x	

Table 4: Study procedures for the crossover trial and Open label

	Open-label study						
Visit #	**10**	**11**	**12**	**13**	**14**	**15**	**16**
Purpose	Month 0 5th infusion	2 weeks later 6th infusion (+/- 3 days)	Month 4 7th infusion (+/- 7 days)	2 weeks later 8th infusion (+/- 3 day)	Month 8 9th infusion (+/- 7 days)	2 weeks later 10th infusion (+/- 3 day)	Month 12 follow-up visit (+/- 14 days)
Patient information and informed consent	X						
Confirmation of consent	X	X	X	X	X	X	X
Inclusion / exclusion criteria review	X						
Pregnancy test ***	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	
IMP/Placebo infusion	X	X	X	X	X	X	
iscorEB	X		X		X		X
EBDASI	X		X		X		X
Pain assessment	X	X	X	X	X	X	X
Itch assessment	X	X	X	X	X	X	X
Photography of wounds	X		X		X		X
Changes to analgesia/itch medication			X		X		X
Quality of life assessment	X		X		X		X
Routine bloods (Safety bloods) ****	X		X		X		X+
C7 serum antibodies (safety bloods)	X		X		X		
Serum cytokines (research bloods)	X	X	X	X	X	X	
Adverse event assessment	X	X	X	X	X	X	X
Concomitant medication assessment(including analgesia and itch)	X	X	X	X	X	X	X
Pain and Itch medication taken 48 hours prior to study visit	X		X		X		X

1 *Visit windows for Period 1 should be calculated from Period 1 Day 0;*
2 *The time from Day 0 period 1 (infusion 1) to Day 0 period 2 (infusion 3) should be at least 9 months*
3 *Visit windows for Period 2 should be calculated from Period 2 Day 0.*

ł Inclusion/Exclusion criteria must reviewed at screening and must be signed off by an appropriate member of the study team before a patient is randomised.
+ These routine bloods should only be taken if there are no clinical blood results available between the infusion date and follow-up visit. These routine bloods are not mandatory.
¥ Please note delays to the month 9 visit should be discussed and agreed with the central team. Ideally, this should be within 8 weeks of the due date.
** Note – outcome measures will be taken pre-dose*
*** For immunofluorescence. ONLY required if this information is not already in the patient notes. If needed, the skin biopsy will be performed according to local procedures.*
**** ONLY required in female participants who are menstruating and confirmed sexually active*
***** Blood tests: Full blood count, bone profile, liver function tests, renal profile, ferritin, CRP, ESR to be analysed in local NHS laboratories. The blood tests will be part of routine clinical care and no additional tests are required for the purpose of this study. The vital signs should be recorded every 15 minutes for two hours on the day of infusion. Refer to protocol section 6.2.1.*

8.2 Baseline assessments

8.2.1 Crossover trial and internal phase I dose de-escalation safety phase

The study baseline data will be taken prior to dosing after randomisation on Period 1 Day 0 (visit 2). The first infusion of MSC (Period 1 Day 0) must occur within 4 months of randomisation. For the first study period of the crossover trial this will be the pre-dose value for that period.

The pre-dose assessment for the second study period will be taken prior to dosing at month 9 (Period 2 Day 0).

8.2.3 Open-label trial

Baseline data for the open label trial will be the study pre-dose data from day 0. A pre-dose value at visit 10 will also be taken.

8.3 Subsequent visits

The study assessment schedule (Table 4) and Figure 3 detail the visits and assessments required during the course of the study. Follow-up visits should be calculated from Day 0 specific to the treatment period of the crossover. For example, scheduling of the month 12 visit (Period 2 Month 3) should be calculated as 3 months after Day 0 of Period 2.

The acceptable window to complete each visit is indicated in the study assessment table. These windows should be adhered to except where extraordinary circumstances prevent this (e.g., in case of a pandemic that prevents access to the treatment), in which case the site will contact CTRU for advice.

The allowed window for the month 9 (crossover Treatment Period Infusion 1) should be discussed with the central study team if the patient has had to be delayed to illness (e.g. infection requiring treatment with antibiotics). Delay to the month 9 visit will not be considered a protocol deviation.

8.4 Unscheduled visits

Participants' local care team may also be part of the research team for MissionEB. Therefore, participants may be seen at additional visits outside of those scheduled in the study, but these visits would be part of usual care. Any reportable adverse events identified at additional care visits will be documented in the CRF.

8.5 Procedures for assessing efficacy

8.5.1 Disease severity

As described in Section 4.1 the primary outcome for the main trial will be change in disease severity as measured by EBDASI (Jain *et al.,* 2017). This will be completed by a Clinical Fellow that is blinded to treatment allocation at screening, 1st and 3rd infusion visits, and month 3, 6, 9, 12 and 15 of the crossover study and month 0, 4, 8 and 12 for the open-label study. Disease severity will also be assessed as measured by iscorEB at the same time points, except screening. (Bruckner *et al.* 2018). Where the iscorEB measure requires blood results, (at month 3 and 12 for the crossover study),

assessors should use the latest blood results available to them (e.g., from clinical or routine bloods taken as part of standard care) and record the date when this most recent 'standard of care' blood was taken on the CRF. If there are no blood results between baseline and follow-up, bloods should only be taken if reasonable to do so without causing distress to the participant. This will not be a mandatory blood test. If it is not possible to take bloods, the latest blood results will be used, even if this is baseline bloods. The relationship between the timing of any 'standard of care' bloods used and the overall iscorEB score will be monitored.

8.5.2 Pain and itch

Assessment of pain will occur at all visits except screening (all infusions, and all follow-up visits) during the crossover trial and open-label study. Pain will be assessed using the Faces Pain Scale (Wong *et al*., 1988) for children over 6 years old. There is no validated score for under 6 years of age. Parents/guardians will complete the Visual Analogue Scale (VAS) for children of all ages (Shields *et al.*, 2003). Pain score will be collected at two time points on the above visits, incorporating daily average pain over the past week and worst pain experienced during the past week.

Assessment of itch will also occur at all visits during the crossover trial and open-label study. Itch will be assessed using the Leuven itch scale (Haest et al., 2011) in children aged over 14 years. Children aged 4-13 years will use the Itchy assessment scale (Morris *et al.,* 2012). Itch will not be assessed in children aged under 4.

8.5.3 Wound Assessment

Photography of wounds and body will be taken by the blinded Clinical Fellow with assistance from the research nurse at the hospital at each clinical assessment during the phase 1 and crossover trial.

Photography equipment and services will be provided by the photography vendor, Canfield Scientific, Inc. (Parsippany, NJ) to document body wound involvement at specified time points. All consenting subjects' study photographs will be captured using the equipment, supplies, and guidelines provided by Canfield to have consistent visual representation of the disease during the study treatment.

Images will be captured, viewed, and uploaded using the provided equipment and procedures and will be transferred to the secure, validated and compliant web servers hosted by Canfield. Only individuals approved by the Sponsor have access to the study database on the website.

Images will be pseudonymized per specifications prior to trial use. Detailed instructions for all aspects of the photography procedures will be supplied separately in the investigator user manual to be provided by Canfield, please refer to MissionEB_Photography_SOP. A clinical assessment of the photographed areas will be compared with pre-dose photographs by a central assessment panel of at least 2 blinded independent EB experts. The clinical assessment of the photographed area will be compared using a 5 point scale based on skin appearance at the primary outcome endpoint (3 months after receiving IMP/placebo):

1: a lot worse
2: a bit worse
3: much the same
4: a bit better
5: much better

Each participant will be given a score for the trunk (front and back), arms, and legs. The image will then be subject to a 'global' assessment for overall changes, using the same 5 point scale. Where any discrepancy exists between the assessments of the blinded independent EB experts, a mutually agreed assessment will be reached. During the open label study routine clinical photographs will be taken at 0, 4 ,8 and 12 months using standard NHS photography.

8.5.4 Changes to amount of analgesia and itch medications

Analgesia and itch medication use will be recorded as part of the concomitant medication assessments at each study visit. Additionally, at the month 3 follow-up visit, changes to analgesia and itch medications should be reviewed using the 'Changes to analgesia and itch meds' CRF. At day 0 and month 3 participants will be asked exactly what pain and itch medication they have taken in the last 48 hours. These logs are designed to reflect a snapshot of participant medication use, and to ensure the information collected is accurate as the parent/guardian will be able to recall and list them within this timeframe. Daily or weekly diaries are generally poorly filled in and often leads to missing or inaccurate data. Study clinicians, who are blinded to the treatment allocation, will refer to these logs to compare the amount of medications they are receiving at month 3 with the amount they were receiving before they had their first infusion on day 0. Clinicians will make a judgment whether participants took their medications 'more than usual' 'about the same as usual' or 'less than usual'.

This will be repeated for the second leg of treatment, i.e., comparing month 12 to month 9.

8.5.5 Quality of life

Quality of life assessment will be conducted using the validated CHU-9D (Furber *et al*., 2015) This measure will be collected at infusion 1 and 3 (pre-dose), month 3, 6, 12 and 15 follow-up during the crossover trial, and month 0, 4, 8 and 12 months during the open-label study.

8.6 Procedure for assessing safety

All adverse events will be recorded in the case report form during the participant's involvement in the trial - see Section 12 for definitions and procedures.

All trial participants will be offered to enter a separate long-term follow up trial so that the total duration of follow-up will be 15 years from their last dose of IMP, in accordance with ATMP guidance. The nature of the monitoring will be agreed with the Sponsor following the risk assessment at trial outset. This procedure is detailed in the long term follow up protocol.

Safety bloods

All bloods will be drawn by the Clinical Fellow or experienced phlebotomist at screening, and month 9 of the crossover study, and then month 0, 4, and 8 of the open-label study. Procedures for collection and processing will be outlined in MissionEB Sample collection SOP.

(i) Blood tests for liver, bone and renal function, ferritin, CRP, ESR as well as full blood count will be analysed in local NHS laboratories. The blood tests will be part of routine clinical care and no additional tests are required for the purpose of this study.

(ii) Blood tests for C7 antibodies (safety blood tests) will be collected at the respective clinical sites and transported at room temperature to the NHS Immunodermatology laboratory at St Thomas' hospital, London for analysis.

8.7 Procedures for economic analysis

We do not expect the intervention to lead to any reduction in cost of care over the study period. This is due to the fact the children will stay on their medication, and will continue to have to attend reviews and investigations and will continue with their current skin care. Even if the skin and wounds improve, the way they will be dressed is unlikely to change as often the dressings are used for protection. As such, we will not collect resource use data on current treatments and the cost analysis will focus on the costs associated with the infusion of UC-MSCs.

Health benefits will be measured using the CHU-9D, with QALYs compared over the randomised interval.

Mathematical modelling, including external evidence, will be used to explore the potential longer-term health benefits and costs associated with UC-MSCs (e.g., long-term reductions in costs of bandages and dressings, avoidance of skin cancer). This analysis will be exploratory.

8.8 Procedure for assessing treatment acceptability

Qualitative assessment

We will aim to interview at least 10 patient and parent pairs (approx. 5 from each site) at the 3 month and 12 month visit during the trial to gather their views on the effectiveness of treatment and the impact on their lives. This information will add value to the quantitative data and help commissioners to contextualise the findings. We will involve patients and parents in developing the interview questions and methods used in the interviews. The TMG will be involved with the topic guide development and a research assistant/qualitative researcher will undertake the interviews, this will be overseen by the CTRU who will also undertake the data analysis (see Section 10.2).

Interviews will be conducted with children aged 6 and over, and we will interview parents of all age groups where possible. We will aim to interview the children and parents separately whilst maintaining comfort for the child and parent. Interviews will be face-to-face but we will provide an option of interview over video call or the

telephone for all participants. Remote interviews will be arranged as close as possible to the 3 and 12 month visits.

For more details refer to the MissionEB qualitative protocol.

8.9 Mechanism of action

Mechanistic blood samples

Research bloods (for cytokines) will be collected at the respective clinical sites, stored at -80 degrees Celsius and then transferred on dry ice to King's College London Research Laboratories at Guy's hospital, London. At the end of the study, samples will be transferred to St John's Institute of Dermatology Tissue Bank for storage until a REC application is approved for analysis which will be funded through a future grant application. Research bloods will be taken at all infusions of the crossover study. Research bloods will also be taken at all infusion visits of the open-label study.

8.10 Participant withdrawals

Participants may wish to withdraw from study treatment, or there may be a clinical need to withdraw the participant (see Section 5.8).

Participants may withdraw their consent for the study at any time, without providing a reason for this. The investigator also has the right to withdraw patients from the treatment or the study as appropriate in the event of intercurrent illness, AEs, SAEs, SUSARs, protocol violations, cure, administrative reasons or other reasons. If this occurs, this will be documented on a study completion/ discontinuation form and the patient notes. Although the participant is not required to give a reason for discontinuing their study treatment, a reasonable effort will be made to establish this reason while fully respecting the participants' rights. Any data collected up to the point of the participant's withdrawal will be retained, and used in the final analysis, and this is made clear to the patient at the time of consent. The information sheet also informs participants that data collection for ongoing SAEs and long-term safety data will continue even if they withdraw from further follow up, unless they explicitly state that they do not wish this data to be collected. This data will be collected via a review of the medical records, i.e., a study visit will not be required, and this should be discussed with participants at the point of withdrawal to ensure their wishes are documented and respected.

Excessive participant withdrawal from follow-up has a negative impact on a study. Centres will explain the importance of remaining on study follow-up to participants. Nevertheless, if participants do not wish to remain in the study their decision must be respected. If the participant explicitly states their wish not to contribute further data to the study, this will be recorded.

8.11 Loss to follow-up

Patient's being lost to follow up is highly unlikely due the small patient population receiving treatment and because both sites involved in the study are the only specialist centres for treating children with EB.

8.12 Definition of end of Trial

The end of the trial is defined as last patient last visit (LPLV).

9. Safety Reporting

9.1 Definitions

The definitions of the EU Directive 2001/20/EC Article 2 based on the Principles of ICH-GCP apply to this protocol. These definitions are given in Table 5 below.

Table 5: Definitions of Adverse Events and Reactions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical study patient to whom a medicinal product has been administered irrespective of relationship
Adverse Reaction (AR)	Any AE that is judged, in the opinion of the PI, to be related to an investigational medicinal product or is the result of an interaction between an investigational medicinal product and a non-investigational medicinal product.
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the information about the medicinal product in question set out in the Information Brochure (IB).

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)	Respectively any adverse event, adverse reaction or unexpected adverse reaction that: • Results in death • Is life-threatening* • Requires hospitalisation or prolongation of existing hospitalisation** • Results in persistent or significant disability or incapacity • Congenital anomaly/birth defect • Is another important medical event***

*The term life-threatening in the definition of a serious event refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe, for example, a silent myocardial infarction.

**Hospitalisation is defined as an inpatient admission, regardless of the length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, that has not worsened or for an elective procedure do not constitute an SAE.

***Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event/experience when, based upon appropriate medical judgement, they may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.2 Expected Adverse Drug Reactions

The sponsor may conduct expectedness of serious adverse reaction. If required, the CI may be involved in this decision. In this case, the Chief Investigator or delegate will be responsible for the assessment of expectedness to confirm agreement with the site investigator. An unexpected adverse event is defined as one not defined in the RSI section of the Investigator Brochure (IB), or one that is more frequent or more severe than reported in the IB. The RSI is in Section 5.2 of the IB and will be the current version as approved by the MHRA.

9.3 Expected Serious Adverse Events (Exemption from reporting)

All hospitalizations that are expected to take place as a result of disease progression will not be subject to immediate reporting, including any planned elective surgeries. The following list will be exempt from reporting:

- Skin infection
- Review of a wound
- Dental extractions/ abscess
- Hand surgery
- De-gloving injury
- Occupational therapy review and splints

- Transfusions and iron infusions
- Overnight stay for reviews
- Blood monitoring, routine blood tests
- Corneal abrasions
- Eye Infections
- Gastrointestinal problems
- Dysphagia, oesophageal stricture and dilation
- Gastrostomy insertion, leakage or blockage/ jejunal tube insertion, leaking/ blockage
- Nasogastric tube insertion
- Constipation
- Vertebral or other fractures
- Intravenous bisphosphonates
- Contractures requiring physiotherapy
- Hydrotherapy
- Tonsillitis
- Otitis externa and Otitis media
- Pain assessment for acute or chronic pain

Thus, any hospitalizations that are expected to take place as a result of disease progression (listed above) AND not associated with the use of the IMP will not require immediate reporting but will be recorded as per non-serious 'adverse event' guidelines, unless the use of the IMP results in a prolongation of existing hospitalization. Exceptions include any expected SAE that is graded 4 or above for severity (see Section 9.6.1 for severity grading). Unscheduled and/or emergency hospitalizations not expected due to the natural course of the disease will be reported via the sponsor's normal SAE reporting practice (see Section 9.6).

9.4 Adverse Events of Special Interest

Any incidence of squamous cell carcinoma (SCC) will be reported as per the reporting procedures for SAEs (see Section 9.5).

9.5 Recording and evaluation of adverse events

As the IMP has a relatively unknown safety profile, all adverse events and adverse reactions (i.e., those events that are potentially attributable to the IMP) should be recorded. Investigators must record all AEs occurring for each participant from the time of randomisation until the last visit of the participant in the trial.

All adverse events/reactions should be added to the participant's medical record and recorded on an adverse event form within the case report form (CRF). These should be entered onto the MissionEB database as soon as possible. Investigators must record all AEs occurring for each participant from the time of randomisation until the participant has completed the trial (i.e., final visit of the open-label study).

Out of range lab values will only be recorded as an AE if they are considered clinically significant and require intervention to treat.

The following adverse events will be exempt from recording requirements:

Adverse event as a result of venesection and cannulation include:

i) Mild bruising at site of needle puncture

Adverse event as a result of a shave skin biopsy include:

ii) Mild bruising at the site of the skin biopsy
iii) Cutaneous skin infection requiring oral course of antibiotics
iv) A small scar will result after each skin biopsy, resembling an old chickenpox scar.

9.6 Reporting Procedures for Serious Adverse Events

Investigators must record all SAEs occurring for each participant from the time of randomisation until the last visit of the participant in the trial.

All SAEs (other than those defined in the protocol as not requiring immediate reporting) must be reported on the **Adverse Event** reporting form within 24 hours of the Site Study Team becoming aware of the event. The event will be recorded on the **Adverse Event** reporting form and emailed to CTIMP.safety@gosh.nhs.uk and ctru-saes-group@sheffield.ac.uk or faxed to the Joint R&D office (0207 905 2201) and CTRU (0114 222 0870) within the reporting timelines. Sheffield CTRU will perform an initial check of the report, request any additional information if required. Additional and further requested information (follow-up or corrections to the original case) will be detailed on a new SAE Report Form and faxed/emailed to the CTRU. Further details are outlined in MissionEB AE/SAE reporting SOP.

The SAE form must be completed by the investigator (a clinician named on the delegation log who is responsible for the participant's care). In the absence of the investigator the form will be completed by a member of the study team and emailed as appropriate. The responsible investigator will subsequently check the SAE form, make changes as appropriate, sign and re-send the form to CTRU as soon as possible. The seriousness and causality must be assessed by the principal investigator/delegated medical doctor. Participants must be followed up until clinical recovery is complete and laboratory results have returned to normal or baseline, or until the event has stabilised. Follow up information will be provided on an SAE report marked as such.

All SAEs will be included in each Data Monitoring and Ethics Committee (DMEC) report and an annual safety report will be submitted to the MHRA and the Research ethics committee.

It is anticipated that a treatment-related death would result in a halt to the trial and immediate convening of the DMEC and review of safety data. This will be discussed and agreed with the DMEC at the study outset and documented in the DMEC charter. If the trial is put on halt following a treatment-related death the trial can restart only after approval of a substantial amendment from the competent authorities.

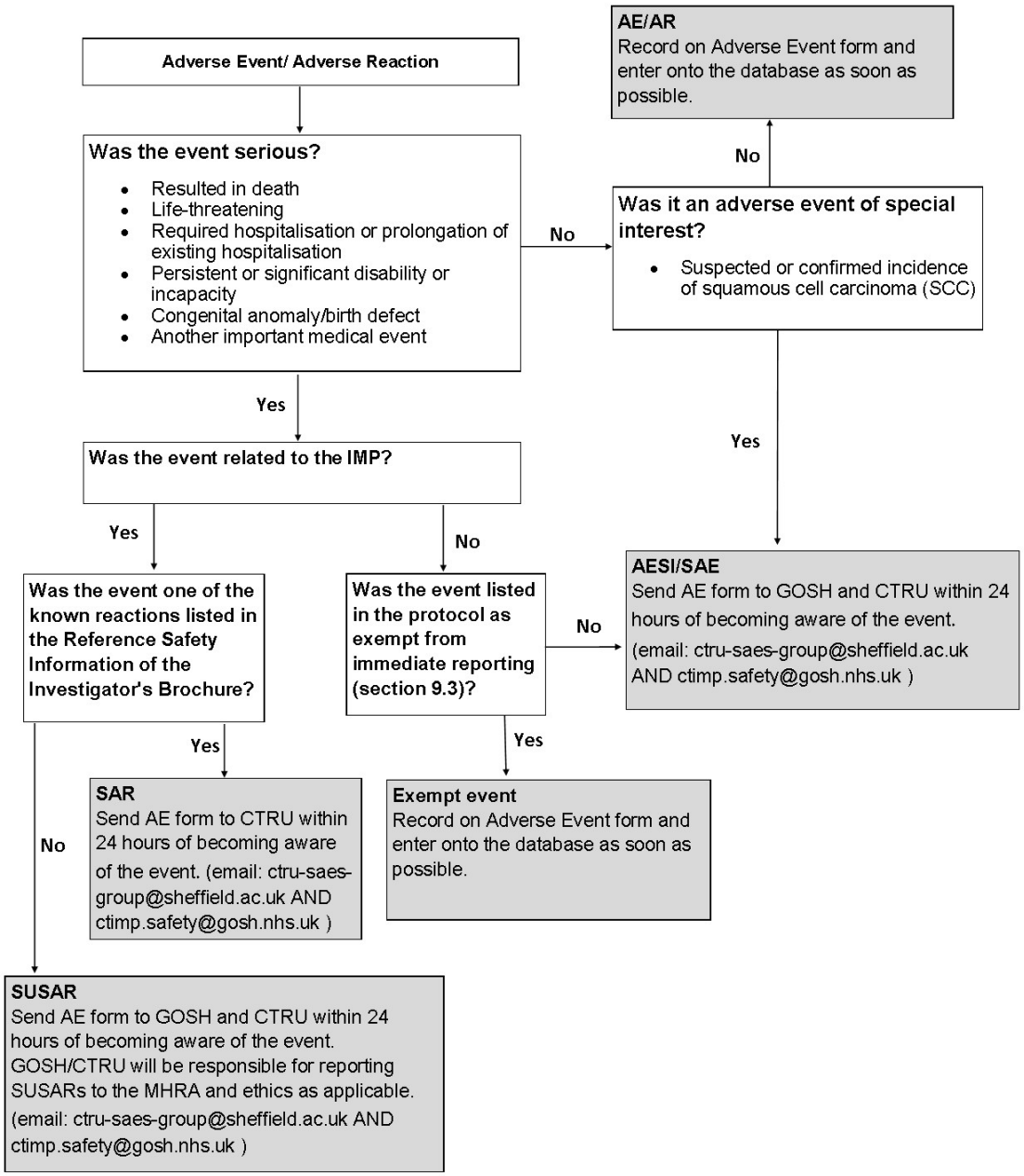

Figure 5: AE/SAE decision tree

9.6.1 Assessment of seriousness and severity

See Table 5 for the definitions and how to assess for a serious event.

The severity of all AEs will be assessed using the Nation Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) criteria version 4.03. According to the NCI-CTCAE, adverse reactions are reported by grade (level of severity) on a scale of 1 to 5. The event is graded as mild (Grade 1), moderate (Grade 2), severe (Grade 3), or life-threatening (Grade 4), or Death (Grade 5).

9.6.2 Assessment of causality

The investigator should make an assessment of relatedness prior to sending the SAE form to the sponsor and CTRU.

Definitely: There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

Probable: A causal relationship is clinically / biologically highly plausible and there is a plausible time sequence between the onset of the AE and administration of the investigational medicinal product and there is a reasonable response on withdrawal.

Possible: A causal relationship is clinically / biologically plausible and there is a plausible time sequence between the onset of the AE and administration of the investigational medicinal product.

Unlikely: A causal relation is improbable and another documented cause of the AE is most plausible.

Unrelated: A causal relationship can be definitely excluded and another documented cause of the AE is most plausible.

Not assessable: There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

9.6.3 Expectedness

Expectedness will be determined according to the Reference Safety Information section in the Investigators' Brochure.

When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected. See Section 9.2 for additional information.

9.7 Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

All suspected adverse reactions related to an investigational medicinal product (the tested IMP and comparators) which occur in the concerned trial, and that are both unexpected and serious (SUSARs) are subject to expedited reporting.

9.7.1 Who should report and whom to report to?

The sponsor should report all the relevant safety information previously described to

the concerned competent authorities and to the Ethics Committee concerned. The CTRU shall inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of subjects.

9.7.2 When to report?

Fatal or life-threatening SUSARs

The MHRA and the Research Ethics Committee should be notified as soon as possible but no later than 7 calendar days after the sponsor has first knowledge of the minimum criteria for expedited reporting.

In each case relevant follow-up information should be sought and a report completed as soon as possible. It should be communicated to the MHRA and the Ethics Committee within an additional eight calendar days.

Non-fatal and non-life threatening SUSARs

All other SUSARs and safety issues must be reported to the competent authority and the Ethics Committee in the concerned Member States as soon as possible but no later than 15 calendar days after the sponsor has first knowledge of the minimum criteria for expedited reporting. Further relevant follow-up information should be given as soon as possible.

Follow-up reports of SUSARs

In case of incomplete information at the time of initial reporting, all the appropriate information for an adequate analysis of causality should be actively sought from the reporter or other available sources. The sponsor should report further relevant information after receipt as follow-up reports.

In certain cases, it may be appropriate to conduct follow-up of the long-term outcome of a particular reaction.

9.8 Reporting of Pregnancies

If a participant becomes pregnant at any time during the study this will be recorded on the Pregnancy Information CRF. Participants will be withdrawn from treatment, but will continue with follow-up visits as per protocol. Pregnancies will be reported to the TMG. The TSC and DMEC will be advised at each meeting if any pregnancies have occurred.

9.9 Development Safety Update Reports

The sponsor or delegate will submit (in addition to the expedited reporting above) DSUR once a year throughout the clinical trial, or on request, to the Competent Authority (MHRA in the UK), Ethics Committee and the Host NHS Trust (if applicable).

10. Statistics

10.1 Sample size

RDEB is a rare condition and the sample size of 36 (for the crossover trial) is based on feasibility including availability of the patients and not formal power considerations. As such, the statistical analysis focuses on estimation rather than hypothesis testing. Table 6 gives the standardised widths for the precision of the trial (for a continuous outcome) as assessed by the half-width of a 95% confidence interval.

Table 6: Standardised widths for the precision of the trial

Completed	Precision
36	0.49
30	0.53
25	0.59

Section 7.1 describes the sample sizes for safety gatekeeping during the internal dose de-escalation phase based on a 4+5 design which is a variant of a 3+3 design with controls to allow seamless transition into the main crossover trial. The open-label follow-on study will depend on available participants following the crossover trial and further treatment is deemed appropriate.

Detailed analyses of all outcomes will be described in a pre-specified Statistical Analysis Plan to be developed and reviewed by the TSC and DMEC. Here, we only summarise the key statistical analysis principles.

10.2 Statistical analysis

10.2.1 Internal dose de-escalation phase

The objective of this phase is to offer safety gatekeeping of the proposed dose based on the assessment of toxicity data that relates to all SUSARs due to study treatment as deemed by the study clinicians. These include, but are not limited to, immediate reactions such as severe allergic reactions, severe hypoxia, and severe shortness of breath, and/or chest pain. These data will be assessed by the DMEC who will recommend whether to continue with the proposed dose, halve the proposed dose to the main crossover trial or stop the trial if the proposed dose if deemed unsafe. This assessment will be completed within 15 days in line with reporting procedures for non-fatal SUSARs. Detailed decision rules are presented in Figure 1. AEs and SAEs will be descriptively reported by treatment group.

10.2.2 Crossover trial

The main trial will be reported according to the CONSORT extension for reporting randomised crossover trials (Dwan *et al.*, 2019). The primary analysis will be based on intention to treat principle that will include participants with outcome data on two periods of the crossover design.
The study is not formally powered and estimation than formal hypothesis testing is the primary aim of the analysis although P values may be provided when frequentist statistical models are fitted.

The primary outcome is the change in disease severity as measured by the change in EBDASI total score (across all five domains) at 3 months from day 0 (Jain *et al.*, 2017). This outcome will be analysed using a linear mixed-effects model that will include treatment, period, and baseline (for each period, if necessary) in the model with a random effect on the participant. The difference in means (mean difference) with 95% confidence intervals giving a range of plausible effects will be estimated using restricted maximum likelihood (REML) methods and Satterthwaite degrees of freedom. To aid interpretation and ability to make probabilistic statements about the distribution of the treatment effect, an equivalent Bayesian linear mixed-effects model will be fitted using non-informative priors on model parameters. This will allow us to estimate the probabilities of the mean difference (treatment effect) being within a certain interval of potential interest to clinicians. For example, the probability of UC-MSCs causing any improvement in disease severity. The analysis of the primary outcome at 3 months and all secondary continuous outcomes will be analysed similarly. In case of missing data, the missing data mechanism will be explored and multiple imputation may be applied as a sensitivity analysis as appropriate (where necessary). Other sensitivity analyses will be performed to evaluate the robustness of the primary analyses. The statistical analysis plan will detail methods including handling of endpoints measured across multiple domains.

There will be no interim analyses during the crossover trial and open-label follow-on study. However, safety data including toxicities will be monitored continuously by the DMEC throughout the trial.

It should be noted that judgements on the efficacy of UC-MSCs will be based on totality of evidence from both primary and secondary clinical outcomes.

10.2.3 Open-label follow-on study

We plan to undertake no formal statistical analyses of the 12-month open-label data. This follow-on phase does not have a control group so no formal comparisons will be made. As a result, the outcomes assessed during the 12-month continued treatment open-label study will be analysed descriptively (e.g., using graphs) based on available data. The objective is to assess whether the efficacy observed in the crossover phase (if any) is maintained over these 12 months.
This open-label follow-on study will thus be interpreted in context with the initial two-period crossover trial. We will fit a regression of treatment effect against time for the follow-on phase. As all patients in this phase will be receiving active treatment, the interpretation will be to a degree qualitative and data-dependent (e.g., the slope may not be linear). Hopefully, the analysis will allow some assessment of the treatment effect over time.

11. Health economics analysis

A health economic analysis will be undertaken in order to assess the additional health impacts and costs associated with UC-MSCs compared with usual care. The analysis will take the form of a cost consequences analysis, with health outcomes focussing on quality-adjusted life years (QALYs) and costs focussing on those associated with UC-MSCs. The analysis will be undertaken from the perspective of the NHS and Personal Social Services (PSS).

Under current care, the main types of resources consumed in EB are bandages and dressings and frequent hospital visits across a wide range of specialities. However, within the follow-up period of the trial, we are not expecting any reduction in either of these areas. We are also conscious that asking caregivers to try to monitor this resource use over the trial period, or to recall it all at the end, would be very burdensome for them. Our expectation is that over the trial period, the only difference in costs between the groups will be the additional costs associated with the stromal cell infusions, additional follow-up and monitoring, and adverse events. For these reasons, we will only consider the additional costs directly associated with UC-MSC infusions. These costs will be estimated using information on the research costs and anticipated proprietary costs of UC-MSCs and the number of doses administered during the treatment phase of the crossover trial, together with any additional care directly associated with the infusions.

It is possible that UC-MSCs could lead to additional health benefits in the longer-term, for example, reductions in the need for bandages and dressings and the avoidance of skin cancer. We will use simple mathematical modelling, informed by estimates of costs avoided from the literature and expert opinion, to explore the potential magnitude of these longer-term benefits and cost-savings. Where appropriate, health outcomes and costs will be discounted at a rate of 3.5% per annum.

Value of information analysis will be conducted to explore areas in which further data collection may reduce decision uncertainty.

12. Qualitative analysis

The TMG will be involved with the topic guide development and undertake the interviews, this will be overseen by the CTRU who will also undertake the data analysis. The framework method which involves identifying initial themes, labelling and sorting the data by theme and then synthesising the findings, is useful in health research in multidisciplinary teams (Gale *et al*, 2013) and will be used by two independent coders for the analysis of the interviews. We will explore the impact of the MSCs on the participants' and families' lives. Input from clinicians, patients and families will inform the key factors to consider in clinical benefits, costs, and impact on quality of life.

13. Trial supervision

13.1 Trial Steering Committee

The TSC will consist of an independent statistician, paediatric dermatologists and a patient representative. The role of the TSC is to provide supervision of the protocol and statistical analysis plan, to provide advice on and monitor progress of the study, to review information from other sources and consider recommendations from the DMEC. The TSC meet at regular intervals, as defined in the TSC terms of reference.

13.2 Data Monitoring and Ethics Committee

This study will use an independent Data Monitoring and Ethics Committee (DMEC). The DMEC will consist of an independent statistician, paediatrician, and dermatologist with experience in clinical trials.

The DMEC will be responsible for on-going monitoring of the efficacy, safety and toxicity data of subjects in the internal phase 1 trial, crossover trial, and open label study, according to the Charter. The recommendations made by the DMEC to alter the conduct of the study will be forwarded to the TSC chair, in writing. The Sponsor will forward such decisions to regulatory authorities, as appropriate.
The DMEC will be independent of the study team and will have no direct involvement in other aspects of the trial. The DMEC will develop its own operation procedures in consultation with the sponsor which will be documented in the DMEC charter.

13.3 Trial Management Group

The TMG consists of the CI, investigators and staff from Sheffield CTRU, GOSH and Birmingham Children's Hospital. The CI will chair regular meetings to discuss the day-to-day running of the study, including any implementation issues.

14. Data handling and record keeping

Participant confidentiality will be respected at all times and the principles of the General Data Protection Regulation (GDPR) will be followed. The investigator will ensure that identifiable data is kept securely and protected from unauthorised parties.

Data management will be provided by the University of Sheffield Clinical Trials Research Unit (CTRU) who adhere to their own Standard Operating Procedures (SOPs) relating to all aspects of data management, including data protection and archiving. A separate data management plan (DMP) will detail data management activities for the study in accordance with SOP (Shef/CTRU/DM009).

The investigator or delegate at each site will maintain comprehensive and accurate source documents to record all relevant study information regarding each participant. The CTRU will provide worksheets (shadow CRFs) to allow the site staff to check what is required for a visit. The worksheets do not need to be completed if alternative source documentation is provided. However, they must be completed for data points where source documentation is not collected elsewhere and where completed, worksheets must accurately reflect the database as they form part of the source data.

If a participant consents to being sent information about the study, such as being informed of the results once the study is complete, their name and email address and/or postal address will be collected. All other CRFs will only identify the participant by their study ID number. All participants will be assigned a unique study ID number at initial approach that will link all of the clinical information collected for them on the study database. It will also be used in all correspondence between CTRU and participating centres.

Study records, including source data, will be stored for 25 years after the completion of the study by participating sites, before being destroyed. Each investigator is responsible for ensuring records are retained and securely archived during the retention period and information supplied to the Chief Investigator and Sponsor. Where trial related information is documented in the medical records, those records will be retained for at least 25 years after completion of the study. Access will be restricted to authorised individuals.

Data held by the CTRU will be stored in accordance with the archiving Standard Operating Procedure (CTRU SOP PM012) for 25 years following completion. Archived documents will be logged on a register which will also record items retrieved, by named individuals, from the archive. Electronic data will be stored in an 'archive' area of the secure CTRU server for a minimum of 25 years to ensure that access is future-proofed against changes in technology. Electronic data may also be stored (e.g., on a compact disc or encrypted USB flash drive) with the paper files.

Laboratory specimens to be preserved or stored will be labelled without the use of patient identifiable information. Labels will contain study ID, type of sample, and the date the sample was taken, and will be cryo-labels to withstand freezing of the sample.

Source Documents

Source documents are original documents, data, and records from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

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

Access to source data/documents

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

14.1 Archiving

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

Essential documents will be retained for a **minimum** of 25 years after completion of the trial. These documents will be retained for longer if required by the applicable regulatory requirements. The IMP for this trial is classed as an ATMP, therefore records related to traceability of the IMP at site along with the patient identifiers will be retained at site for at least 30 years after the expiry date of the product or longer if required by the clinical trial authorisation. This will include the relevant documentation contained in the sponsor and investigator files as well as the trial subjects' medical records.

15. Data access and quality assurance

The study will use the CTRU's in-house data management system (Prospect) for the capture and storage of study specific participant data. Access to Prospect is controlled by usernames and encrypted passwords, and a comprehensive access management feature will be used to ensure that users have access to only the minimum amount of data required to complete tasks relevant to their study role. This feature can also be used to restrict access to personal identifiable data.

The study team at each site will enter data from source documents into the study specific Prospect database when available. After data have been entered, electronic validation rules are applied to the database on a regular basis; discrepancies are tracked and resolved through the Prospect database. All entries and corrections are logged with the person, date and time captured within the electronic audit trail.

Participant confidentiality will be respected at all times. All research data will be anonymised, and will only be identifiable by the participant's study ID number. No patient identifiable data will be transferred from the database to the statistician.

Participating investigators shall agree to allow study-related monitoring, including audits, ethics committee review and regulatory inspections by providing direct access to source data and documents as required. Participants' consent for this will be obtained as part of the consent process.

15.1 Site assessment

Throughout this protocol, the trial 'site' refers to the hospital at which trial-related activities are conducted. Participating sites must be able to comply with:

- Trial treatments, imaging, clinical care, follow up schedules and all requirements of the trial protocol,
- ICH GCP R2,
- Requirements of the UK Policy Framework for Health and Social Care Research,
- The Medicines for Human Use (clinical trials) Act (SI 2004/1031 and all amendments),
- General Data Protection Regulation 2018,
- Advance Therapy Medicinal Product 1394/2007 regulations,
- Human Tissue Act.

All site staff, including research staff, must be appropriately qualified by education, training and experience to perform the trial related duties allocated to them, which must be recorded on the site delegation log. CVs for all staff must be kept up to date, and copies held in the Investigator Site File (ISF), and the Trial Master File (TMF). Staff should also have completed GCP training within the last two years, ensure this is renewed every two years, and copies of the GCP certificate are held within the ISF and TMF.

Before each site is activated, capacity and capability to conduct the trial will be assessed and documented using a site assessment form. The CTRU will arrange a

site initiation with each site, which may be carried out face-to-face or remotely. Site staff will be trained in the day-to-day management of the trial and essential documentation required for the trial will be checked. Once all the required documentation is in order and site staff have been trained, CTRU will formally activate the site to start recruitment. Sites should not open to recruitment until CTRU have provided this confirmation of activation.

15.2 Risk Assessment

A risk assessment has been performed by the Sponsor and CTRU, in accordance with GOSH and Sheffield CTRU Standard Operating Procedures. The study has been categorised as Type C = markedly higher than the risk of standard medical care. The level of risk has been agreed with the Sponsor. The risk assessments detail the risks identified, including those associated with the IMP, and details of how the trial has been designed to mitigate these risks. The dosages of IMP are based on previous clinical evidence (as discussed in Section 3.4) and the trial design includes an internal de-escalation study (see Section 10 for more details). The trial will be monitored by independent committees and the safety data for the initial blinded crossover study will be analysed before commencing the open-label study.

The study is being carried out across two sites - Great Ormond Street Hospital and Birmingham Children's hospital. Both sites are specialist centres for treatment of children with EB. Both sites have the necessary facilities to deliver the IMP and assess the outcomes. Site staff will be trained in trial procedures.

Central and/or on-site monitoring (including Pharmacy) will be undertaken at a level appropriate to the detailed risk assessment, and will be documented in the Site Monitoring Plan (SMP).

15.3 Reporting serious breaches and non-compliances

A "serious breach" is a breach of either: the conditions and principles of GCP in connection with the trial or; the protocol relating to the trial; which is likely to effect to a significant degree –

- the safety or physical or mental integrity of the participants of the trial; or
- the scientific value of the trial.

The sponsor will be notified immediately of any case where the above definition may apply during the trial conduct phase. The sponsor of a clinical trial will notify the Research Ethics Committee (REC) and, for CTIMPs, the MHRA in writing within 7 days of becoming aware of a serious breach.

All serious breaches and protocol non-compliances should be reported to CTRU within 24 hours of site staff becoming aware.

15.4 On-site monitoring

On-site or remote monitoring will be performed according to the monitoring plan and in line with the GOSH SOPs.

Regular site monitoring visits will occur throughout the study as specified in the Site Monitoring Plan and additional visits will be undertaken where required. At these visits, the Monitor will review activity to verify that the:

1. data are authentic, accurate and complete,
2. safety and rights of the patient are being protected and,
3. study is conducted in accordance with the approved protocol and study agreements, GCP and all applicable regulatory requirements.

Accurate and reliable data collection will be assured by verification and cross-check of the eCRF against Investigator's records by the Study Monitor (source document verification) (see Section 13 for further details on data collection). Study Monitor will contact and visit sites regularly to inspect CRFs throughout the study, to verify adherence to the protocol and completeness, consistency and accuracy of the data being entered on the CRFs. Monitoring visits will also include a pharmacy visit to review processes, documentation and accountability of study drug.

A close-out visit will be performed after the last patient last visit at each site. Further close-out activities may be carried out remotely after this time, up to database freeze.

15.5 Central monitoring

CTRU staff will review entered data for possible errors and missing data points. A central review of consent forms will also be completed, and sites will be requested to email consent forms via secure nhs.net emails to the CTRU on an ongoing basis. This will be made clear to the participant prior to their consent to the trial. CTRU will receive pharmacy dispensing logs centrally, which will be taken to on-site monitoring visits to allow full source data verification. Details will be included in the IMP and Pharmacy manual.

15.6 Regulatory information

As a CTIMP, the trial will be conducted in accordance with ICH GCP and the Clinical Trials and Medicine for Human Use (Clinical Trials) Regulations 2004.

16. Publication

Results of the study will be disseminated through peer reviewed scientific journals and at clinical and academic conferences, as well as submission of a final report to the funder, which will be made available online.

Details of the study will also be made available on the Sheffield CTRU website. Summaries of the research will be updated periodically to inform readers of ongoing progress.

The results will be published on a freely accessible database within one year of completion of the trial.

Full details, including guidance on authorship, are documented in the Publication and Dissemination Plan.

17. Finance

MissionEB is funded by NHS England/National Institute for Health Research and full details are included in a separate agreement. Payments for research activity at participating centres including participant travel costs will be detailed in the site agreements.

18. Ethics approval

Before initiation of the study at participating sites, the protocol, informed consent forms, and information materials to be given to the participants will be submitted to an NHS Research Ethics Committee for approval. Any further amendments will be submitted and approved by the ethics committee.

In addition, the study will be submitted for HRA review and approval. Recruitment of study participants will not commence until the letter of approval has been received from the HRA.

The study will be submitted to local participating Trusts to confirm Capacity and Capability before any research activity takes place.

19. Regulatory Compliance

To demonstrate that the trial will comply with regulations, the trial will also not commence until a Clinical Trial Authorisation (CTA) is obtained from the MHRA and Favourable REC opinion. The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.

20. Sponsor and site approval

Before initiation of the study at participating sites, the protocol, informed consent forms, and information materials to be given to the participants will require sponsor approval.

A site agreement between the Sponsor, participating sites and Sheffield CTRU outlines responsibilities of all parties and is to be signed prior to commencement of recruitment at sites.

Recruitment of study participants will not commence at a site until a letter of local R&D Confirmation of Capacity and capability (CCC) or equivalent has been issued.

21. Trial Organisation and Responsibilities

21.1 Principal Investigators

Each site will have a local Principal Investigator (PI) who will be delegated responsibility for the conduct of research at their centre and must sign a declaration to acknowledge these responsibilities. The local PI should ensure that all relevant staff involved are well informed about the trial and trained in study procedures, including obtaining informed consent and conduct of the trial according to GCP. The local PI will liaise with the Trial Manager on logistic and administrative matters connected with the trial.

21.2 Sheffield Clinical Trials Research Unit (CTRU)

The Sheffield CTRU at Sheffield University will provide set-up and monitoring of the trial conduct to CTRU SOPs and the GCP conditions and principles as detailed in the UK Policy Framework for Health and Social Care Research 2017. CTRU responsibilities include randomisation design and service, database development and provision, protocol development, CRF design, trial design, source data verification, monitoring schedule and statistical analysis for the trial. In addition, the CTRU will support the main REC, HRA and site-specific submissions, clinical set-up, on-going management including training, monitoring reports and promotion of the trial.

The CTRU trial manager will be responsible for supplying investigator site files to each collaborating centre after relevant ethics committee approval and local R&D Confirmation of Capacity and Capability approval has been obtained. The CTRU will be responsible for the day-to-day running of the trial including trial administration, database administrative functions, data management, safety reporting and all statistical analyses. The CTRU and GOSH will develop the site monitoring plan and data management plan and will assist the CI to resolve any local problems that may be encountered during the trial including any issues of non-compliance.

22. Patient & Public Involvement

A stakeholder meeting was held on 9th October 2018 with representatives from the two UK patient advocacy groups (DebRA UK and Cure EB) to discuss the study design. Also, two parents of children with RDEB that have previously received the cells were shown the study timeline with proposed interventions, the inclusion of placebo and the number of MSCs infusions.

The parents stressed the need for high quality photographs to capture changes to skin redness which was commented on by the parents but not adequately captured during the EBSTEM trial. The parents also requested the frequency of photographs is increased and we added additional photographs prior to each infusion. Attendees agreed the inclusion of a placebo arm was justified; however, there would be concerns if there a greater length of time in between children being crossed over between the trial treatments.

Another important point raised from that meeting was the need for the MSCs, if effective, to be available after the trial completion. They also asked if it would be possible to give the MSCs on compassionate grounds to children over the age of 16.

GOSH held a meeting with 3 families of children with RDEB on 21st November 2019. We discussed the amended study design, study timelines, source of cells, the use of placebo, frequency of visits, outcomes and interventions. Families expressed their frustration about the delay in the decision about the study and the start date proposed for infusions being in January 2021. They also commented on the use of placebo and how difficult it was for them to accept their children receiving an inactive product, but they also acknowledged the need to include placebo in a blinded manner. We also explained and discussed the introduction of a phase 1, safety cohort and they understood the value of that for safety reasons. They were happy with the rest of the study design and frequency of visits and outcomes.

The updated design was also discussed with two children aged 14 and 16 and their parents attending clinics in at BCH in November, and both patients and parents were keen to take part in the trial.

The PPI panel at GOSH meets regularly and we will attend their meetings annually for the duration of the study to update them on the project, request their input to the study and recruitment plans, and to gain their insight into any issues with the project. They were consulted during the development of the participant information leaflets and will be involved in the trial results dissemination.

23. Indemnity / Compensation / Insurance

The University of Sheffield has in place clinical trials insurance against liabilities for which it may be legally liable, and this cover includes any such liabilities arising out of this clinical study.

Standard NHS indemnity operates in respect of the clinical treatment which is provided. Additionally, GOSH has clinical trial insurance for conduct of this study.

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