FERN: Intervention or Expectant Management for Early Onset Selective Fetal Growth Restriction in Monochorionic Twin Pregnancy

Version 2.0, 29-Jul-2022

SPONSOR:	**The University of Liverpool**
SPONSOR REFERENCE:	**UoL001539**
FUNDER:	**National Institute for Health Research (NIHR) Health Technology Assessment (HTA)**
FUNDER REFERENCE:	**NIHR128596**
RESEARCH ETHICS COMMITTEE:	**South West – Cornwall & Plymouth**
REC REFERENCE:	**20/SW/0156**

Protocol Approval

I, the undersigned, hereby approve this clinical study protocol.

Signature: **Date:** 10/02/2021

Professor Asma Khalil
Chief Investigator
Department of Women's and Children's Health
The University of Liverpool (Honorary)
Department of Fetal Medicine, University of London
St Georges University Hospital NHS Foundation Trust (Substantive)

Signature: **Date:**

Karen Wilding
Senior Clinical Research Governance Manager
The University of Liverpool, Clinical Directorate, Faculty of Health and Life Sciences
Sponsor

General Information

This document describes the FERN study and provides information about procedures for entering patients into it. The protocol should not be used as an aide-memoir or guide for the treatment of other patients. Every care has been taken in its drafting, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the study, but centres entering patients for the first time are advised to contact the coordinating centre Harris Wellbeing of Women Research Centre to confirm they have the most up to date version.

Clinical Queries

Clinical queries should be directed to Professor Asma Khalil who will direct the query to the appropriate person.

Statement of Compliance

This study is designed to comply with the guideline developed by the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and will be conducted in compliance with the protocol, Sponsor Standard Operating Procedures (SOP).

UK Registration

This study will have Health Research Authority (HRA) Approval. All research sites will confirm capacity and capability to conduct the study and will sign a Research Site Agreement (RSA).

Funder

This study is funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) funding body as part of call 18/107, with an associated study reference of NIHR-HTA-128596.

Sponsor	**Chief Investigator**
Karen Wilding	Professor Asma Khalil
The University of Liverpool Clinical Directorate Faculty of Health and Life Sciences Brownlow Hill Liverpool L69 3BX	Department of Fetal Medicine University of London St Georges University Hospital NHS Foundation Trust Blackshaw Road Tooting London SW17 0QT
Tel: 0151 794 8373 / 07717 863747	Tel: 07917400164
Email: sponsor@liverpool.ac.uk	Email: akhalil@sgul.ac.uk

Research Management	**Co-Applicant / Statistics**
FERN Study Management Team	Dr Richard Jackson
Harris Wellbeing of Women Research Centre Department of Women's and Children's Health The University of Liverpool Liverpool Women's NHS Foundation Trust Crown Street Liverpool L8 7SS	Liverpool Clinical Trials Centre University of Liverpool 1st Floor, Block C Waterhouse Building Brownlow Street Liverpool L69 3GL
Tel: 0151-795 9562 / 9565	Tel: 0151 795 5288
Email: fern1@liverpool.ac.uk	Email: R.J.Jackson@liverpool.ac.uk

Co-Applicant / Qualitative Lead	**Co-Applicant / Health Economics**
Dr Kerry Woolfall	Dr Andy Healey
University of Liverpool Department of Public Health, Policy and Systems 1st Floor, Block B Waterhouse Building 3 Brownlow Street Liverpool L69 3GL	Department of Health Service & Population Research Kings College London Strand London WC2R 2LS
Tel: 0151 794 4634	Tel: 0207 836 5454
Email: K.Woolfall@liverpool.ac.uk	Email: andy.healey@kcl.ac.uk

Co-Applicant	**Co-Applicant**
Dr Andrew Sharp	Professor Zarko Alfirevic
Harris Wellbeing of Women Research Centre Department of Women's and Children's Health The University of Liverpool Liverpool Women's NHS Foundation Trust Crown Street Liverpool L8 7SS	Harris Wellbeing of Women Research Centre Department of Women's and Children's Health The University of Liverpool Liverpool Women's NHS Foundation Trust Crown Street Liverpool L8 7SS
Tel: 0151 795 9560	Tel: 0151 795 9550
Email: asharp@liverpool.ac.uk	Email: zarko@liverpool.ac.uk

Co-Applicant	**Co-Applicant**
Professor Jane Sandall	Dr Christine Cornforth
Department of Women's and Children's Health Kings College London Strand London WC2R 2LS	Harris Wellbeing of Women Research Centre Department of Women's and Children's Health The University of Liverpool Liverpool Women's NHS Foundation Trust Crown Street Liverpool L8 7SS
Tel: 0207 836 5454	Tel: 0151 795 7330
Email: jane.sandall@kcl.ac.uk	Email: C.Cornforth@liverpool.ac.uk

Co-Applicant	**Co-Applicant**
Professor Mark Turner	Professor Baskaran Thilaganathan
Harris Wellbeing of Women Research Centre Department of Women's and Children's Health The University of Liverpool Liverpool Women's NHS Foundation Trust Crown Street Liverpool L8 7SS	Department of Fetal Medicine University of London St Georges University Hospital NHS Foundation Trust Blackshaw Road Tooting London SW17 0QT
Tel: 0151 795 9558	Tel: 0208 725 0071
Email: mark.turner@liverpool.ac.uk	Email: baskaran.thilaganathan@stgeorges.nhs.uk

Co-Applicant	**Co-Applicant**
Professor Richard Ashcroft	Dr Brigitte Vollmer
City Law School City, University of London Northampton Square London EC1V 0HB	Faculty of Medicine University of Southampton University Road Southampton SO17 1BJ
Tel: 0207 040 3038	Tel: 0238 120 6678
Email: richard.ashcroft@city.ac.uk	Email: B.Vollmer@soton.ac.uk

Co-Applicant	**Co-Applicant**
Professor Shakila Thangaratinam	Professor Jamie Kirkham
WHO Collaborating Centre for Women's Health Institute of Translational Medicine University of Birmingham Heritage Building Mindelsohn Way Birmingham B15 2TH	Centre for Biostatistics University of Manchester Jean McFarlane Building Oxford Road Manchester M13 9PL
Tel: 07887775891	Tel: 0161 275 1135
Email: s.thangaratinam.1@bham.ac.uk	Email: jamie.kirkham@manchester.ac.uk

Co-Applicant / PPIE	**Co-Applicant / PPIE**
Mrs Jessica Mendoza	Mrs Michelle Watson
PPI representative based in England	PPI representative based in England
Tel: TBC	Tel: TBC
Email: jjacksonwinter@yahoo.co.uk	Email: michelleklwatson@gmail.com

Co-Applicant / PPIE	**Co-Applicant / PPIE**
Mr Joel Marsden	TBC
PPI representative based in England	Twins Trust (formerly Twins and Multiple Births Association (TAMBA)) The Manor House Manor Park Aldershot GU12 4NH
Tel: TBC	Tel: 0125 233 2344
Email: joelmarsden@gmail.com	Email: natashafenwick@twinstrust.org

Lead NHS Site (R&D Contact)
Ms Louise Hardman
R&D Department Liverpool Women's NHS Foundation Trust Crown Street Liverpool L8 7SS
Tel: 0151 702 4241
Email: louise.hardman@lwh.nhs.uk

GLOSSARY OF ABBREVIATIONS

AE	*Adverse Event*
BCC	*Bipolar Cord Coagulation*
CI	*Chief Investigator*
CRN	*Clinical Research Network*
eCRF	*Electronic Case Report Form*
CSG	*Clinical Study Group*
DPA	*Data Protection Act*
EDF	*End-diastolic Flow*
EFW	*Estimated Fetal Weight*
EU	*European Union*
GCP	*Good Clinical Practice*
GDPR	*General Data Protection Regulation*
HCA	*Hierarchical Cluster Analysis*
HRA	*Health Research Authority*
HTA	*Health Technology Assessment*
ICH	*International Conference on Harmonisation*
ICF	*Informed Consent Form*
ICO	*Information Commissioners Office*
IQR	*Inter Quartile Range*
ISF	*Investigator Site File*
ITT	*Intention to Treat*

IUD	*Intrauterine Demise*
LCTC	*Liverpool Clinical Trials Centre*
MC	*Monochorionic*
NHS	*National Health Service*
NIHR	*National Institute for Health Research*
PCA	*Principal Components Analysis*
PDR	*Performance Development Review*
PI	*Principal Investigator*
PIS	*Participant Information Sheet*
PPIE	*Patient and Public Involvement and Engagement*
RCOG	*Royal College of Obstetricians and Gynaecologists*
RCT	*Randomised Controlled Trial*
REC	*National Research Ethics Committee*
RFA	*Radiofrequency Ablation*
RSA	*Research Site Agreement*
SAE	*Serious Adverse Event*
SAP	*Statistical Analysis Plan*
sFGR	*Selective Fetal Growth Restriction*
SIV	*Site Initiation Visit*
SMF	*Study Management Folder*
SMG	*Study Management Group*
SOP	*Standard Operating Procedure*

TTTS	*Twin to Twin Transfusion Syndrome*
UK	*United Kingdom*
UoL	*University of Liverpool*
UA	*Umbilical Artery*
WP	*Work Package*

KEYWORDS

sFGR (selective fetal growth restriction), monochorionic (MC), twin pregnancy

PROTOCOL SUMMARY

This protocol describes the FERN Study and provides information about procedures for entering participants. Every care has been taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the Study. Problems relating to this Study should be referred, in the first instance, to the Chief Investigator (CI), Professor Asma Khalil.

This study will adhere to the principles outlined in the UK Policy Framework for Health and Social Care Research (v3.2 10th October 2017). It will be conducted in compliance with the protocol, the General Data Protection Regulation (GDPR) 2016/679 and Data Protection Act (DPA) 2018, and other regulatory requirements as appropriate.

Title: FERN: Intervention or Expectant Management for Early Onset Selective Fetal Growth Restriction in Monochorionic Twin Pregnancy

Design: Feasibility, Cohort, Mixed methods study of 3 work packages

Aim: To assess the feasibility of conducting a randomised controlled trial (RCT) of active intervention versus expectant management in monochorionic (MC) twin pregnancies with early-onset (prior to 24 weeks) selective fetal growth Restriction (sFGR)

Objectives: To develop 3 work packages (WP) to address the aims of the study:

WP1 - Collect prospective data on the management and clinical outcomes of MC pregnancies complicated by sFGR;

WP2 - Perform a qualitative study involving interviews and focus groups with parents and clinicians to explore trial design, acceptability, feasibility and decision making related to intervention or conservative management; and

WP3 - Utilise information provided in WP1 and WP2 to develop a consensus on a future definitive study.

Outcomes: To recommend whether an RCT of intervention versus expectant management of sFGR in MC twin pregnancy is feasible by exploring women's preference, clinician's preference, current practice and equipoise and numbers of cases.

Inclusion Criteria:

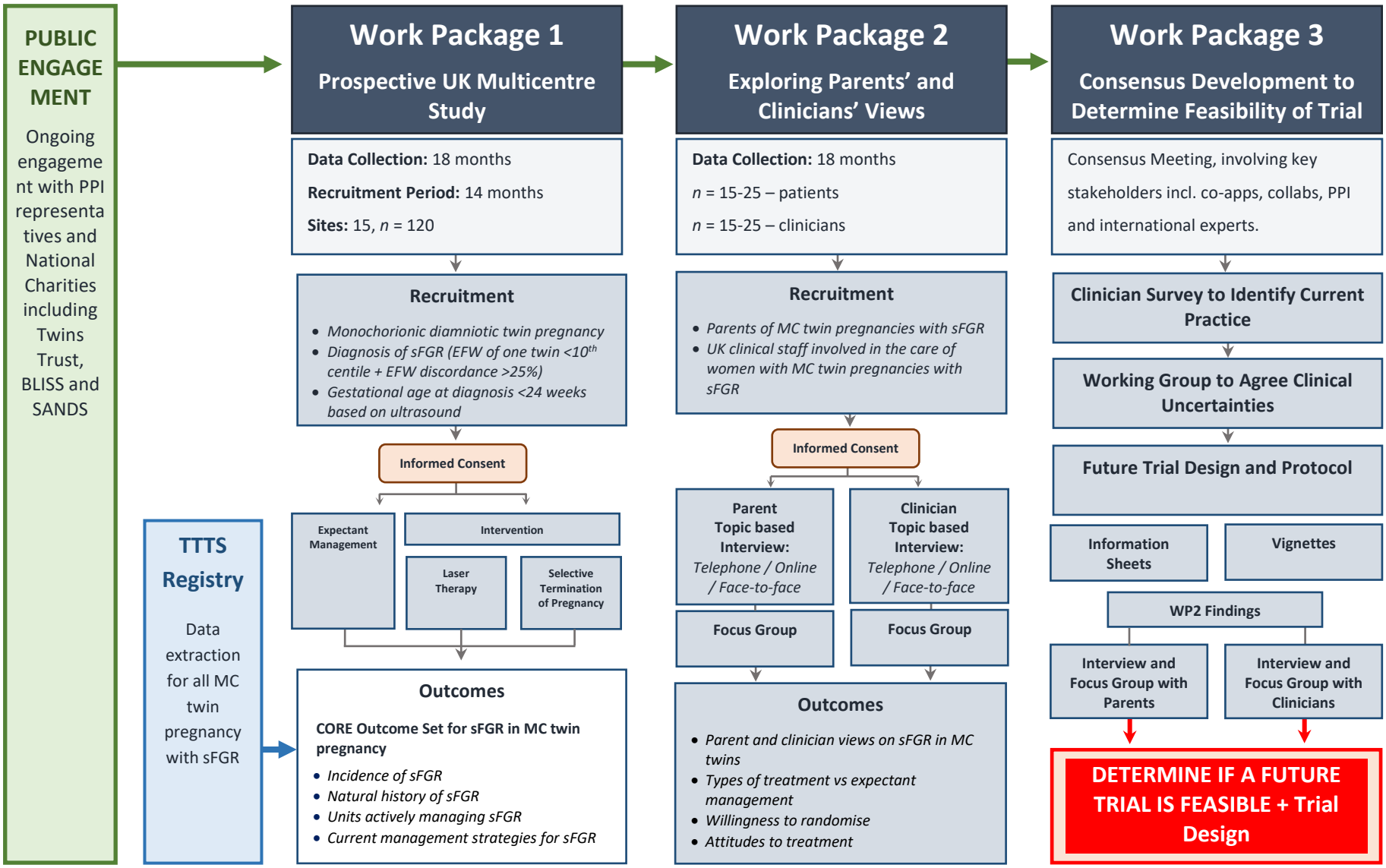
- Monochorionic diamniotic twin pregnancy
- Diagnosis of sFGR (estimated fetal weight (EFW) of one twin <10^{th} centile + EFW discordance >25%)
- Gestational age at diagnosis between 16^{+0} - 23^{+6} weeks based on ultrasound
- Informed consent given by the participant and consent form completed and signed

Exclusion Criteria:

- Singleton pregnancies
- Maternal age under 18 years
- Other MC complications; twin to twin transfusion syndrome (TTTS), twin anaemia polycythaemia sequence (before enrolment), other rare complicated MC twin pregnancies, such as twin reversed arterial perfusion syndrome
- Known karyotype abnormality at enrolment
- Known major fetal structural abnormality at enrolment, defined as a lethal, incurable or curable severe abnormality with a high risk of residual handicap
- Indication for immediate delivery
- Pre-term pre-labour rupture of membranes before enrolment
- Women who lack the capacity to give informed consent
- Any medical or psychiatric condition which compromises the woman's ability to participate

DURATION: 27 months (6 months set-up, 18 months recruitment / data collection, 3 months data analysis, report writing, recommendations)

Figure 1: FERN Study Flowchart



Contents

List of Figures

1. INTRODUCTION

1.1 Research Question

Is it feasible to conduct a randomised controlled trial (RCT) of active intervention versus expectant management in monochorionic (MC) twin pregnancies with early-onset (prior to 24 weeks) selective fetal growth restriction (sFGR)?

1.2 Overview

sFGR in MC twin pregnancy is associated with stillbirth and neurological disability and poses the unique issue of co-twin demise (40%) or co-twin neurological handicap (30%). Early delivery to prevent death of the sFGR twin may expose the larger twin to prematurity, which will increase the risk of lifelong physical, emotional and financial cost from neurodisability, such as cerebral palsy.

There are 3 main management options for sFGR: (1) Expectant management: carries a risk of intrauterine demise (IUD) of the sFGR twin. (2) Selective termination of the sFGR twin. (3) Selective placental laser photocoagulation of connecting vessels: could be technically challenging and in some cases may worsen outcomes for the sFGR twin.

Our recent survey of 29 UK fetal medicine clinicians from 13 units demonstrates equipoise and highlights the need for high quality evidence to guide the management of sFGR in MC pregnancies. However, there are many challenges for a potential RCT, including the small number of eligible pregnancies, uncertainty whether the pregnant women will agree to participate in such a trial and whether they will agree to be randomised to expectant management or active fetal intervention.

1.3 Background

The UK has approximately 11,000 twin pregnancies per year, representing 2% of all births. Twin pregnancy is associated with an increased risk of adverse fetal and neonatal outcome, such as stillbirth (x2.5), neonatal death (x5) and cerebral palsy (x7). 25-30% of twin pregnancies are MC, where both fetuses originate from the same conception. This poses unique difficulties for management because of complications from a shared placenta with communication between the fetal circulations leading to two important pathologies: twin to twin transfusion syndrome (TTTS) or sFGR.

sFGR, when one fetus grows normally whilst the other is growth restricted, affects approximately 300-500 (10-15%) MC twin pregnancies annually. Early-onset sFGR, occurring before 24 weeks' gestation, is less common but may pose greater risk to the fetus and poses substantial management difficulties

due to the distance from viability. sFGR in MC twin pregnancy is classified into 3 subtypes based on umbilical artery (UA) Doppler (Figure 1): Type I (positive end-diastolic flow (EDF)) has the best outcome, Type II (absent / reversed flow) the worst prognosis, Type III (variable absent / reversed flow) has an unpredictable course [1-5].

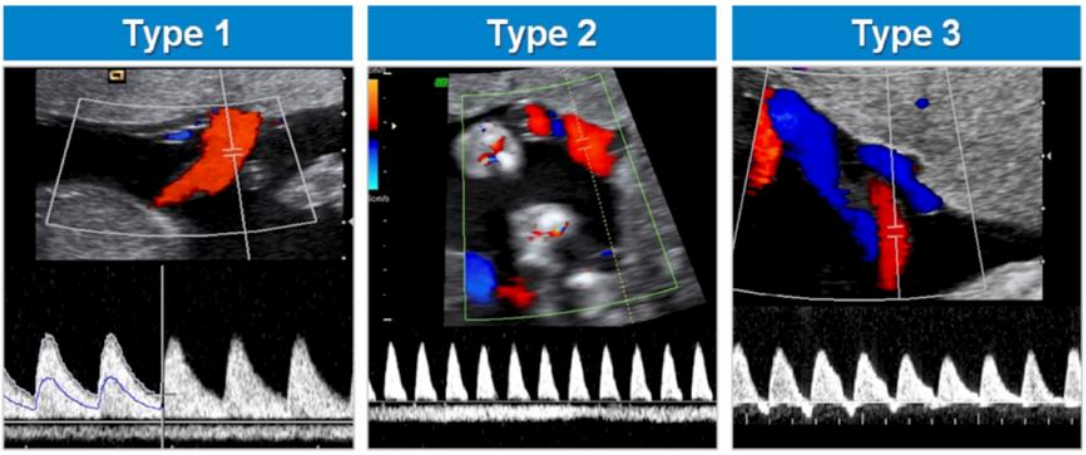


Figure 1. Classification of selective fetal growth restriction in monochorionic twin pregnancy. In Type I, the umbilical artery Doppler waveform has positive end-diastolic flow, while in Type II there is absent or reversed end-diastolic flow (AREDF). In Type III there is a cyclical/intermittent pattern of AREDF.

Figure 2: Classification of sFGR (Gratacos et al.)

There are 3 main management options for sFGR:

(1) Expectant: close monitoring but no active intervention. This carries a risk of IUD of the sFGR twin. Death of one twin may result in co-twin demise (40%) or neurological handicap (30%), thought to be secondary to transfusion from the larger twin into the dead twin through placental vascular communications [1-5];

(2) Selective termination by bipolar cord coagulation (BCC), radiofrequency ablation (RFA) or selective laser photocoagulation of the sFGR twin. This may protect the larger baby from harm if the sFGR twin were to subsequently die [1-5]. However, termination may not be acceptable to some parents; and

(3) Selective placental laser photocoagulation of connecting vessels. This is complex and may worsen outcomes for the sFGR twin [1-5].

We conducted a survey of 29 UK fetal medicine clinicians from 13 units to establish their current practice for the management of sFGR MC twin pregnancies. More than half (57%) define sFGR as estimated fetal weight (EFW) of one twin less than the 10th centile with EFW discordance of 25% or

more, while 36% use a threshold of 20% (rather than 25%). A minority (11%) use EFW less than the 10th centile regardless of the inter-twin discordance. When asked about management options for early-onset (less than 24 weeks) sFGR, most (93%) pursued expectant management. Other options included Laser photocoagulation of the placental communicating blood vessels (57%), selective reduction of the smaller twin (71%) and termination of the entire pregnancy (50%). When asked about management according to the pattern of the UA Doppler, the responses varied, most likely taking into account the expected prognosis. The presence or absence of UA end-diastolic flow (EDF) in the affected twin at the time of diagnosis forms the basis of the Gratacos classification system (Figure 1). The majority (82%) of UK fetal medicine specialists surveyed do not consider active fetal intervention in type 1 sFGR; however, 43% would be willing to participate in a trial of expectant management versus active fetal intervention. Around half (57%) deliver these pregnancies at 34-36 weeks' gestation, while 32% deliver at 32-33 weeks. More than one third (36%) routinely offer active fetal intervention for type 2 sFGR, while a further 43% would offer it only to selected cases. The majority (71%) would be willing to participate in a trial of expectant management versus active fetal intervention, reflecting clinicians' need for more evidence to guide management. Half of these pregnancies deliver at 32-33 weeks' gestation, 29% at 30-31 weeks and 18% at 28-29 weeks. Comparable figures were reported in type 3 sFGR, with more than a third (36%) routinely offering active fetal intervention. The majority (75%) would be willing to participate in a trial of expectant management versus active fetal intervention. More than half (57%) deliver these pregnancies at 32-33 weeks, 32% at 30-31 weeks, and 14% before 29 weeks.

Our survey revealed significant variation in the management of the 3 different types of sFGR and established that there is equipoise potentially suitable for an RCT [5]. Great uncertainty also remains over what interventions, if any, women would be willing to accept at different gestations [5]. The current paucity of qualitative and patient experience information may hamper a subsequent clinical trial [5].

sFGR is associated with stillbirth and neurological disability [1-4] and poses the unique risk of co-twin demise. Early delivery to prevent death of the sFGR twin may expose the larger twin to the consequences of prematurity. The loss of a fetus is associated with long-term psychological effects for the parents [6]. Furthermore, the lifelong cost of prematurity-associated neurodisability, such as cerebral palsy, may be substantial [7-9].

Research is required to determine the optimal management (expectant or intervention) for sFGR in MC twin pregnancies and the most appropriate timing of delivery. Each management option carries risks and benefits in terms of the key outcomes of stillbirth and cerebral palsy; what is currently unknown is the relative risk-benefit ratio for each option.

At present, we do not have an effective system to collate the outcomes from sFGR in MC twin pregnancies. This study will aim to address this and determine the potential risks and benefits associated with each management option, and define the optimal design for a future definitive RCT.

Definitions of sFGR in MC twin pregnancy vary but current UK guidelines define sFGR as an inter-twin EFW discordance of >20% after 20 weeks [10]. However, a recent international consensus group (led by the CI) established diagnostic criteria of the smaller twin being <10th centile and an inter-twin discordance of >25% (Figure 2) [11].

Any MC twin pregnancy with the solitary parameter	MC twin pregnancy with at least two contributory parameters
Estimated fetal weight in one twin below the 3rd centile	Estimated fetal weight of one twin <10th centile
	Abdominal circumference of one twin <10th centile
	Estimated fetal weight discordance >25%
	Umbilical artery pulsatility index of the smaller twin >95th centile

Figure 2. Consensus diagnostic criteria for selective fetal growth restriction in monochorionic (MC) twin pregnancies. (Khalil 2018)

Figure 3: Consensus Diagnostic Criteria for sFGR in MC Twin Pregnancies.

No RCTs or Cochrane reviews have investigated sFGR. Until recently, published systematic reviews assessed mortality [2] and morbidity, especially cerebral injury [12], but did not compare outcomes based on management. We have recently published a meta-analysis of the perinatal mortality and morbidity in sFGR according to management [1] which demonstrated significant bias in the published literature. Studies were retrospective and non-randomised, with significant heterogeneity in their populations, management and outcomes [13]. This meta-analysis was therefore unable to explore the association between gestational age at delivery and neonatal outcomes. This is fundamental as gestational age at delivery is the main determinant of perinatal outcome in twins. [14]

Primary research has not identified a significant difference between RFA and BCC for selective fetal reduction for sFGR in MC twin pregnancy [15,16].

In summary, to quote the Royal College of Obstetricians and Gynaecologists (RCOG) [10], 'Due to a lack of available high quality evidence, there is no clear guidance on how to manage sFGR in such pregnancies.

1.4 Aims and Objectives

Research question: Is it feasible to conduct an RCT of active intervention versus expectant management in MC twin pregnancies with early-onset (prior to 24 weeks) sFGR?

There are currently several uncertainties in sFGR management:

1) Clinicians' preference: in preparation for this study, we organised a Delphi consensus group of international experts to develop diagnostic criteria for sFGR (Figure 2) [11];

2) Women's preference: a major focus of our study will be to identify barriers to an RCT by establishing what would influence women's and clinicians' willingness to participate;

3) The natural history of sFGR: the limited literature on the relative benefits of intervention over expectant management is very biased, as demonstrated in our recent systematic review [1]; and

4) The ethical dilemmas related to the management options of sFGR in MC twin pregnancy.

The FERN study has three central Work Packages (WP) to address these uncertainties. As part of these WPs we aim to determine:

Work Package 1 (WP1), A Prospective UK Multicentre Study - The number of cases of sFGR and the management strategies currently offered, highlighting any equipoise in practice and outcomes.

Work Package 2 (WP2), Exploring Parents' and Clinicians' Views - Whether women with sFGR and the clinicians managing them would consider a trial acceptable and feasible and explore views and decision making on randomisation to different management options which may be offered in an RCT.

Work Package 3 (WP3), **Consensus Development to Determine Feasibility for a Trial** - The design of a future RCT on management of sFGR in MC twin pregnancy: power calculation, economic feasibility, identifying the research cohort (involving subtypes, gestation, intervention and control arms) and key outcomes.

1.5 Potential Risks and Benefits

The potential risks and benefits of involvement are detailed below.

1.5.1 Potential Risks

As this is a short, non-interventional study the potential risks of participation are minimal. Following on from the initial study related risk assessment it has been identified that the main potential risk of participation is the mismanagement of study related data. To mitigate any potential risks a detailed Data Management Plan will be put in place to ensure that all study related data is managed in accordance with regulatory procedures. Furthermore, all central and site clinical research staff will have up to date GCP training in addition to study specific training for all study related procedures.

1.5.2 Potential Benefits

This study will have no direct benefit for the women participating within it other than to allow greater scrutiny of their care and it may increase accessibility to all currently available management options than may have previously been perceived. There may be some emotional and supportive benefits for women and their partners from being involved in the qualitative component of the study and these will be recognised in the participant information available. Long-term benefits of the study will be greater recognition of the outcomes for sFGR in MC twin pregnancies managed in a variety of ways. This will benefit women for counselling as to which management option to pursue and may provide evidence for appropriate powering of a future study to investigate management options.

2. STUDY DESIGN

This study has three distinct WPs to determine the overall research objectives. WPs 1 and 2 involve direct contact with patients and clinicians and therefore will be presented here in line with the standard clinical research management procedures. WP3 is set out in Section 6.2.3 of this protocol. Furthermore, as WP3 will continue to be developed over the course of the initial study period, further details will be set out in a separate management plan.

2.1 Work Package 1 - A Prospective UK Multicentre Study

For WP1, we will conduct a prospective UK multicentre study to determine the incidence, natural history and outcomes for sFGR in MC twin pregnancies according to whether they had expectant management or intervention. MC twin pregnancies complicated by sFGR have high rates of fetal

mortality and morbidity; we have designed a study that will provide vital up-to-date outcome data on untreated pregnancies with which to form a benchmark for comparisons of outcomes in a future RCT.

Some of these pregnancies are complicated by single or double IUD, and detailed data on their management are required to correlate with the relevant outcomes. We also need data on the EFW recorded using prenatal ultrasound. Unfortunately, this level of detail is not usually available in national datasets.

We will approach all women with sFGR as defined by our international consensus [11]. There will be an 18-month data collection period (14 months active recruitment) from 15 UK sites. Our recent survey suggests that we should be able recruit 2 women per month per centre; if we assume a conservative 40% recruitment rate, we will recruit over 120 women in the study period.

The data will provide the following key outcomes:

1) Proportion of women who opt for expectant management, active fetal intervention or termination of the entire pregnancy. We will have reasonable unbiased precision of these estimates from routine practice, which is critical for any future RCT;
2) We will learn about management of these pregnancies, i.e. frequency of monitoring, timing of delivery, thresholds for intervention, etc; and
3) Incidence of adverse outcomes however, some subgroups may be small so the precision of some estimates might be inaccurate with wide 95% confidence intervals. We will use the data from the UK twin registry to ascertain the accuracy of these estimates.

This study will assess the feasibility of recruiting women with a MC twin pregnancy complicated by sFGR to collect detailed information about pregnancy management and outcome. No formal power calculation or primary outcome data has been determined. Success of the study will instead be determined on the acceptability of the study for women and clinicians. This will be determined by an ability to recruit and retain participants within the study.

2.2 Work Package 2 – Exploring Patients' and Clinicians' Views

WP2 will involve a qualitative element, including interviews and a focus group with women and their partners (if applicable), as well as with clinicians involved in the management of MC twin pregnancies.

Qualitative methods will explore parents' and clinicians' perspectives on:

1) Future trial design including views on active intervention and expectant management, randomisation, outcomes, and approach to recruitment and consent, including consent, decision making and length and content of trial information materials;
2) Factors influencing parent and clinician decision-making when potential outcomes include death or serious disability of one or both twins; and
3) Acceptability of a future trial, including potential barriers to recruitment, consent decisions, trial procedures, equipoise; inclusion / exclusion criteria and training needs.

2.2.1 Eligibility Criteria

The following inclusion criteria will be adopted in this WP:

- Mothers and partners (if applicable) of MC twin pregnancies complicated by sFGR in the previous three years; and
- Clinical staff involved in the management of MC twin pregnancies.

The following exclusion criteria will be adopted:

- Mothers / partners who do not speak English.

2.2.2 Mother and Partner Recruitment and Sampling

Women and their partners (if applicable) will be recruited to this WP through two routes to maximise the potential sample within the recruitment period and ensure that women from all management groups are represented.

Route 1: Information regarding this study WP will be detailed in the FERN Participant Information Sheet (PIS). All women and partners (if applicable) recruited to WP1 will be invited to consent to be contacted by a member of the WP2 research team to discuss taking part in this aspect of the study. Women who do not consent for their use of data in WP1 are eligible to take part in WP2 of this study. In such cases they will consent only to their contact information being passed to the WP2 research team for future contact. Alternatively, women can also opt out of being contacted to take part in WP2

when consented as part of WP1. Site staff will be given clear guidance and training on the consent process for this study as part of the Site Initiation Process.

For women who agree to be contacted regarding taking part in WP2, a separate contact sheet will be completed at site that will include the participant's name and contact information. Once complete this will be securely transferred to the FERN study management team based at the Harris Wellbeing of Women Research Centre together with the completed Informed Consent Form (ICF). Once validated by the Research Manager, this information will be provided (in a secure manner) to the Qualitative Research Team (WP2), who will then make direct contact with women to discuss their potential participation.

Route 2: The qualitative research team will contact gatekeepers (e.g. charity leads / Chief Executive Officers) of international twin support groups (e.g. Twins Trust - formerly Twins and Multiple Births Association; TAMBA) inviting them to post a FERN study media advert on the support group's website and / or social media pages (e.g. Facebook and Twitter) or member email lists. The advert will also be printed in a national newspaper and posted on our own patient and public involvement and engagement (PPIE) group social media sites. The advert will include a description of the purpose of the study and what is involved, as well as contact details for parents / legal representatives to register their interest in taking part. The study website will also provide additional information about the qualitative work package, including the PIS and contact information.

2.2.3 Arranging and Conducting Mother and Partner Interviews and Focus Group

The FERN Qualitative Research Team will make contact with women and their partners (if applicable) to arrange an interview (or focus group, please see below) within approximately one month of their original informed consent. Interviews will be carried out over the telephone, online (via Microsoft Teams or Zoom) or face-to-face (in line with the latest government guidance on COVID-10). All interviews will be conducted by the Qualitative Research Team using the FERN Women and Partner Interview Topic Guide. For telephone or online interviews the Qualitative Researcher will begin by explaining the aims of the study, providing an opportunity for questions and obtaining verbal informed consent for this aspects of the study. This will involve the researcher reading out loud each consent item from the FERN Qualitative ICF to participants, including consent for audio recording and to receive a copy of the findings when the study is complete. The researcher will initial each box on the consent form when the participant provides verbal consent. Informed consent discussions will be audio recorded for auditing purposes. For face to face interviews, the researcher will seek written

informed consent for the study using the FERN Qualitative ICF. The participant and the researcher will both sign the consent form. A copy will be given to the participant, one will be retained by the Qualitative Researcher and the original will be forwarded to the Harris Wellbeing of Women Research Centre Research Manager to be held with all core confidential study documentation as per Sponsor and Research Ethics Committee (REC) / Health Research Authority (HRA) approvals.

The topic guide used within this study has been informed by previous pilot studies conducted in the NHS, a literature review and ethical theory. Respondent validation will be used so that previously unanticipated topics will be added to the topic guide and discussed with participants as interviewing and analyses progress.

If divergence in opinions on trial intervention and acceptable outcomes is observed in the early analysis of interviews, we will use social media (route 2) to recruit parents to a focus group (~6-10 parents) in the North West of England with the aim of reaching consensus about an acceptable trial design. A Focus Group Topic Guide will be developed based on interview findings. A parent focus group specific media advert and PIS will also be developed (if required) during the early interview analysis phase. Written informed consent will be sought from recruited parents prior to the commencement of the focus group, as described above.

Any distress during the interviews (or focus group) will be managed with care and compassion in accordance with the FERN Interview Distress Protocol. Participants will be free to decline to answer any questions that they do not wish to answer or to stop the interview / leave the focus group at any point. Following on from this, such individuals will be supported in obtaining appropriate help via the standard NHS pathway or relevant support group (e.g. Twins Trust). After the interview / focus group is complete, participants will be sent a letter, copy of the consent form and a £30 Amazon® voucher to thank them for their time.

Interviews will be conducted until data saturation point, this is when major themes identified in the analysis of new data are reoccurring from previous participants / transcripts, and no new major themes are being discovered. Based on previous similar pilot studies, this is anticipated to be approximately 15-25 interviews. Participating sites (route 1) will be informed when they can stop recruitment to the qualitative element. All women and partners (if applicable) who express an interest in taking part but are not selected for an interview / focus group will be contacted via email or by postal letter to thank them for their interest in the study.

2.2.4 Clinician Recruitment and Sampling

Clinicians will be recruited to this WP via one of two routes as detailed below.

Route 1: A comprehensive database of clinicians, nationally and internationally, who lead in the management of sFGR will be developed by the CI, co-applicant team and collaborators. This database will be used to identify which clinicians will be invited to take part in this aspect of the study. In the first instance, an email invitation will be sent to each identified clinician.

Route 2: A FERN Practitioner Online Recruitment advert will be posted on relevant social media pages (e.g. Facebook and Twitter) targeting hashtags or groups followed by the target group (e.g. @nctcharity, @NIHR Research @RCObsGyn). The advert will include a description of the purpose of the study and what is involved.

The email invitation and social media advert will include information relating to why the study is taking place, why clinicians have been invited to participate and what their participation will involve. Contact details will be provided for clinicians to register their interest in taking part and their preference for an interview or focus group, which can be by telephone, online (via Microsoft Teams or Zoom) or face to face (in line with the latest government guidance on COVID-19). The invite and advert will also contain a link to the study website which will provide additional information, including the Practitioner PIS. Clinicians who register interest will be selected to ensure geographical stratification and role. Those invited to participate will be sampled in light of a) their management views (e.g. those in favour of expectant management and fetal intervention, respectively), and b) to ensure adequate representation of the different kinds of clinical staff involved in recruiting into the proposed trial (e.g. fetal medicine specialists, Obstetricians, Neonatologists, Midwives, Research Midwives, etc).

Arranging and Conducting Clinician Interviews and Focus Group

Clinician interviews will be arranged separately by the FERN Qualitative Research Team. Telephone, online or face to face (in the North West) interviews will be arranged at their convenience and conducted to the point of data saturation (approximately 15-25). Consent processes will be the same as described for the women and partner interviews.

Clinician interviews will be informed by a FERN Practitioner Interview Topic Guide, which will help the discussion stay relevant to the study aims, while allowing flexibility for individuals to raise and discuss issues, which they perceive as salient, including those potentially unforeseen at the study outset. The topic guide will be informed by a literature review, ethical theory, and revised in light of emerging

findings (including, potentially, findings from concurrent interviews with women). Clinicians will be sent a brief summary (a short protocol) of the proposed trial design in advance of their interview and this will form the focus of the discussion. Interviews will explore clinicians' views on key topics (described above), as well as seeking their views on whether (and why) they would be willing to recruit and randomise women. Clinicians will be asked about the training, resourcing and other support they would need to deliver a future trial. We will also ask the clinicians to define the details of management options and thresholds. The management of post-intervention complications, such as premature rupture of the membranes, will also be defined.

As with the women and partner interviews, if divergence in opinions is observed in the early analysis of interviews, clinicians will be recruited to a focus group (~8-10 site healthcare professionals) with the aim of reaching consensus about an acceptable trial design. A Focus Group Topic Guide will be developed based on interview findings.

3. STUDY POPULATION

The following section will detail the procedures for WP1. WP2 is set out in Section 2.2 of this protocol.

3.1 Pre-Registration Procedures

All women will be recruited directly from the fetal medicine or antenatal clinic. Prior to taking part in the study all women will have confirmation of their sFGR status completed by their attending clinician based on an ultrasound scan performed within the preceding 72 hours. Screening logs will be kept locally at site and forwarded on a regular basis to the study management team as per the local study screening process.

3.2 Inclusion Criteria

The following inclusion criteria will be adopted for this study:

- MC diamniotic twin pregnancy;
- Diagnosis of sFGR (EFW of one twin <10^{th} centile + EFW discordance >25%);
- Gestational age at diagnosis between 16^{+0} - 23^{+6} weeks based on ultrasound; and
- Informed consent given by the participant and consent form completed and signed.

3.3 Exclusion Criteria

The following exclusion criteria will be adopted for this study:

- Singleton pregnancies;
- Maternal age under 18 years;
- TTTS;
- Twin anaemia polycythaemia sequence before enrolment;
- Other rare complicated MC twin pregnancies, such as twin reversed arterial perfusion syndrome;
- Known karyotype abnormality at enrolment;
- Known major fetal structural abnormality at enrolment, defined as a lethal, incurable or curable severe abnormality with a high risk of residual handicap;
- Indication for immediate delivery;
- Pre-term pre-labour rupture of membranes before enrolment;
- Women who lack the capacity to give informed consent; and
- Any medical condition that compromises the woman's ability to participate.

3.4 Withdrawal Criteria

We do not have formal stop criteria, however, we will establish a Study Oversight / Steering Committee that will meet regularly throughout the course of the study. The remit of the committee is to provide independent oversight of the study in terms of participant safety and data integrity.

In consenting to take part in the study, participants are consented to the study procedures, potential participation in the qualitative sub-study, data collection and follow-up. If voluntary withdrawal occurs, the participant should be asked to allow continuation of scheduled evaluations, complete an end-of-study evaluation, and be given appropriate care until delivery.

Foreseeable reasons where a participant may withdraw from the study generally include:

- Participant withdraws consent;
- Loss of capacity during the study; and
- Any other change in the participant's condition that justifies the discontinuation in the clinician's opinion.

A participant is free to withdraw from the study at any time. In addition, the CI may decide, for reasons of medical prudence, to withdraw a participant. In either event, the Sponsor will be notified and the date and reason(s) for the withdrawal will be documented in the participant source data. If a participant withdraws or is withdrawn ideally they should remain in the study for the collection of safety data and / or treatment of any Adverse Events (AEs), until these have resolved. Generally, follow-up will continue unless the participant explicitly also withdraws consent for follow-up. The CI may also request that the participant return for an additional follow-up visit, for the purpose of collecting safety data, or ensuring resolution / adequate treatment of an AE.

Participants who withdraw from the study for other reasons have previously consented to follow-up in the study. Data up to this time can be included in the study if anonymised. Each participant may need to reaffirm consent to follow-up through usual NHS mechanisms. If the participant explicitly states their wish not to contribute further data to the study, a withdrawal electronic Case Report Form (eCRF) should be completed.

3.5 Patient Transfers

For participants moving from the area, every effort should be made to encourage them to remain part of the study. Such circumstances will be dealt with on a case-by-case basis.

3.6 End of Study

The study will end when all associated study data has been collected and analysed as part of the overall objectives of the research.

3.7 Stopping Criteria

The need to stop the study will be determined by the Study Oversight / Steering Committee. The decision will be based upon participant safety and integrity of the data.

4. ENROLMENT AND REGISTRATION

4.1 Participant Selection

All participants will be recruited from their local fetal medicine or antenatal clinic. They will be contacted in person by a member of the core clinical research team (Principal Investigator (PI) / Research Midwife) and invited to take part in the study. At this point participants will be given written and verbal information on the FERN study, as well as an opportunity to ask questions. All potential

participants will be given a unique screening ID that will subsequently be used to detail the reasons for the continuation or discontinuation at the screening stage.

4.2 Consent

Potential participants will be given written and verbal information on the FERN study and provided with the opportunity to ask questions and take any additional time required to consider taking part in the study. Following this, participants will be asked to sign the study-specific ICF in the presence of the site researcher, for whom a signature is also required. Four copies of the participant consent form will be collected. A copy will be given to the participant, a copy will be placed in the participant's medical records, the original should be held in the Investigator Site File (ISF) and a copy should be sent to the FERN Research Manager at the Harris Wellbeing of Women Research Centre. The site PI is also required to review and sign all consent forms.

4.3 Enrolment / Registration and Baseline

Once eligibility has been confirmed by the PI at site, the participant will be registered and then entered onto the study using an electronic registration platform. Although it will be recommended that participants take a minimum of 24 hours to consider taking part in this study, the provision for allowing participant consent within a shorter period of time must be permitted, as the nature of the condition often requires prompt intervention. Documentation of reasons for non-inclusion will be detailed in the site screening logs and forwarded to the Research Manager at the Harris Wellbeing of Women Research Centre. Once a participant consents to taking part in the study, they will be registered on a bespoke electronic data capture system that will generate a unique participant identification number.

4.4 Co-enrolment Guidelines

Participant enrolment in other research studies is permitted, however, it is expected that consultation regarding this has taken place with the site PI and participant to ensure that this poses no risk to patient safety or affects the integrity of the FERN study data.

4.5 Concomitant Medications / Procedures

Any medications that are taken and / or medical procedures / interventions that take place at the time of participation in the FERN study will be detailed for each participant on the eCRF by the site research staff.

5. ASSESSMENTS AND PROCEDURES

5.1 Schedule of Study Procedures

For WP1 participants will remain in the study for a maximum of 25 weeks (from 16^{+0} weeks' gestation [earliest point of eligibility] to 40^{+6} [recommended gestation of delivery for singleton pregnancy if one baby dies]. If MC twins between $36+^{0}$ and $37+^{0}$ [nationally recognised recommended gestation of delivery for MC twins]). On the completion of eligibility checks and the provision of written informed consent, participants will be registered onto the study. Following registration, clinical care will be as per the local clinical team and the patient's wishes.

5.2 Clinical Procedures

The timings of all measurements to be performed during the course of the study may be subject to change based on an ongoing review of study procedures. All changes will be agreed with the Sponsor and documented in the Study Management Folder (SMF).

5.3 Safety Reporting

AEs will be recorded as part of standard routine data collection. No additional data will be recorded on the study eCRF. All Serious Adverse Events (SAEs) will be reported to the Sponsor, REC and HRA in line with regulatory requirements. All SAEs will be reviewed as part of central monitoring by the Study Management Group (SMG).

5.4 Study Closure

Investigators will be informed when recruitment is to stop. Study enrolment may be stopped at a site when the total requested number of participants for the study have been recruited. The Study Oversight / Steering Committee may recommend that the study be stopped prematurely. In such circumstances of premature termination / suspension of the study, the REC and HRA will be notified according to the standard reporting guidelines.

6. STATISTICAL / DATA ANALYSIS CONSIDERATIONS

6.1 Introduction

In the following section a brief overview of the planned analyses for this study will be set out. Further analysis plans are provided separately from this document in a study specific Statistical Analysis Plan (SAP) which will include information on all aspects of analysis for this study (including Health

Economics and Qualitative work packages). Both this protocol and the SAP will be formally approved by the Study Oversight / Steering Committee.

Participants will be registered onto the study database in accordance with the study registration operating procedures. This system will be available 7 days per week, 24 hours a day and will be accessed by delegated site staff using a secure password protected website. All site staff will receive comprehensive training on the use of this system, which will be documented and stored in the ISF.

In the unlikely event that the back-up registration process is activated, participant registration will be performed by the Research Manager.

Data from the FERN study workbooks / CRFs at site will be entered onto a bespoke study database with extensive data validation checks alerting all missing data to be queried. Missing data will be monitored and strategies will be developed to minimise its occurrence. Central statistical data monitoring will summarise missing or inconsistent data periodically. The study workbook will be approved by the CI and validations will also be made that will cross check the study workbook with the FERN study eCRF.

6.2 Outcome Measures

6.2.1 Work Package 1 - A Prospective UK Multicentre Study

WP1 of this study will assess the feasibility of collecting outcome data from women with a MC diamniotic twin pregnancy affected by sFGR. Post Hoc analysis of gestation at diagnosis, treatment and severity of sFGR will also be conducted. No formal power calculation or primary outcome data will be determined. Success of the study will instead be determined on the acceptability of the study to women and clinicians. This will be determined by an ability to recruit and retain participants to the study.

6.2.2 Work Package 2 - Exploring Parents' and Clinicians' Views

The current study will involve a qualitative element, including interviews and a focus group with women and their partners (if applicable), as well as with clinicians involved in the management of MC twin pregnancies.

Qualitative methods will explore parents' and clinicians' perspectives on:

1) Future trial / study design including views on active intervention and expectant management, randomisation, outcomes, and approach to recruitment and consent, including consent, decision making and length and content of trial information materials;
2) Factors influencing parent and clinician decision-making when potential outcomes include death or serious disability of one or both twins; and
3) Acceptability of a future trial, including potential barriers to recruitment, consent decisions, trial procedures, equipoise; inclusion/exclusion criteria and training needs.

Thematic analysis of qualitative data from the interviews and focus group will be assisted using NVivo 10 qualitative data analysis package and SPSS software for statistical analysis. Whilst data will be analysed thematically the focus will be modified to fit with the criterion of catalytic validity, whereby findings should be relevant to future research and practice (in particular, the design of the potential definitive RCT). Analysis will also draw upon philosophical theory, concepts and methods (such as conceptual clarification and balanced argumentation) in an aim to develop recommendations that are defensible and consistent with ethical principle. This empirical ethics approach will facilitate the identification of practices or processes that should be challenged or modified in trial design. Quantitative analysis will involve simple descriptive statistics and the chi-square test for trend. Data from each method will be analysed separately then synthesized through the use of constant comparative analysis.

6.2.3 Work Package 3 - Consensus Development to Determine Feasibility for a Trial

A review will be conducted in order to identify current practices and opinion. This will enable us to understand clinical uncertainties around management decisions (see Section 1.4). The results of this survey will then be used to inform a Delphi consensus process that will ultimately formulate optimal trial design for use in a planned clinical trial in women with MC twin pregnancies complicated by sFGR. The consensus opinion of relevant stakeholders on key preferred scenarios will then be used to develop a protocol for this planned trial. The feasibility of this protocol will then be further consolidated using qualitative research and a final consensus process.

This review of current practice will be performed via electronic survey to clinicians. All questions will be defined in collaboration with co-applicants, patient representatives and key stakeholders (including international experts). The survey will be electronic in the first instance however for those who prefer a paper-based method, this will be made available upon request. The scope and specific plans relating to

the survey will be developed during the set-up phase of the study and detailed in either a separate plan or an update to this protocol.

We will build on our initial pilot of 29 UK fetal medicine clinicians from 13 units with a more in-depth survey of clinicians regarding current practice and equipoise in key clinical scenarios. We will do this by offering examples of key clinical scenarios of varying severity (types of sFGR) and placental location, etc, and ask clinicians their views on the optimal management (expectant, laser surgery or selective reduction). The survey will focus on scenarios where there is greatest clinical uncertainty (for example, type 1 sFGR is usually managed expectantly in view of its good prognosis, so fetal medicine specialists may not consider active fetal intervention in these pregnancies). This survey will be piloted to determine completion rates, ease of completion, and to identify any questions which are unclear to respondents.

We will use a standardised format, and present options in the form of tick boxes and / or ratings scales. We will be careful to vary our “agree” or “highest rating score” between expectant management and active fetal intervention to avoid bias from “yeasayers” [17].

The survey will be distributed through our professional networks of contacts. Contacts will include clinicians participating in existing twin studies currently led by co-applicants involved in this study. We will also invite participation through the RCOG Fetal Medicine Clinical Study Group (CSG). We will also advertise the survey through the RCOG and British Maternal and Fetal Medicine Society. We will ask participating clinicians if they would be willing to be contacted to take part in an interview for Phase 3 (WP2), and for their consent for us to collect and keep their contact details for this purpose. We plan to engage at least 50 UK clinicians.

Following the performance of the survey to identify current practices and opinion, the steering group will use the results to formulate a list of items and scenarios considered potentially important for a planned trial. This list of options will then be subjected to a Delphi process to reach consensus on a preferred trial question and design.

The Delphi process will consist of two rounds of electronic-based questionnaire, anonymised response and feedback. The first round of the survey will include scoring on the relative importance of each of these items and scenarios, and will invite additional items not included in the list. A second round will then be undertaken providing feedback from the previous round and inviting a further response from participants. Additional items / scenarios identified by participants in Round 1 will be included for

consideration in Round 2. The process will reduce the clinical uncertainties identified in Phase 1 into a short-list, prioritising clinical scenarios which are both uncertain and important.

We will use a Likert scale and analyse with appropriate non-parametric and / or parametric tests. Where more than 85% of individuals responding to the surveys agree on an answer to a clinical scenario, we will designate the scenario as having good agreement, and being accepted clinical practice. Where 70-85% agree, we will designate the scenario as having some uncertainty. Where 50-70% agree, we will designate the scenario as having moderate uncertainty. Where less than 50% agree on an answer, we will assume that there is significant uncertainty.

Stakeholder groups will be invited to participate in the Delphi process, including PPIE co-applicants, parents, parent representatives, healthcare professionals and researchers. Participation is optional and informed consent will be assumed if a participant responds to the Delphi survey.

6.2.3.1 Delphi Scoring

Participants will be asked to score each item / scenario using a scale of 1 to 9, with 1 to 3 labelled 'not an important consideration for the planned trial', 4 to 6 labelled 'important consideration for the planned trial but not critical' and 7 to 9 labelled 'critical for the planned trial'. Participants will also be allowed to score 'unsure' if they are unable to offer an opinion as to whether the item / scenario is important or not.

6.2.3.2 Delphi Analysis and Feedback

For each item, the number of participants who have scored the item and the distribution of scores will be summarised from Round 1. In Round 2, each participant who took part in Round 1 will be shown the number of respondents and distribution of scores for each item / scenario, for all stakeholder groups separately, along with their own score from Round 1. They will be asked to consider the responses from other Delphi participants, and to re-score the item / scenario.

6.2.3.3 Consensus Definition

Consensus will be defined *a priori*. Items / scenarios will be prioritised if they gain the support of at least 70% of participants scoring 'Critical', i.e. score 7-9.

6.2.3.4 Final Consensus Meeting

Following the completion of Round 2 of the Delphi process, the results will be analysed as in Round 1. The Round 2 results will be fed into an interactive consensus meeting that will inform the final set of

items / scenarios. The meeting will present items / scenarios retained and dropped, and discuss any scenarios in Round 2 where “no consensus” was found. Participants will be asked to score on the items / scenarios, and the same consensus criteria will be used as in the Delphi exercise. Only those stakeholders who completed both rounds of the Delphi study will be invited to participate. It is anticipated that 2-3 key participants from each stakeholder group will participate. At this interactive meeting we will finalise the shortlist of scenarios that will inform the development of resources for the subsequent qualitative phases of the study. The aim is to use the prioritised scenarios to plan the single most important trial. Any scenarios not possible to cover in a single trial will be discussed for future separate exploration.

6.2.3.5 Development of a Trial Protocol

Following the discussions with the consensus meeting participants, the steering group will draft the protocol for the planned trial. We anticipate that this trial will use an efficient design. The PICO model will be core to the formulation of the trial protocol.

6.2.3.6 Consensus Group Meeting

A consensus group including patients, patient representatives, clinicians and researchers will collate data from this study and published data (systematic reviews and available relevant studies). We will aim to employ representation from healthcare professionals with experience in treating MC twin pregnancies complicated by sFGR as well as patient / partners both from the earlier work packages as well as various charities, e.g. Twins Trust (Formerly TAMBA) (twin related), BLISS (neonatal) and other groups (ARC / James Lind Alliance). We will try to ensure that our stakeholders represent as diverse a population as possible to ensure that all views are expressed.

At this stage, if deemed feasible, we will define a clinically valuable definitive trial. We will ensure a study design that is deliverable with relevant clinical outcomes that will change practice. Further methodological details will be specified (eligible population; inclusion and exclusion criteria; primary and secondary outcomes; sample size; selection and size of participant pool; patient flow from recruitment to completion; timing of randomisation; the intervention; the management of the control group; the possibility of randomising at the level of hospitals, e.g. using a cluster RCT or stepped wedge RCT; the potential use of an adaptive trial design; whether an initial smaller scale pilot study is required). The feasibility of the study, including staff capacity, skills mix, analysis of iteration output and definitions of group consensus, will be determined as part of the study and with adherence to

recommendations from HTA guidance on consensus development methodology (HTA report 1998 Consensus development methods, and their use in clinical guideline development).

6.3 Sample Size

No formal power calculation or primary outcome data will be determined for any WP in this study.

6.3.1 Work Package 1 - A Prospective UK Multicentre Study

WP1 will assess the feasibility of recruiting women with a MC twin pregnancy complicated by sFGR to collect detailed information about pregnancy management and outcome. The success of this WP will be determined on the acceptability for women and clinicians. This will be determined by an ability to recruit and retain participants. We propose that we should expect to recruit in the region of 120 participants across the UK over a 14 month period but we will continue to recruit until the recruitment period is complete. This is a pragmatic figure which is based on the typical number of sFGR patients seen per annum in large consultant led NHS units within the UK.

6.3.2 Work Package 2 - Exploring Parents' and Clinicians' Views

WP2 will utilise interviews and focus groups to understand parents' and clinicians' views on the management of sFGR in MC twin pregnancy and the barriers to the use of interventions. To ensure sample variance we will include parents with experience of intervention and expectant management of sFGR, bereaved and non-bereaved parents and clinicians in favour of both fetal intervention and expectant management. Interviews will be conducted until data saturation and sample variance are achieved, i.e. when no new major themes are being discovered. Based on previous similar pilot studies, this is anticipated to be approximately 15-25 interviews in both the parent and clinician groups. If divergence in opinions is observed, we will hold focus groups (approximately 6-10 participants per group) with the aim of reaching consensus.

6.3.3 Work Package 3 - Consensus Development to Determine Feasibility for a Trial

A survey of clinicians will be performed as part of WP3 in order to identify current practices and opinion. Engagement of at least 50 UK clinicians is planned, however we will aim to maximise the number of responses by issuing periodic reminders for survey completion. The information obtained from the clinician survey will be subjected to a Delphi process, the results of which will be fed into an interactive consensus meeting. It is anticipated that 2-3 key participants from each stakeholder group (PPIE co-applicants, parents, parent representatives, healthcare professionals and researchers) will participate.

6.4 Interim Analysis and Monitoring

As there are no formal hypotheses being tested, there are no formal stopping rules (other than safety) or mechanisms defined here to stop the study prior to the planned end of study. The study does have a formal oversight committee that will be able to review at regular intervals all accumulating data. The main responsibility of this committee will be to review the recruitment of participants, the collection of all essential data and to assess patient safety.

6.5 Statistical Methodology

Full details of the statistical analyses for this study will be detailed in the SAP. As the analysis being carried out are based on feasibility, the details in terms of the methodology may be altered during the course of the study. It will nonetheless be set out in the SAP and finalised prior to the final data lock and analyses. Some basic information to be followed are detailed here.

6.5.1 Patient Groups for Analyses

Patients will be summarised on an intention to treat (ITT) basis retaining all patients irrespective of any protocol deviations. Further secondary analysis will be carried out on a per protocol population. Further analyses may be carried out on planned subgroups (e.g., those who meet the inclusion criteria for a future study) as is required.

6.5.2 Significance Levels

As this is an exploratory study no formal levels of significance are set. All statistics presented will be presented alongside 95% confidence intervals so as to give an indication of the level of precision only.

6.5.3 Missing Data

The likelihood of missing data is small given the standard procedure in place to manage the study centrally. Final analyses will take place on a complete-case basis with no adjustments made (e.g. multiple imputation) in the case of missing data.

6.5.4 Exposure to Intervention

The intervention will be data collection only. Management will be determined by the local clinicians in discussion with the participants.

6.5.5 Trigger for Final Analyses

Analysis of study data will take place once all participants have received the planned follow-up and all

data are available for analysis.

6.5.6 Data Descriptions

Continuous data will be summarised as median, inter-quartile range (IQR) and ranges. Categorical data shall be summarised as frequencies of counts and associated percentages.

6.5.7 Exploratory Analyses

Multivariate data analysis techniques will be used to attempt to find natural groupings in the generated data. In particular hierarchical cluster analysis (HCA) and principle component analysis (PCA) techniques will be used.

7. REGULATORY ASPECTS

7.1 Medical Research Ethics Approval

As this study is within NHS England, assessment of governance and legal compliance will be undertaken by dedicated HRA staff, with the independent REC opinion provided through the UK Health Department. No patients will be entered onto the study before ethical approval has been confirmed.

The CI is responsible for updating the ethics committee of any new information related to the study.

The study protocol has received the favorable opinion of the HRA Ethics Committee South West – Cornwall and Plymouth Research Ethics Committee but all participating sites must undergo site specific assessment of capacity and capability via the HRA. Copies of site agreements to take part and copies of the PIS and ICF with local site headers must be forwarded to the Harris Wellbeing of Women Research Centre before participants are entered. The Harris Wellbeing of Women Research Centre should receive a confirmation of capacity and capability for each new centre via the site's R&D department.

The study will be conducted in accordance with, but not limited to, the Human Rights Act 1998, the Data Protection Act 2018, Freedom of Information Act 2000 subject to the provisions of sections 41 and 43 thereof, the EU (European Union) Clinical Trials Directive, ICH-GCP, the Declaration of Helsinki 1996 and the UK Policy framework for Health and Social Care research as amended from time to time. All data will be recorded, collected, stored and processed, in accordance with GDPR (EU) 2016/679. As the Sponsor of the FERN study is a non-commercial organisation the legal basis

for the handling and processing of data is 'task in the public interest.'

This study may be terminated at the request of the CI, REC or other regulatory authority if during the course of the study, concerns about participant safety and / or data integrity emerge.

7.2 Informed Consent Process

Informed consent is a process initiated prior to an individual agreeing to participate in a study and continues throughout the individual's participation. Informed consent is required for all patients participating in University of Liverpool co-ordinated trials and studies. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.

Discussion of objectives, risks and inconveniences of the study and the conditions under which it is to be conducted are to be provided to patients by staff with appropriate experience. An appropriate PIS and consent form, describing in detail the study procedures and risks will be approved by an independent ethical committee and the participant will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the participant and answer any questions that may arise. A contact point where further information about the study may be obtained will be provided.

After being given adequate time to consider the information, the participant will be asked to sign the consent form. A copy of the completed consent document will be given to the patient for their records, a copy will be placed in their medical records, and one further copy will be sent to the FERN Research Manager by secure email to fern1@liverpool.ac.uk. The original consent form should be retained in the ISF.

The participant may withdraw from the study at any time by revoking their informed consent. The rights and welfare of the participants will be protected by emphasising to them that the quality of medical care will not be adversely affected if they decline to participate in this study.

7.3 Study Discontinuation

If this study is prematurely discontinued (e.g. due to safety) all participants must be informed and the reason for the discontinuation should be written on the end of study form for each participant. If a participant has been withdrawn completely from the study whilst the study is still ongoing, an end of study form should be completed.

7.4 Confidentiality

Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. All eCRFs will be labelled with participants' unique study ID. Consent forms sent to the Harris Wellbeing of Women Research Centre as part of the registration process may contain patient identifiers for the purpose of monitoring as described in the study risk assessment. Such information will be stored in secure, locked cabinets and participants will be asked to explicitly consent to this transfer.

7.5 Quality Assurance and Quality Control of Data

Systems of quality assurance, including all elements described in this protocol will be implemented within relevant institutions with responsibility for this study. Quality control is applied to each stage of data handling to ensure that data are accurate, reliable and processed correctly.

The study sites, facilities and all data (including sources) and documentation must be available for audit and inspection by competent authorities or independent ethical committees. Such audits / inspections may take place at any site where study related activity is taking place (the Sponsor's site(s), the Harris Wellbeing of Women Research Centre or at any investigator's site).

The site staff should assist in all aspects of audit / inspection and be fully cognisant of the Sponsor communication strategy for single and multicentre studies. This includes management systems for the greenlight process prior to participant recruitment at site.

7.6 Records Retention

The investigator at each study site must make arrangements to store the essential study documents, (as defined in Essential Documents for the Conduct of a Clinical Trial (ICH E6 (R2), Guideline for Good Clinical Practice) including the ISF, until the Sponsor or the Harris Wellbeing of Women Research Centre informs the investigator that the documents are no longer to be retained.

In addition, the investigator is responsible for archiving of all relevant source documents so that the study data can be compared against source data after completion of the study (e.g. in case of inspection from authorities). The investigator is required to ensure the continued storage of the documents, even if the investigator, for example, leaves the clinic / practice or retires before the end of the required storage period. Delegation must be documented in writing. The Liverpool Clinical Trials Centre (LCTC) undertakes to store all electronic data related to completed eCRFs, except for source documents pertaining to the individual investigational site, which are kept by the investigator only. At

the point where it is decided that the study documentation is no longer required; the Investigator will be responsible for the destruction of all site study specific documentation and the Sponsor / LCTC / Harris Wellbeing of Women Research Centre will be responsible for the destruction of all study related materials retained.

Verification of appropriate informed consent will be enabled by the provision of copies of participants' signed ICFs being supplied to the Harris Wellbeing of Women Research Centre by recruiting centres. This requires that name data will be transferred to the Harris Wellbeing of Women Research Centre, which is explained in the PIS. The Harris Wellbeing of Women Research Centre will preserve the confidentiality of participants taking part in the study and the University of Liverpool is a Data Controller registered with the Information Commissioners Office (ICO).

7.7 Indemnity

This study is sponsored by the University of Liverpool and co-ordinated by the Harris Wellbeing of Women Research Centre, Department of Women's and Children's Health within the University of Liverpool. The University of Liverpool has vicarious liability for the actions of its staff, when through the course of their employment they are involved in the design and initiation of a clinical research study, including but not limited to the authorship of the study protocol. The University of Liverpool has appropriate insurance in place to cover this liability.

In terms of liability, NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical study, and they are legally liable for the negligent acts and omission of their employees. Compensation is therefore available in the event of clinical negligence being proven.

Clinical negligence is defined as:

"A breach of duty of care by members of the health care professions employed by NHS bodies or by others consequent on decisions or judgments made by members of those professions acting in their professional capacity in the course of their employment, and which are admitted as negligent by the employer or are determined as such through the legal process".

7.8 Sponsor

The University of Liverpool will act as Sponsor for this study. It is recognised that as an employee of the University, the CI has been delegated specific duties, as detailed in the Sponsorship Approval

letter and Internal Delegation of Responsibilities Agreement.

7.9 Funding

The Health Technology Assessment (HTA) programme are funding this study. Study participants do not receive payments to take part in the WP1. Participants who take part in WP2, the qualitative work package of this study will receive payments for their travel as well as a gesture of goodwill.

A per patient payment has been calculated for this study. This has been approved by the Lead NHS Trust and North West Coast Clinical Research Network (CRN). All per patient payments will be set out in the study Research Site Agreement (RSA) where sites will also be provided with guidance on invoicing arrangements for processing payments.

7.10 Audits

The study may be subject to inspection and audit by the University of Liverpool under their remit as Sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Framework for Health and Social Care Research (v3.2 10th October 2017).

8. STUDY MANAGEMENT / OVERSIGHT

The day-to-day management of the study will be co-ordinated through the Harris Wellbeing of Women Research Centre, Department of Women' and Children's Health, University of Liverpool.

8.1 Study Management Group (SMG)

A SMG will be formed comprising the CI and lead investigators / core study management staff who are central to the day-to-day running of the study. The SMG will be responsible for the day-to-day running and management of the study and will meet at regular intervals throughout the course of the study. The frequency of meetings will be decided by the CI. However, it is expected that they should take place at least monthly. This group may consist of the following members of the core research team however all are not required to attend each meeting in person. Compulsory attendance is denoted by a *.

- *CI
- *Research Manager
- Qualitative Work Package Representative
- Health Economics Work Package Representative

- Study Statistician

8.2 Study Oversight / Steering Committees

The FERN study will convene an Independent Study Oversight / Steering Committee. The details for which follow:

8.2.1 Membership

The Study Oversight / Steering Committee will consist of:

- CI / PI;
- Independent Clinician (Chair);
- Research Manager;
- Study Statistician;
- One further Independent Clinician;
- PPIE Co Applicant;
- Sponsor; and
- Lead Site Representative

The role of the Oversight / Steering Committee is to provide oversight of the study. In particular, this committee will concentrate on the progress of the study, adherence to the protocol, participant safety and consideration of new information. This committee must be in agreement with the final protocol and, throughout the study, will take responsibility for:

- Major decisions such as the need to change the protocol for any reason;
- Monitoring and supervising the progress of the study;
- Reviewing relevant information from other sources; and
- Informing and advising the SMG on all aspects of the study.

In addition, this committee will convene to review individual participant data at regular time points throughout the recruitment period. In this way, they will review:

- Real time and cumulative safety data for evidence of study-related Aes;
- Adherence to the protocol;
- Factors that could affect the study outcomes / compromise the study data; and
- Data relevant to informing the next stage of the study or a future study.

This committee should conclude each meeting with a recommendation to the SMG as to whether the study pathway should be modified. This committee may convene at other times to assess any emerging safety data or other study related issues.

The committee will include experienced clinical researchers and other medical experts within the area. Meetings will be held (face to face or via teleconference) at regular intervals determined by need, but no less than once a year. The ultimate decision for the continuation of the study lies with this committee. Separate charters which will detail the committee Terms of Reference will be agreed at the first meeting which will detail how it will conduct business.

All members of the committee will be invited formally on behalf of the CI during the study set-up phase. Following confirmation of their acceptance to become a committee member, they will review and approve the committee Charter / Terms of Reference which will also inlcude details on the frequency of meetings. The first committee meeting will be before the study opens to recruitment as part of the overall study greenlight requirements.

9. MONITORING

Central and study site monitoring is conducted to ensure protection of participants in the study, and that procedures, and data collection processes are of high quality and meet sponsor and, when appropriate, regulatory requirements. A risk assessment will be carried out to determine the level of monitoring required, and a subsequent monitoring plan will be developed to document who will conduct the central (and potentially site) monitoring, at what frequency monitoring will be carried out and the level of detail at which monitoring will be conducted.

A full quality control check of the protocol has been completed by the Harris Wellbeing of Women Research Centre and the CI. In addition, a SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) check has also been carried out in line with standard guidelines.

9.1 Risk Assessment

In accordance with the requirements of the Sponsor, a risk assessment has been completed in partnership with:

- Representatives of the Study Sponsor (University of Liverpool);
- CI;

- Members of the SMG;
- Research Manager; and
- Statistician.

In conducting this risk assessment, the contributors considered potential patient, organisational and study hazards, the likelihood of their occurrence and resulting impact should they occur. The outcome of the risk assessment is categorised based upon the potential risk associated with the study intervention in accordance with MRC / DH / MHRA Project on Risk-adapted Approaches to the Management of Clinical Trials:

http://www.mhra.gov.uk/home/groups/l-ctu/documents/websiteresources/con111784.pdf

- Type A: No higher than that of standard medical care
- Type B: Somewhat higher than that of standard medical care
- Type C: Markedly higher than that of standard medical care
- Non-CTIMP

The initial risk assessment for this study resulted in a study category of Low Risk. This is a non-CTIMP.

9.2 Source Data

Source data are all information, original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies). (ICH E6 (R2), 1.51).

9.2.1 Source Documents

Original documents and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy and laboratory departments involved in the clinical study. (ICH E6 (R2). 1.52)

For data where no prior record exists and which are recorded directly in the study workbooks (e.g., vital signs) the study workbooks will be considered the source document unless otherwise indicated by

the investigator.

All data recorded in the workbooks should be consistent and verifiable with source data in source documents other than the workbook (e.g., medical record, laboratory reports and medical notes, scan reports). For this reason the study sites should maintain appropriate medical and research records for this study in compliance with ICH E6 (R2) GCP, Section 4.9 and regulatory and institutional requirements for the protection of the confidentiality of study participants for the purpose of source data verification.

9.3 Data Capture Methods

Study data will be captured using eCRFs transcribed to a bespoke study database. This database is designed and maintained by the University of Liverpool, IT Services in collaboration with the CI and Research Manager. The eCRF is the primary data collection instrument for the study. All data requested on the eCRF must be recorded and all missing data explained.

9.3.1 Electronic Case Report Forms (eCRF)

All eCRFs are entered directly into the bespoke study database that can be accessed via a secure webpage by research site staff and the Research Manager. The client application is secured with a unique username / password combination allocated to each delegated member of the research team. When data is entered into an eCRF it is electronically stamped with the date, time and the person who entered it. If data is changed on an eCRF, it is electronically stamped with the change and will be accompanied with the date, time, person and a reason for making the change or correction. The previous value is recorded in an audit trail for each data item.

Each eCRF contains specific validation checks on the data being entered. If any values are outside what is expected, or data are missing, this is flagged and will be raised as a discrepancy on the database system. Regular reports will be generated to identify discrepancies in the data, and allow for follow up. Comprehensive guidelines for eCRF data entry will be provided to all staff who have been delegated the responsibility for data collection. Where the site is unable to upload data using the eCRF a backup paper CRF will be available to use and accessed from the File Repository within the study database. In such cases the site research staff will enter the data onto the study database following the assessment.

Electronic and paper screening logs will be kept in clinics to record the number of patients declining participation and when volunteered the reason given. All data will be kept in a secure locked location

on NHS premises. All routine eCRFs should be completed within a calendar month of the study visit occurring.

Paper workbooks will be available for download from the File Repository within the study database. These will be used as an aid to research staff. To ensure current versions of the workbook are used, pages should be printed directly from the File Repository as and when they are needed. Quality Control processes including on site source data verification will be put in place in line with the eCRF platform. Workbooks should be kept in the ISF at the study site.

9.4 Monitoring Methods

There are a number of monitoring features in place to ensure reliability and validity of the study data.

9.4.1 Greenlight Process

The greenlight process ensures that all regulatory and ethical approvals are in place, contracts / agreements are signed and study management standard operating procedures (SOPs) are in place prior to the study opening. Furthermore, a site greenlight process will also be followed that ensures all study specific and ICH GCP training has been completed for site research staff before a study site is open and able to register participants. The greenlight process for opening this study will be managed by the Harris Wellbeing of Women Research Centre.

9.4.2 Site Research Staff

All site research staff involved in the study must be included on the site staff delegation log. The PI at each site signs off on the delegation log only those staff members s/he feels are able and competent to complete the assigned tasks. The delegation log provides clearly defined delegation of responsibility thus ensuring site research staff are aware of their responsibilities, and is continuously checked (as part of the Data Management Plan) against staff named on eCRFs, SAE reports and registration forms.

The Research Manager will ensure that as a minimum the PI, a Research Midwife and a site study data management staff member have study-specific training (on the protocol, SAE reporting and consent process), all of which is provided at site initiation (either on site or by teleconference) by the Research Manager and the CI. The PI is responsible for ensuring that site staff named on the delegation log but not present at site initiation receive study-specific training (on the protocol, SAE reporting and consent process). Sites are provided with copies of training aids presented at site

initiation to provide a constant reminder of key issues.

To ensure that site research staff maintain up to date ICH GCP training (to be renewed every 3 years as agreed by the Sponsor), delegated site research staff must provide the date of their last ICH GCP training along with their CV. An email reminder will be sent to site research staff when their next ICH GCP training is due. Non-NHS staff must have honorary NHS contracts and evidence of CRB checks must be obtained for staff (when necessary by UK law).

Email reminders (from site opening) will be sent to sites requesting that an updated delegation log is faxed or secure mailed (depending upon local practice) to the Harris Wellbeing of Women Research Centre. On receipt of updated delegation logs, the Research Manager will ensure that new staff members have submitted their CVs and date of last ICH GCP training.

9.4.3 Oversight

The FERN study will have an SMG and Independent Study Oversight / Steering Committee to monitor study progress (see Section 9.2).

9.4.4 Safety Reports

Monthly safety reports will be generated by the Research Manager which allow monitoring of SAE reporting rates. Any concerns raised by the Oversight / Steering committee or inconsistencies noted may prompt additional training, with the potential for the Research Manager to carry out site visits if there is suspicion of unreported SAEs in participant case notes. Additional training will also be provided if unacceptable delay in safety reporting timelines is noted at a given site. AE's will be reviewed regularly by the Oversight /Steering Committee.

9.4.5 Eligibility and Consent

The Research Manager will verify that all site research staff attended study-specific training relating to eligibility screening and the informed consent / registration process. The Research Manager will carry out a check of all consent forms sent to the Harris Wellbeing of Women Research Centre. This includes checking that the patient is eligible, the correct versions of the PIS and ICF forms have been used and the patient and clinician signatures are present and dated on the same day.

9.4.6 Participant Confidentiality

All study management and site research staff have received ICH GCP training and are thus aware of the importance of patient confidentiality. The Research Manager will consistently check that all study

documentation sent to the Harris Wellbeing of Women Research Centre are anonymised and identifiable only by a unique study identification number (except for signed consent forms, which are stored in a separate locked cabinet in the Harris Wellbeing of Women Research Centre). The Research Manager will monitor site performance on maintaining patient confidentiality and will provide additional training if a particular site sends any patient identifiers to the Harris Wellbeing of Women Research Centre (other than on the signed consent form).

9.4.7 Recruitment

The Research Manager will produce regular recruitment reports, to allow the Study Oversight / Steering Committee and SMG to review recruitment. Slow or inconsistent recruitment will trigger further action centrally. The Research Manager may liaise directly with site staff in order to query reasons for slow recruitment and try to resolve any problems that could impact recruitment. The Research Manager will check that the study is being actively promoted at the research site, and site recruitment schedules will be reviewed during the course of the study as necessary.

9.4.8 Protocol Violations / Deviations

All protocol violations and deviations will be recorded by the Research Manager in the study site status database and are included in regular reports. The Research Manager will send details of all protocol violations and deviations to the CI as soon as they have been made aware of them. The CI will then consider whether any are potential serious breaches that would need to be forwarded immediately to the Sponsor. If it is noted that a particular site is making consistent protocol violations or deviations, additional training will be provided by the Research Manager.

9.4.9 Withdrawals / Losses to Follow-up and Missing Data

The Research Manager will produce reports on withdrawals, losses to follow-up and the quantity of missing eCRF data across sites for review by the SMG and Study Oversight / Steering Committee. Identified problems will be discussed and remedial action taken as necessary.

As outlined in the Data Management Plan, the Research Manager will check that the withdrawal eCRF is completed for all withdrawn participants (including the reasons for withdrawal). The Research Manager will compare withdrawal rates and reasons for withdrawal, paying particular attention to withdrawals close to dates of registration. If a site experiences an excessive rate of withdrawals, additional training on the informed consent procedure will be provided.

9.4.10 Data Management Plan

All eCRF data entered into the bespoke study database will be centrally monitored by the Harris Wellbeing of Women Research Centre to ensure that data collected are consistent with adherence to the study protocol. The bespoke database used for this study includes validation features which will alert the user to certain inconsistent or missing data on data entry. If any problems are identified via automated validation or central monitoring, a query is raised and emailed to site. A complete log of discrepancies and data amendments is automatically generated, including the date of each change, the reason for the change and the person who made the change, thus providing a complete audit trail. Automated email reminders are generated by the database if follow up data from a scheduled patient visit is overdue.

Additional site training will be carried out if recurring problems are noted with data from a certain site, such as consistently incorrect or incomplete data, a backlog of unresolved queries, or unacceptable time delays in the submission of eCRFs. This study will have a separate Data Management Plan which will detail all components of data management for this study.

9.4.11 Harris Wellbeing of Women Research Centre Staff

All Harris Wellbeing of Women Research Centre study management staff will receive regular ICH GCP training, have in-house training records and undergo regular individual Performance Development Review (PDR) sessions, all of which are used to ensure that appropriate training is received and any problems are identified and resolved in a timely fashion.

9.4.12 Statistical Monitoring

Central statistical monitoring is carried out by the study statistician prior to providing each Oversight / Steering Committee report. The statistician checks registration numbers to ensure that none are duplicated or missing, registration data, eligibility criteria and informed consent. Monitoring is used to highlight suspicions of fraudulent data (by carrying out range checks for unusual values, checking for consistency within participants and comparing data across sites to highlight inconsistencies). Safety and withdrawal data are also reviewed for completeness. If there is compelling evidence to suggest that data from a particular site may be fraudulent, the SMG may request a site visit to carry out source document verification of patient case notes and other source documentation.

9.5 Clinical Site Monitoring

9.5.1 Direct access to data

If necessary, the Research Manager may need direct access to primary participant data, e.g. participant records, appointment books, etc. Each PI therefore permits study related monitoring, audits, ethics committee review and regulatory inspections by providing direct access to source data / documents. As this affects the participant's confidentiality, this fact is included on the PIS and ICF.

9.5.2 Confidentiality

Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. CRFs will be labelled with participant unique study identification numbers only. Consent forms sent to the Harris Wellbeing of Women Research Centre as part of the registration process may contain patient identifiers for the purpose of monitoring as described in the study risk assessment. Such information will be stored in secure, locked cabinets and participants will be asked to explicitly consent to this transfer.

9.5.3 Quality Assurance and Quality Control of Data

Systems of quality assurance, including all elements described in this protocol have been / will be implemented within relevant institutions with responsibility for this study. Quality control is applied to each stage of data handling to ensure that data are accurate, reliable and processed correctly. The study sites, facilities and all data (including sources) and documentation must be available for audit and inspection by competent authorities or independent ethical committees. Such audits / inspections may take place at any site where study related activity is taking place (the Sponsor's site(s), the Harris Wellbeing of Women Research Centre or at any investigator's site, etc.).

9.5.4 Records Retention

The lead investigator at each study site must make arrangements to store the essential study documents, until the Sponsor informs the investigator that the documents are no longer to be retained.

In addition, the investigator is responsible for archiving of all relevant source documents so that the study data can be compared against source data after completion of the study (e.g. in case of inspection from authorities). The investigator is required to ensure the continued storage of the documents, even if the investigator, for example, leaves the clinic / practice or retires before the end of required storage period. Delegation must be documented in writing.

At the point where it is decided that the study documentation is no longer required; the Investigator will be responsible for the destruction of all site study specific documentation and the Sponsor / Harris Wellbeing of Women Research Centre will be responsible for the destruction of all study related materials retained by the Sponsor.

10. ARCHIVING

The site files will be archived at each site under the custodianship of the site PI. Clinical data will be stored for up to 25 years after the end of the study. Research data will be stored up to 10 years after the end of the study. All data will be stored and archived in line with requirements of ICH-GCP and the Data Protection Act 2018.

The PI at each site must make arrangements to store the essential study documents, including the ISF, until the Harris Wellbeing of Women Research Centre informs the PI that the documents are no longer to be retained. In addition, the PI is responsible for the archiving of all relevant source documents so that the study data can be compared against source data after completion of the study (e.g. in case of inspection from authorities). The PI is required to ensure the continued storage of the documents, even if the PI, for example, leaves the clinic / practice or retires before the end of required storage period. Delegation must be documented in writing.

The Harris Wellbeing of Women Research Centre undertakes to store original documents completed for the study research except for source documents pertaining to the individual investigational site, which are kept by the PI only.

At the point where it is decided that the study documentation is no longer required; the PI will be responsible for the destruction of all study specific documentation and the Sponsor / Harris Wellbeing of Women Research Centre will be responsible for the destruction of all study related materials retained by the Sponsor / Harris Wellbeing of Women Research Centre.

11. PUBLICATION

The results of this study will be analysed and published once all study data has been collected, validated and analysed. Individual researchers must undertake not to submit any part of their individual data for publication without the prior consent of the SMG.

The SMG will form the basis of the Writing Committee and advise on the nature of publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (*http://www.icmje.org/*) will be respected. All publications shall include a list of participants, and if there are named authors, these should include the study's CI, Statistician(s) and Study Manager(s) involved at least. If there are no named authors (i.e. group authorship) then a Writing Committee will be identified that would usually include these people, at least.

The members of the Study Oversight / Steering Committees should be listed with their affiliations in the Acknowledgements / Appendix of the main publication. All publications arising from the FERN study will be open access, according to the conditions of the funder of the study.

12. PROTOCOL AMENDMENTS

All versions of this protocol prior to ethics submission are referred to as DRAFT.

Original Version	Original Date	New version	New date	Submitted to	Summary of Changes
DRAFT 1.0	**07-Nov-2019**	**n/a**	**n/a**	**Study Management Group**	**n/a**
DRAFT 1.0	**07-Nov-2019**	**DRAFT 2.0**	**11-Nov-2019**	**Study Management Group**	**General revisions to entire document**
DRAFT 2.0	**11-Nov-2019**	**DRAFT 3.0**	**04-Feb-2020**	**Study Management Group**	**General formatting changes** **General revisions to Potential Risks and Benefits (1.5, Pg 26), Study Design (2.0, Pg 26-32), Study Population (3.0, Pg 32-34), Statistical / Data Analysis Considerations (6.0, Pg 36-43), Safety (7.0, Pg 43-44) and Study Management / Oversight (9.0, Pg 48-50) Sections**
DRAFT 3.0	**04-Feb-2020**	**DRAFT 4.0**	**21-Feb-2020**	**Sponsor**	**General formatting changes** **Addition of substantive employer address for CI to Protocol Approval page (Pg 2)** **Removal of Section 7.0 Safety and addition of Section 5.3 Safety Reporting (Pg 36)** **Addition of individual sample size Sections for each work package (Section 6.3, Pg 41-42)**

					Addition of Section 13.0 References (Pg 61-62)
DRAFT 4.0	**21-Feb-2020**	**DRAFT 4.1**	**09-Jun-2020**	**Sponsor**	**Revised wording to Medical Research Ethics Approval (7.1, Pg 44), Records Retention (9.5.4, Pg 57) and Archiving (10,0 Pg 57-58) Sections** **Addition of secure email as a communication method to Section 9.4.2 Site Research Staff (Pg 53-54)**
DRAFT 4.1	**09-Jun-2020**	**1.0**	**26-Aug-2020**	**REC / HRA**	**Update to Contact Details Section (Pg 4-9)** **Revised wording to Work Package 2 Objective (Pg 13, Section 1.3 Pg 25)** **Update to Study Flowchart (Figure 1 Pg 15)** **Addition of online interviews and reference to COVID-19 guidance regarding face to face interviews to Sections 2.2 Work Package 2 – Exploring Patients' and Clinicians' Views (Pg 28-32)** **Revised wording to Section 2.2.3 Arranging and Conducting Mother and Partner Interviews and Focus Group (Pg 29-30) to include reference to the FERN Interview Distress Protocol and addition of relevant support group as a means of support for distressed participants**
1.0	**26-Aug-2020**	**2.0**	**29-Jul-2022**	**REC/HRA**	**Update to Cover Page (Pg 1)** **Update to Protocol Footer (Pg 1-64)** **Update to Sponsor Contact Details (Pg 2)** **Updates to Contact Details Section (Pg 4-9)** **Update to Study Flowchart (Figure 1 Pg 15)** **Update to 5.1 Schedule of Study Procedures to clarify recommended gestation of delivery (Pg 36)** **Update to 7.1 Medical Research Ethics Approval – committee name**

					included (Pg 44) **Update to 9.3 Data Capture Methods – change of University of Liverpool department maintaining the database (Pg 52)** **Update to 9.4.4 Safety Reports – reference to Safety Plan removed (Pg 54)**

13. REFERENCES

1. Khalil A, Beune I, Hecher K, Wynia K, Ganzevoort W, Reed K, Lewi L, Oepkes D, Gratacos E, Thilaganathan B, Gordijn SJ. Consensus definition and essential reporting parameters of selective fetal growth restriction in twin pregnancy: a Delphi procedure. Ultrasound Obstet Gynecol 2019;53:47-54.

2. Townsend R, D'Antonio F, Sileo FG, Kumbay H, Thilaganathan B, Khalil A. Perinatal outcome of monochorionic twin pregnancies complicated by selective fetal growth restriction according to management: a systematic review and meta-analysis. Ultrasound Obstet Gynecol 2019;53:36-46.

3. Buca D, Pagani G, Rizzo G, et al. Outcome in monochorionic twin pregnancies with selective intrauterine growth restriction according to the umbilical artery Doppler pattern of the smaller twin: a systematic review and meta-analysis. Ultrasound in Obstet and Gynecol 2017;50:559-68.

4. Townsend R, Khalil A. Twin pregnancy complicated by selective growth restriction. Curr Opin Obstet Gynecol 2016;28:485-91.

5. Monaghan C, Kalafat E, Binder J, Thilaganathan B, Khalil A. Prediction of adverse pregnancy outcome in monochorionic- diamniotic twin pregnancies complicated by selective fetal growth restriction. Ultrasound Obstet Gynecol 2019;53:200-207.

6. Khalil A, Thilaganathan B. Selective fetal growth restriction in a monochorionic twin pregnancy: a Dilemma for clinicians and a challenge for researchers. Ultrasound Obstet Gynecol 2019;53:23-25.

7. Ishii K, Nakata M, Wada S, et al. Feasibility and preliminary outcomes of fetoscopic laser photocoagulation for monochorionic twin gestation with selective intrauterine growth restriction accompanied by severe oligohydramnios. The Journal of Obstetrics and Gynaecology Research 2015;41:1732-7.

8. Chalouhi GE, Marangoni MA, Quibel T, et al. Active management of selective intrauterine growth restriction with abnormal Doppler in monochorionic diamniotic twin pregnancies diagnosed in the second trimester of pregnancy. Prenatal Diagnosis 2013;33:109-15.

9. Heazell AE, Siassakos D, Blencowe H, Burden C, Bhutta ZA, Cacciatore J, et al. Stillbirths: economic and psychosocial consequences. Lancet 2016;387:604-16.

10. Marlow N, Wolke D, Bracewell MA, Samara M. Neurologic and developmental disability at six years of age after extremely preterm birth. N Engl J Med 2005;352:9–19.

11. Brodszki J, Morsing E, Malcus P, Thuring A, Ley D, Marsal K. Early intervention in management of very preterm growth-restricted fetuses: 2- year outcome of infants delivered on fetal indication before 30 gestational weeks. Ultrasound Obstet Gynecol 2009;34:288–96.

12. Morsing E, Asard M, Ley D, Stjernqvist K, Marsal K. Cognitive function after intrauterine growth restriction and very preterm birth. Pediatrics 2011;127:e874–82.

13. Royal College of Obstetricians and Gynaecologists. Green-top Guideline No. 51. Management of Monochorionic Twin Pregnancy. November 2016.

14. Inklaar MJ, van Klink JM, Stolk TT, et al. Cerebral injury in monochorionic twins with selective intrauterine growth restriction: a systematic review. Prenatal Diagnosis 2014;34:205-13.

15. Sileo FG, Duffy JMN, Townsend R, Khalil A. Addressing the variation in outcome reporting in high risk twin studies: The key to reducing research waste and improving clinical care. Ultrasound Obstet Gynecol. 2018 Aug 6. doi: 10.1002/uog.19192. [Epub ahead of print].

16. Rustico MA, Consonni D, Lanna M, et al. Selective intrauterine growth restriction in monochorionic twins: changing patterns in umbilical artery Doppler flow and outcomes. Ultrasound Obstet Gynecol 2017;49:387-93.

17. Boynton and Greenhalgh. Selecting, designing, and developing your questionnaire. BMJ 2004;328:1312–1315.