Sheffield Children's NHS
NHS Foundation Trust

Assessment of Diagnostic Accuracy of Indocyanine Green Fluorescence Imaging in Children and Young People with Testicular Pain Requiring Surgical Exploration

Is ICG imaging safe and accurate to predict testicular torsion?

STUDY NUMBER SCH 2769

IRAS: 1008108

ISCTRN -

16/6/2024 Version 3

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LAY SUMMARY

Testicular torsion is a time critical condition for children and young people (CYP). It is difficult to diagnose without an operation. Missing it means the child will lose a testicle. There are no good diagnostic tests, only tests that delay the child's journey to theatre, which puts them at further risk of losing the testicle. Most boys with a painful testicle get a surgical exploration to see if it is torsion and to twist and fix it. Up to 85% of children having surgery will not have torsion. They will have something they didn't need surgery for. We want to see whether a new, low risk, fast investigation could be used to diagnose the problem, meaning no torsions are missed and less children have unnecessary surgery.

SIGNATURE PAGE

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

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

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

For and on behalf of the Trial Sponsor:

Signature: Date:

..../...../.....

Name (please print):

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Position:

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Chief Investigator:

Signature: Date:

..../...../.....

Name: (please print):

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Statistician:

Signature: Date:

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Name: (please print):

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Position:

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Key Trial Contacts

Chief Investigator / Site PI (Sheffield Children's Hospital)	Ms Caroline MacDonald University of Sheffield Sheffield Children's Hospital Western Bank Sheffield, S10 2TH carolinemary.macdonald@nhs.net
Sponsor	Sheffield Children's NHS Foundation Trust Western Bank Sheffield, S10 2TH
Sponsor Representative	Dr Keith Pugh Research & Development Manager Research & Innovation Care Group Sheffield Children's NHS Foundation Trust Western Bank Sheffield, S10 2TH **scn-tr.research.governance@nhs.net**
Funder	The Children Hospital Charity D Floor Stevenson Wing SCNFT Western Bank, Sheffield, S10 2TH Telephone: 0114 226 7980
Trials Pharmacist	Sheffield Children's Hospital: Laura Godden Lead Trials Pharmacist Pharmacy Department Sheffield Children's Hospital Sheffield, S10 2TH laura.godden1@nhs.net

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	Jayne Clements Clinical Trials Pharmacy Technician Pharmacy Department Sheffield Children's Hospital Sheffield, S10 2TH jayne.clements@nhs.net 0114 226 0560
Statistician	Kathleen Baster University of Sheffield Western Bank Broomhall S10 2TN k.baster@sheffield.ac.uk

i. List of Abbreviations

AE – Adverse Event

C&C – Capacity and Capability

CI – Chief Investigator

CRF – Case Report Form

CTIMP – Clinical Trial of an Investigational Medicinal Product

CYP - Children and young people

DMEC – Data Monitoring Committee

GA – General Anesthetic

GCP – Good Clinical Practice

GDPR – General Data Protection Regulation

HRA – Health Research Authority

ICG – Indocyanine green fluorescence

IMP – Investigational Medicinal Product

IV – Intravenous

ISF - Investigator Site File

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MHRA – Medicines and Healthcare Products Regulatory Agency

NIR – Near Infrared Camera

PIS – Participant Information Sheet

PPIE – Patient and Public Involvement and Engagement

R&D – Research & Development

REC – Research Ethics Committee

SAE – Serious Adverse Event

SAR – Serious Adverse Reaction

SCNFT – Sheffield Children's NHS Foundation Trust

SOP – Standard Operating Procedure

SUSAR - Suspected Unexpected Serious Adverse Reaction

TUoS – The University of Sheffield

ii. Trial Summary

Trial Title	Assessment of Diagnostic Accuracy of Indocyanine Green Fluorescence Imaging in Children and Young People with Testicular Pain Requiring Surgical Exploration.	
Short Title	Is ICG imaging safe and accurate to predict testicular torsion?	
Clinical Phase	Iv	
Trial Design	Prospective Cohort Study of Diagnostic Accuracy	
Trial Participants	Male Children ages 0 – 19 with identified painful testis going to theatre for scrotal exploration	
Planned Sample Size	107	
Planned Trial Period	24 months	
	Objectives	**Outcome Measures**
Primary	A. Diagnostic Accuracy of ICG for torsion versus non torsion findings at surgery	A. Diagnostic Accuracy- NPV / PPV/ sensitivity/ specificity
Secondary	B. Diagnostic Accuracy of ICG for torsion versus non	B. Diagnostic Accuracy- NPV / PPV/ sensitivity/ specificity

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	torsion findings at 12 months follow up	
Investigational Medicinal Product(s)	Indocyanine green	
Formulation, Dose, Route of Administration	Intravenous injection 2.5 mg indocyanine green reconstituted with manufacturer solvent 0.2 mg/kg will be made for infants up to 2 years (maximum 2.5mg) 2.5mg > 2 years of age. i.e., 0.5ml of 2.5 mg/ml NB not to reconstitute in sodium chloride (dextrose if no manufacturers solvent)	
Planned Study Sites	Sheffield Children's NHS Foundation Trust	

iii. Trial Roles and Responsibilities

The Sponsor of the trial is Sheffield Children's Hospital NHS Foundation Trust, who will hold overall responsibility for the trial. The trial will be managed by the Chief Investigator (CI), Ms Caroline Macdonald.

•**Chief Investigator (CI)** – The CI, Ms Caroline MacDonald, will have overall responsibility for the design, set-up, conduct, coordination and management of the trial, and for investigational medicinal product (IMP) drug supply and pharmacovigilance. This includes trial authorisation (responsibility for the protocol and obtaining approvals from the Medicines and Healthcare products Regulatory Agency (MHRA), Research Ethics Committee (REC) and site Research & Development (R&D) departments); ensuring that the trial is conducted according to the UK Clinical Trials Regulations, and to Good Clinical Practice (GCP) and assessment of serious adverse events (SAEs) and expedited reporting of any suspected unexpected serious adverse reactions (SUSARs) to the MHRA.

•**Trial Sponsor** – The Sponsor, Sheffield Children's Hospital NHS Foundation Trust, will hold responsibility for overall project oversight and will be responsible for trial initiation management.

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•**Trial Statistician** – The trial statistician, Kathleen Baster, at TUoS will oversee the statistical aspects of the trial, including drafting of the analysis plan, the conduct of analyses and the reporting of results.

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1.0 BACKGROUND

Torsion is a condition whereby the testis twists its suspensory axis containing its blood supply. It is left more than 6-10 hours the resulting injury, ischemia, is such that the testis is likely to die. Leading to loss of testis. It presents itself as testicular pain. But there are other not so serious causes of testicular pain which do not need surgery. These can be difficult to identify. Previously the mantra for surgeons in cases of testicular pain in children and young people is to explore[1,2] due to the poor diagnostic tools available to us and the litigious risk of missing a torsion [3]. That being said, unnecessary surgical exploration is not without risk[4]. A growing number of paediatric surgeons are questioning this ethos and are looking for diagnostic procedures to identify true torsion and to decrease unnecessary explorations [5]. Ultrasound is being tested to predict torsion. The diagnostic accuracy is moderate[6]. It is user dependent and the process to diagnosis can be slow and has been shown to increase testicular loss[7]. Indocyanine green (ICG) is an interesting technology. It is novel imaging technique whereby an intravenous injection of a fluorescent dye is given and imaged with a near infra-red spectrum camera. It accurately shows flow and perfusion to organs, and has been used in case studies to show flow or no flow in testes at surgery to aid surgical decision making in torsion[8,9]. The technology requires an injection of dye which is commonly used in laparoscopic, robotic and ophthalmic surgery in children [10]. Side effects include hot flush, nausea and vomiting and itching. Bronchial spasm is rare with 1 case in 82 prospectively monitored patients but other studies putting the rate much lower[11]. Generally, ICG is quoted at 1/40,000 for anaphylactic reaction.

We aim to investigate ICG as a diagnostic tool for torsion. We hypothesise that ICG could be used as an immediate test performed by the surgical team to diagnose torsion or non-torsion in children and young people (CYP) with painful testis. We aim to perform a study which does not disrupt the current pathway of patient care to test the diagnostic accuracy of ICG. There will be no delay from the imaging and therefore will not put any CYP at increased testis loss.

The study will be of benefit to CYP as it could highlight a diagnostic technique to avoid missing any torsion of testis in future and decrease children having unnecessary surgery for a non-surgical condition of the scrotum.

2.0 TRIAL AIMS AND OBJECTIVES

The objective of the study is to develop a protocol with which ICG might be used to safey and effectively diagnose torsion of testis opposed to non torsion, through transcutaneous imaging. Once the protocol is established the longer term aim is to calculate diagnostic accuracy for a new

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application of imaging technology for the detection of torsion and non-torsion in the setting of testicular pain in children. It aims in the longer term to validate or refute ICG to change care pathways and improve patient care.

2.1 Primary and Secondary Objectives

Primary aim:

Develop the diagnostic pathway and calculate the diagnostic accuracy for torsion of testis versus non-torsion diagnoses of ICG imaging in the setting of testicular pain requiring surgical intervention.

Secondary aim:

To understand the diagnostic value of ICG by skin type and tanner stage

To establish the protocol for application for a multicentre study to validate diagnostic accuracy of ICG for torsion.

2.2 Primary and Secondary Endpoints

Primary end point:

- Diagnostic accuracy of ICG for testicular torsion as compared to non-torsion diagnosis.

Secondary end points:

- ICG diagnostic accuracy by tanner stage and skin pigmentation
- ICG to predict late testicular atrophy
- Adverse reactions from ICG injection

3.0 TRIAL DESIGN

Children being taken to theatre for testicular pain for suspected torsion over a 1-year period will be registered prospectively. A clerking proforma will be utilised for all children with testicular pain with details including duration of pain, presentation pathway, address, dob, ethnicity, tanner stage, comorbidities and the standard questions in a clerking for children with testicular pain. Patient identification pathway and consent process are shown in Appendix 1. The children will be identified only by the participants clinical care team. Children proceeding to theatre will be consented for an intravenous injection of ICG within their consent for surgery by appropriately GCP trained and delegated study team members. The CI will spend time on launch of project training and clarifying consent procedures with the junior clinical team. Exclusion criteria will be clearly communicated and an info graphic to aid families in decision making for consent will be provided (Appendix 2).
Data collection form for clerking is found in Appendix 3 form 1.

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Age-appropriate information leaflets will be provided, and consent and assent taken as appropriate from potential participants and their guardians (if required). Children having consented will have allocation of a participant ID by the CI Ms MacDonald, CI will update the participant number on Edge. They will then proceed for an intravenous injection of indocyanine green after safe establishment of anaesthetic and with the surgical team present. A video recording will be initiated at injection of ICG and record make for 2 minutes, until the dye dissipates. A still image will be taken at 30 seconds post injection. The images are taken using a specialist near infra-red (NIR) camera. This is a new imaging system for SCNFT, but technology used at Sheffield Teaching Hospitals and in other children's hospitals in the country. When utilising a theatre stacker NIR camera head the images will be taken under the category ICG scrotum on the theatre tablets. These will be stored on a tablet and printed from the theatre stack and exported to the server as standard practice for all images in the surgical department. Participant ID will be attached to the images and the images will be stored in the electronic notes. When utilising the hand help devices the images are simply stored on the device.The diagnostic green IC flow device will be kept with the ICG in a locked cupboard. It will be calibrated prior to use using the reference cards. A photo will be taken of the patient details. As above a video will be taken from injection of ICG for 2 minutes and a still image at 30 secs.. The research team will download these images and store than marked with the participant study number. The investigating research team member will be blinded to the patient details. Process in theatre in described in Appendix 4.

The findings at surgery will be recorded and describe torsion, degree of torsion, colour at surgery, bleed time. Appendix 3, form 2 describes data collection taken in theatre. Fixation will proceed as standard practice.

There will be no change in the patient pathway for acute scrotum. Any adverse events will be monitored via immediate reporting of side effects to PI Caroline MacDonald, see Appendix for theatre protocol.

At 10 participants, there will be a planned interim analysis by a Data Monitoring Committee. This interim analysis will assess how the ICG works in non-torsion and torsion cases if available in the early findings of the data collected. The DMEC will use these findings to decide about continuing with the study.

All recruited children will have a follow up appointment at 12 months to check testicular status and any adverse events. Ideally these will be face to face, but where that might pose difficulty to the family, a telephone appointment can suffice.

Early analysis of ICG findings with surgical findings will be undertaken. A study investigator (BMedSci Student from University of Sheffield), independent of the surgical or radiology team, blinded to surgical outcomes will assess the printed and electronic images and assess for dichotomous and graduated fluorescence findings. Data collection form is shown in Appendix 3, form 3. These then

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will be compared to surgical outcomes and diagnostic accuracy evaluated using standard diagnostic accuracy calculations. Outcomes will be compared by time to presentation, age and racial identification.

Recommendations for pause and interim analysis have been made by the peer reviewers to refine to protocol. The second phase of the protocol will include a pause and interim analysis at 20 patients, ie 10 with the increased dose of ICG, and the revised timings.

The study starts with the first child recruited and taken to theatre for ICG assessment and closes when the final child receives their 12 month follow up call.

4.0. RECRUITMENT PROCESS

The planned recruitment period for the trial is 12 months.

4.1 Eligibility

4.1.1. Inclusion Criteria

All children presenting with testicular pain, being taken to theatre for scrotal exploration at Sheffield Children's NHS Foundation Trust. Aged 0-19 years of age.

4.1.2 Exclusion Criteria

Children with any allergy to contrast medium or iodine will be excluded.

Any family where parents or young person refuses consent.

CYP 16-18 years but lacking capability for informed consent

Children without a GP will not be exempt from recruitment. No information is required from community care.

4.2 Identification and Approach

The children will be identified by utilising a clerking database which will automatically report children presenting with testicular pain.

Potential participants will be approached by the Surgical Registrars with age-appropriate PIS documents. The data flow process has been refined so that completed case report forms in a box on ward 1 allow the study team to identify patients for the study.

4.4 Informed Consent

Participants will only be enrolled onto the trial once they or their accompanying parent or legal guardian (children) give fully informed, written consent. Older children may be asked to read and sign (with the accompanying signature of their parent/legal guardian) an assent form if deemed developmentally appropriate by the member of the research team receiving consent and in accordance with parent/legal guardian's judgement.

Written consent must be obtained before any trial-specific procedures or intervention are performed.

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The consent for the study will take place alongside the standard SCNFT surgery consent being taken for progression to theatre for exploration of scrotum. A member of the study team appropriately delegated will complete the consenting process. Training of the recruiting team will be undertaken by the CI.

All consent forms will be stored in accordance with local requirements. A copy of the consent form (and assent form if relevant), will be given to the participant, a copy entered into the participant's clinical record and the original signed copy kept in the ISF.

This study will be conducted in compliance with the protocol, GCP and the applicable regulatory requirements.

Consent for the study will follow standard age and competency guidelines. Age-appropriate information leaflets will be provided. Consent will be undertaken by the surgical registrar or middle grade who have GCP training, and will be supported by the study Sub PIs. Attempts will be made to utilise translators either face to face or via language line for those where consent cannot be taken in English. A family friendly study summary will be provided to aid communication in an emergency setting, where consent will need to be obtained in 15 minutes. All children going to theatre are appropriate for recruitment if consent is given, with no tests required for eligibility. The children will be enrolled utilising a clerking database which will automatically report children presenting with testicular pain.

4.6. Withdrawal of Participants

Participants remain free to withdraw at any time from the study without giving reasons and without prejudicing any future treatment. If the participant is willing to provide a reason for the withdrawal, this should be recorded on a Trial Withdrawal log. Data collected up to the point of withdrawal will remain within the study analysis.

5.0. IMP MANAGEMENT

5.1 Trial IMP

The trial intervention includes an intravenous injection of indocyanine green. A Summary of Product Characteristics can be found in Appendix 4.

The product of interest is Indocyanine Green, which is marketed as Verdye Indocyanine Green 5mg/ml (25mg) powder for solution for injection by Kimal PLC. It is licensed in the UK but not for the indication of use in this trial. The drug is supplied in a box of 5 vials.

Manufactured by Kimal PLC Unit 10A Clayfield Road, Worcester Six Business Park, Worcester, Worcestershire, WR4 OAE, United Kingdom.

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Stock will be procured by the Pharmacy Procurement Team at Sheffield Children's Hospital. Procurement and supply records will be kept on the Careflow Medicines Management (CMM) System.

5.2 – IMP Storage and Supply

The IMP is stored in ambient conditions 15°C to 25°C and is subject to temperature monitoring. Pharmacy will risk assess the storage area to ensure it is suitable before the trial starts.
Trial medication will be stored and dispensed by the sponsor's Pharmacy Department in accordance with Good Clinical Practice.

5.3 – IMP Preparation

The dye is prepared by dissolving the powder (25mg) in 10ml of sterile H2Oto make a solution of 2.5mg/ml.

5.4 – IMP Administration

Injection of the indocyanine green fluorescent dye (ICG) will be performed by the anaesthetic practitioner after safe establishment of anaesthetic.
An IV injection of:
0.2 mg/kg will be made for infants up to 2 years (maximum 2.5mg)
2.5 mg > 2 years of age. i.e., 1ml of 2.5 mg/ml
This dosing has been refined by the initial 10 recurits with no side effects, slightly limited views and through literature support 13 i
The route for effective visualisation of perfusion is intravenous. The child will already have an IV cannula. Perfusion can be visualised immediately and disappears at 3 minutes. This is a prescription only medication. The surgical team or anaesthetic team will be responsible for the prescription and dosing of the ICG dye. The injection will be signed for as standard practice and left over solution disposed of via standard procedure, via yellow bins in theatre. The team will fill out the pharmacy log and record the vial number in the notes.
The injection and photography are a one-off event with no long lasting effects. Most symptoms can be managed during the anaesthetic. Emergency drugs are available in theatre and crash trolleys are available outside theatre 2 in the unlikely event of anaphylaxis. The fluorescent effect and image capture offers no risk to the child. ICG dye is excreted via the biliary system with no impact on renal function.
No medications are contraindicated alongside the ICG.
The trial will start with the first child enrolled and ends with the 107th child completing 12 months of follow up.

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5.5- Management of known IMP related harms

The side effects of ICG angiography in children, not under general anaesthetic, include nausea and vomiting 19%, itchy skin 2%, hot flush 2%, bronchial spasm 3%. In a larger meta-analysis no severe adverse reactions were described. The risks are similar to the risks of CT contrast use reported at 1/42000 for an anaphylactic reaction. Use of ICG should be avoided in those with previous anaphylactic reactions. Similarly, ICG injection contains iodine and should be avoided with those with an iodine allergy. If a serious adverse reaction occurs the child will be under anaesthetic and cared for by the anaesthetic team, as is standard for drug reactions. If an adverse reaction rate to ICG injection of >3 % is noted the study will be abandoned.

5.6- Drug Accountability

10 vials of the ICG will be kept in the theatre and be labelled appropriately 'For Clinical Trial Use Only'. The Chief Investigator will be responsible for maintaining the stock levels and supply in theatres. The Chief Investigator will be accountable for the ICG within the Trust. The Chief Investigator will maintain accountability records within theatre and record details of the patients that the drug has been administered to.

Pharmacy will set up and maintain accountability records for the IMP in a pharmacy site file. This will include receipt documentation, record of IMP issued to theatre and storage of the requisition forms.

5.7 – IMP Destruction

Part used vials of Verdye Indocyanine Green will be disposed of in pharmaceutical waste bin in theatre and any expired stock will be returned to pharmacy for disposal as per the local disposal SOP.

6.0. TRIAL PROCEDURES

6.1 Data Collection

A clerking proforma (See Appendix 3, form 1) will be used for children assessed with testicular pain by the surgical directorate. The patients will be identified, and a prospective list will be curated by the Chief Investigator. Adverse reactions will be monitored contemporaneously. Reporting details will be publicised in theatres for severe unexpected or anaphylaxis (see Appendix 4 and 6). The case report forms will be kept as paper copies in a secure office on NHS property and will be destroyed 5 years after the study. Similarly, images will be stored on a tablet device on NHS property and deleted after 5 years of study completion. Outcomes at surgery and 1 year post op will be collected and destroyed after 5 years of study completion.

6.2- Data Analysis

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Outcome data of findings at surgery will be compared to ICG findings. Data will be analysed using 4 x 4 tables to create diagnostic accuracy scores. Focusing on sensitivity, specificity, negative predictive value and positive predictive value. This does not require statistical support. Sub-group analysis will similarly require no additional statistical analysis.

Repeat analysis will take place 12 months later to look at long term outcomes following torsion, and ICG accuracy in this setting.

6.3 – End of Trial

The end of the trial will be after the last recruited child has completed 12 months follow up in clinic.

7.0. DATA MANAGEMENT

7.1. Source Data

The child will undergo a clerking on an electronic form, which is designed with confidentiality in mind. The form is on NHS login Microsoft forms and can be uploaded on the junior surgeon's hospital tablets direct to the child's electronic notes. The clerking is standard protocol and asks no more than a standard assessment should. Following this the junior surgeon has no more interaction with the source data. The images will be taken by the surgical team and uploaded to the hospital server which has IT governance sign off. Following this the surgical team will have no further interaction with the data. Both pieces of data will be allocated a participant ID and will be analysed anonymously by the BMedSci student or the study team. The PI will have oversight of the child details and the participant ID. The University of Sheffield Student will have no access to patient identifiable details.

7.2. – Data Handling and Storage

The Chief Investigator will be responsible for data handling. Data will be collected and retained in accordance with the Data Protection Act 2018. The images will be kept as paper copies in a secure office on NHS property and will be destroyed 25 years after the study. Similarly, images will be stored on a tablet device on NHS property and deleted after 25 years of study completion. Outcomes at surgery and 1 year post op will be collected and destroyed after 25 years of study completion. A letter will be included in electronic records clearly documenting inclusion and a letter to the GP send describing trial inclusion at discharge.

7.3. Access to data

The sponsor will permit monitoring and audits by the relevant authorities, including the Health Research Authority, Research Ethics Committee and inspection by the Medicines and Healthcare products Regulatory Agency (MHRA). The investigator will also allow monitoring and audits by these bodies and the sponsor, and they will provide direct access to source data and documents.

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7.4. Data Sharing

The source data is only to be contributed to by those directly involved in the child's care and working at Sheffield Children's NHS Foundation Trust. The data will be anonymised for use for the University of Sheffield Student so will have no breach of confidentiality. The sharing of data will in line with GCP and GDPR. It will only be accessible on NHS VPN.

7.5. Study File Management

The trial will use a paper Investigator Site File (ISF). This will be kept on an NHS site, in a locked filing cabinet in the SCH NHS Site.

7.6. Archiving

Archiving will be authorised by the Sponsor following submission of the End of Trial Report. All essential trial documents including source documents will be archived in accordance with the SCH Data Management Plan and Archiving SOP for a minimum period of 25 years after trial completion. Destruction of essential documents will require authorisation from the Sponsor. Where permitted by the site NHS Trust, a sticker stating the date after which the documents can be destroyed will be placed on the inside front cover of the clinical record/healthy volunteer file.
The archiving of trial documents and data at site (including consent forms) will be done according to participating site Trust policies and SOPs. Document retrieval from the archive documented will be fully auditable.

8.0. TRIAL MONITORING

The trial will be monitored and audited in accordance with the Monitoring Standard Operating Procedures of the Directorate of Research & Innovation at Sheffield Children's NHS Foundation Trust. All trial related documents will be made available on request for monitoring and audits by the sponsor, the relevant Research Ethics Committee and for inspection by the MHRA or other licensing bodies.

9.0 PHARMACOVIGILANCE

9.1. Definitions

The collection and reporting of data on adverse events and serious adverse events will be in accordance with ICH GCP and the UK Policy Framework for Health and Social Care Research. Monitoring and reporting of pharmacovigilance aspects of the trial will be performed in accordance with the SCH Pharmacovigilance SOP.

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Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence within 24 hours of surgery as a result of the IMP administration that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Unexpected Adverse reaction	An adverse reaction the nature of which is not consistent with the Reference Safety Information for the IMP in question.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product.

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9.2. AE Reporting

The AE reporting period for this study begins as soon as participants have consented to the study and ends 48 hours after the final trial visit. The site research team will be responsible for collecting AE

data and entering data into study AE log. All directly observed AEs and all AEs spontaneously reported by the participant will be recorded.

9.3. Recording and reporting of SAEs, SARs and SUSARs

All SAE's will be reported to the MHRA and the CI will let the R&D department know about the event. SAEs would be consistent of contrast allergy. SUSARs by their nature are unpredictable. The CI will maintain vigilance over any concerns regarding the contrast side effects and has a clear pathway for reporting, see appendix 3.

9.4. Responsibilities for safety reporting

Chief Investigator (CI) / delegate or independent clinical reviewer:

1. Clinical oversight of the safety of volunteers participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgment in assigning seriousness, causality and expectedness of SAEs (in line with the Reference Safety Information) where it has not been possible to obtain local medical assessment.
3. Using medical judgement in assigning whether an event/reaction was anticipated or expectedness in line with the Reference Safety Information.
4. Immediate review of all SUSARs.
5. Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.

Principal Investigator (PI):

1. Checking for AEs and ARs when participants attend for trial visits.
2. Using medical judgment in assigning seriousness, causality and whether the event/reaction was anticipated using the Reference Safety Information approved for the trial.
3. Investigators will report any SAEs, SARs and SUSARs occurring in a participant immediately within 24 hours of discovery of the event to the Sponsor by completing the SCH SAE Report Form and sending a high importance email to scn-tr.research.governance@nhs.net with the phrase "SAE Report" in the email subject. The reporting study team member must then call the research office on 0114 271 7417 to inform a member of the research team of a reported SAE. The telephone number and email of the account will be monitored Monday – Friday 9-5pm.

9.6.Safety Assessments

The risk of the study is the risk from injection of the ICG fluorescence dye. The risk of this compares with other contrast dyes which are utilised commonly in paediatric practice. The risks have been

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described as above with hot flush, itching, nausea and vomiting and rarely bronchospasm. The family will be fully consented for this. The prospective nature of data collection with oversight of side effects by the chief investigator will identify an excessive risk and if this is found to be the case the study will be abandoned. Drug reactions will be collected as detailed in Appendix 6, with any serious adverse events being highlighted.

9.6.1 Stopping/discontinuation rules and breaking of randomisation code

The study will be abandoned if the serious adverse event rate goes over 3%.
Adverse events will be recorded in accordance with Pharmacovigilance Standard Operating Procedures of the Directorate of Research & Innovation at Sheffield Children's NHS Foundation Trust. Reporting will follow standard Heath Research Authority guidance (https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/). With reporting of any serious unexpected adverse events through the local REC and Urgent Safety Measures to MRHA Clinical Trials Unit.
Stopping/discontinuation rules and breaking of randomisation code
Breaking of randomisation is not applicable. The study will end early if ≥3% participants suffer a SUSAR.

10. FINANCE AND INDEMNITY

No payments will be made to participants. This would be considered an ethical compromise. Interviews with families will be undertaken virtually and not incur any costs. Costs are for technologies and materials and study supervision only.
This is an NHS sponsored study. For NHS sponsored research HSG (96) 48 reference no. 2 refers. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity will cover NHS staff, medical academic staff with honorary contracts and those conducting the trial. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

10.2. Justification of Finance

A near infra-red stack could be purchased or hired. On investigation with Arthex, our supplying theatres AV technologies company, a new purchase of a stack is approximately £73,822; whilst hire for 1 year is quoted at £4800. The project has developed after discussion with the Arthex representatives and therefore I would be unkeen to work with other AV companies due to the contribution of the Arthrex team to study design. The other benefit of using Arthrex is the stacker will be compatible with SCNFT current theatre systems and the middle grades are familiar with the

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technology. We will be able to upload the images to the server and will allow us to upload to PACS to allow image manipulation. To test the technology with stack loaned to us, we will need to fund in addition to the AV stack, the ICG dye. This is dosed for children but needs 1 vial per child. Each vial is £97. We would make an initial suggestion of 120 vials to complete the study aim and to leave 13 vials for waste. This is a cost of £11,640. We have made an application, and been successful, for a medical student to undertake image analysis and study investigation for their BMEDSCi programme. The chief investigator can offer 1 PA per month for the project suggesting £3000 for each year of the study period. I would ask for £2000 to hire a software specialist to write a database that links in with NHS email to maintain confidentiality and allow automatic enrolment and identification of participants.

10.3 JUSTIFICATION OF RESOURCES

Whilst the initial outlay for the hiring of the ICG dye and near infra-red imaging stack will involve charity money and involves and initial outlay; long term envisioning of the potential benefits of the technology pertain to the impact of missed torsion and unnecessary exploration. Missed torsion costs the UK approximately £1million per year with 4-5 claims worth £200,000 per claim a year. The funding of 100 unnecessary explorations per year could be calculated as part of the project. If ICG is shown to be effective in diagnosis of torsion or non-torsion it will provide considerable cost savings to the Trust ongoing.

11. STATISTICAL ANALYSIS

11.1. Sample Size

Calculation of sensitivity, specificity, negative predictive value and positive predictive value will be undertaken. Calculation of diagnostic accuracy will entail simple 2 x 2 contingency tables. Repeat analysis will be undertaken by discriminatory demographic. Including age, tanner stage, time from onset to theatre and ethnicity. Discussion with Statistical Specialists at University of Sheffield confirmed the decision making regarding statistical methodology.

Sample size calculation

Utilising calculations provided by Bujang and Adnan 14 a sample size of 107 is required to describe diagnostic accuracy of a disease with a prevalence in the sample of 20%-30% with a sensitivity acceptability of 80%. Between 159 and 200 children are reviewed in a year with a painful testicle and are taken to theatre. There will a predicted refusal of consent rate of 30% we hope to recruit approximately 107 young people in 12 months data collection.

11.1.2 End of Trial

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Results will be published in a high impact paediatric publication and will be nationally leading in validating this technology for assessment of paediatric torsion. The aim will be to present at a high impact national meeting.

This study will validate the technology to allow a larger study with application for a larger research grant to buy a stacker for the department to randomise care between surgery and ICG to assess family acceptability.

11.1.3 IMPACT

We will provide the diagnostic accuracy of ICG for torsion of testis and non-torsion. This will avoidance of missed torsion and decreased unnecessary exploration in children who do not require it. It could change the National, European and International landscape of the care of children with testicular pain. This study is unique and could place SCNFT at the forefront of exploring new technologies for disease with great health inequity and lead on management approaches worldwide.

11.2 Primary Outcome Analysis

Calculation of sensitivity, specificity, negative predictive value and positive predictive value of ICG image capture compared to findings at surgery, i.e. torsion or not torsion, will be undertaken. Repeat analysis will be undertaken by discriminatory demographic. Including age, tanner stage, time from onset to theatre and ethnicity. This will not require statistical support.

11.3 Secondary outcome analysis

Calculation of sensitivity, specificity, negative predictive value and positive predictive value of ICG image capture compared to findings at 12 months following surgery, i.e. testicular presence or loss, will be undertaken. Repeat analysis will be undertaken by discriminatory demographic. Including age, tanner stage, time from onset to theatre and ethnicity. This will not require statistical support.

12. ETHICAL AND REGULATORY CONSIDERATIONS

12.1. Regulatory Compliance

The trial will be performed subject to Research Ethics Committee (REC) favourable opinion, MHRA Clinical Trial Authorisation, and Sponsor and NHS Trust site permissions. The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant subsequent amendments; the International Conference for Harmonisation of Good Clinical Practice (ICH GCP) guidelines; and the UK Policy Framework for Health and Social Care Research. Before a site can enrol participants into the study, a Capacity and Capability (C&C) assessment must be completed and confirmed by the site R&D department.

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12.2. Amendments

Under the Medicines for Human Use (Clinical Trials) Regulations 2004, the Sponsor may make a non-substantial amendment at any time during the trial. There is no requirement for investigators to notify the MHRA of non-substantial amendments; however, the REC and HRA must be notified.
If the Sponsor wishes to make a substantial amendment, all amendments will be submitted via the Combined IRAS Gateway. The MHRA and/or the REC will provide a response regarding the amendment within 35 days of receipt of the notice.
It is the Sponsor's responsibility to decide whether the amendment is substantial or non-substantial for the purposes of submission to the MHRA and/or REC.
Amendments also need to be notified to the participating site R&D departments to assess whether the amendment affects continuing C&C confirmation for that site.

12.3. Non-Compliance

Protocol and GCP non-compliances are defined as departures from the approved protocol and/or principles of GCP identified during study implementation, data management checks and/or monitoring visits. Such non-compliances are further categorised according to the following criteria:

- Deviation – a planned or unplanned departure from the protocol or the conditions or principles of GCP that does not increase risk or decrease benefit; or have a significant impact on participant rights, safety or welfare, and/or on data integrity.
- Violation – an unplanned departure from the protocol or the conditions or principles of GCP that does increase risk or decrease benefit; or may have an impact on participant rights, safety or welfare, and/or on data integrity.
- Serious breach – a breach of the protocol or of the conditions or principles of GCP which is likely to affect to a significant degree either the safety or physical or mental integrity of the participants of the study; or the scientific value of the trial.

Planned deviations may be permitted if they are in place to protect participant safety, rights and welfare, but they should not become standard practice, and if necessary a protocol amendment should be considered. Planned deviations or waivers relating to eligibility criteria will not be permitted. Accidental protocol deviations can happen at any time. They will be adequately documented on the relevant forms and reported to the CI and Sponsor. Prospective or planned violations or serious breaches will not be permitted under any circumstances.

12.4. Ethical Considerations

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 52nd World Medical Association General Assembly, Edinburgh, Scotland, 1996.

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This is a CTIMP as defined by the EU Directive 2001/20/EC. Therefore a Clinical Trial Authorisation (CTA) is required before the trial can commence. This trial protocol will form part of the CTA application for submission to the MHRA.

As part of study set-up and before initiation of the trial at any participating site, the protocol, informed consent forms and any material to be given to prospective participants will be submitted to a national REC for approval. Any subsequent amendments to these documents will be submitted for further approval. Each site will provide R&D C&C approval before the trial can be given green light to start recruitment.

Written informed consent will be obtained from participants prior to study enrolment and randomisation. The right to decline study participation without giving a reason must be respected. The participant must remain free to withdraw at any time without giving a reason and without prejudicing his/her/their further treatment. The study will be submitted to and approved by a REC and the site R&D team for each participating site prior to entering participants into the study.

Children are a vulnerable group. Age-appropriate PISs have been developed for potential participants to understand the trial. These will be provided to potential participants to enable the children to be involved in the decision-making process. Assent will be sought in children aged <16 years if appropriate.

We do not expect any SAE as this is an injection used frequently in children in other settings and the risk is quoted at 1/40000.

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12.5. Patient and Public Involvement and Engagement

Initial public engagement work has been completed and is awaiting write-up and presentation at the conference. This supports examination of ICG in diagnostic accuracy from families who have undergone surgery for torsion, and families naïve to torsion. And compares favourably to ultrasound which is already established.

Families Support Selective Use of Ultrasound and Indocyanine Green in the Setting of the Acute Scrotum: Results from an Online Survey.

12.5.1 Introduction

EAU/ESPU guidelines consider diagnostic techniques, such as doppler ultrasound, an adjunct in the evaluation of the paediatric acute scrotum, to aid diagnosis of torsion. Indocyanine green (ICG) fluoroscopy is a novel technique which may have great diagnostic accuracy than ultrasound. We investigated family attitudes to ultrasound and ICG as opposed to immediate surgery in the setting of the acute scrotum.

12.5.2 Patients and Methods

Two surveys were circulated one described the risks of torsion/surgery and ultrasound and the other identical but for ICG. Likert scores were requested in varying scenarios comparing preference for diagnostic technique versus immediate surgery (1 to 5). Families were telephoned from a database of children having undergone scrotal exploration. the form was also shared online and via parents' social-media groups to get the opinions of those naïve to surgery. Results from the surveys were compared using students t test.

12.5.3.Results

A total of 75 families responded, 48 comparing US versus immediate surgery (of whom 26 had undergone scrotal exploration) and 27 considering ICG versus surgery (of whom 17 had undergone scrotal exploration).

For both US and ICG families expressed increasing preference for imaging over immediate surgery, as the doctors' confidence decreased that the diagnosis was torsion.

Overall, no preference for USS versus ICG was found, though for those where the doctors thought it probably wasn't, preference was for ICG over USS. And in the post-surgical exploration group, preference was for ICG ($p<0.05$).

Conclusions

Families and young people support USS and ICG as potential investigations for torsion when torsion is not highly likely. Those that have had surgery favour surgery over ultrasound and favour ICG over surgery.

This confirms families would support injection as opposed ot immediate surgery where diagnosis was equivocal in testicular pain, and this compares favourably with ultrasound. Which is an established diagnostic entity.

13.0 Dissemination

Results will be published in a high impact paediatric publication and will be nationally leading in validating this technology for assessment of paediatric torsion. Aim will be to present at a high impact national meeting.

TABLES, FIGURES AND REFERENCES

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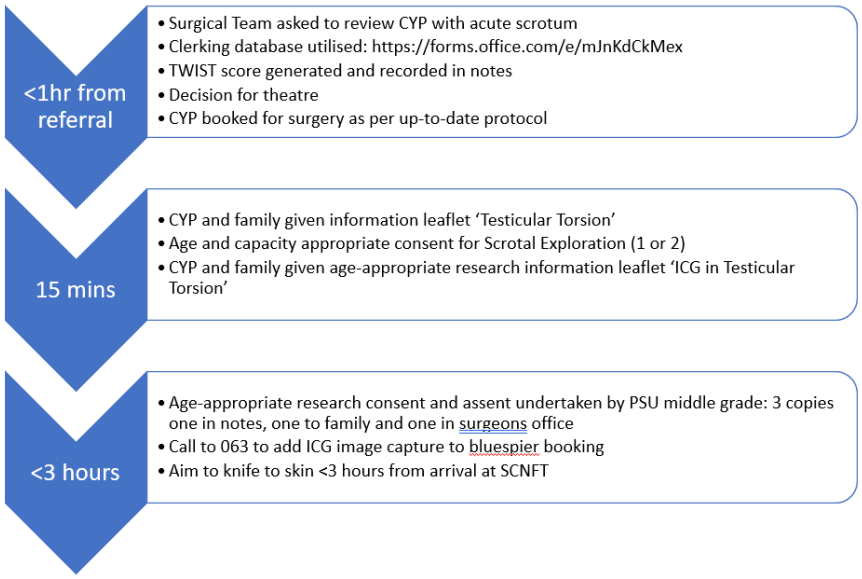
APPENDICES

Appendix 1: Procedure for Identification and Recruitment of Participants



Research Info leaflets available:
0-5 years
6-10 years
11-16 years
16yrs +
Parent / Carers

Exclusion Criteria:
Children with contrast or iodine allergy
Family where parents or young person refuses consent.
CYP 16-18 years but lacking capability for informed consent

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Appendix 2. Data Collection Forms:

Form 1: Patient clerking for CYP presenting with an Acute Scrotum at SCNFT

Patient addressograph

Patient c number
Who presents with child (Role and names):

Patient age
Patient ethnicity demographic:
White
Asian
Black
Other

Presenting compliant
Pain, swelling, erythema
L / R / both testes

Pain localized in scrotum or referring to abdomen

Nausea
Vomited
Precipitating event?
Time of onset of pain, duration of pain
Nature of pain
Pain at rest
Time of swelling
Time of erythema
Urinary symptoms
Feverish
Any other additional symptoms

PMH
PSHx
Last ate and drank / starvation time
Allergies
ASA

Examination
Height weight
Tanner stage
Skin tone: light , medium, dark
Chest
Abdomen
Inspection : red swollen black
Blue dot
Testis present
High riding?
Cremasteric reflex?
Hot

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Swollen
Hard
mass
Tender
TWIST score:
Decision for theatre?

Form 2: Following theatre at time of writing op note:
Patient number

Findings: Torsion / other which side L/R both
Degree of twist xx degree
Bleed time
Outcome : orchidectomy / fixation / not torsion

Form 3: At Rater analysis

Is perfusion present in both testis?
Y / n
Does one side have absent perfusion? L /R / both / neither

Doe one side has worse perfusion? L / R / neither

Is there a relative difference? Estimated percentage difference: xx%

L Midpoint Hounsfield units
R Midpoint Hounsfield units

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Appendix 3a: Procedure for Administration of ICG and data capture using Stacker

Pre-procedure
- Theatre Staff
- Bring NIRS stacker into emergency theatre and ICG from locked cupboard 6
- Patient details into tablet
- Set tablet to ICG research project

Child under GA
- Once safe anaesthetic established, surgeon present
- Time out to check correct patient and side
- Dim lights and anesthetist to Inject ICG & check time
- Take an image of scrotum with NIRS camera at 5 minutes: Capture both testis

Surgery for Acute Scrotum
- Standard approach as per protocol with scrotal exploration
- If torted note degree and colour findings then detort
- If available staff reimage at 5 minutes post detorsion
- Perform bleed test and document time
- Fix or remove as standard. NB do not use NIRS image to guide practice

Post Surgery
- Write operation note as standard
- Note any adverse events email: carolinemary.macdonald@nhs.net / scn-tr.research.governance@nhs.net with the phrase "SAE Report" in the email subject
- On discharge: ensure families have torsion leaflet. If torsion 12 months follow up Urology nurse Sarah Boulby

ICG dose:
<2 years 0.2 mg/kg Max 1.25 mg
>2 years 1.25 mg
NB do NOT reconstitute in NaCl, use manufacturers or dextrose

Side effects to be aware of:
Nausea
Vomiting
Hot flush
Itchy Skin
Severe adverse reaction: Anaphylaxis (risk 1/40000)

Appendix 4:Procedure for Administration of ICG and data capture using Hand heldICG flow machine

Pre-procedure
- Theatre Staff Bring ICG flow device and ICG vial from locked cupboard 6
- Surgeon or theatre staff takes a photo of patient details on ICG device

Child under GA
- Once safe anaesthetic established, surgeon present
- Time out to check correct patient and side
- Dim lights and anesthetist to Inject ICG & check time (anaethetist to sign delegation log)
- Start recording real time ICG flow with NIRS camera from 18 cm.
- Video record from start. Take an image of scrotum at 30 sec. Capture both testis.

Surgery for Acute Scrotum
- Standard approach as per protocol with scrotal exploration
- If torted note degree and colour findings then detort
- Fix or remove as standard. NB do not use NIRS image to guide practice
- Record ICG Vial number on case report form and fill out the pharmacy log form with patient details

Post Surgery
- Write operation note as standard, complete case report form as best as possible
- Note any adverse events email: carolinemary.macdonald@nhs.net / scn-tr.research.governance@nhs.net with the phrase "SAE Report" in the email subject
- On discharge: ensure families have torsion leaflet. If torsion 12 months follow up Urology nurse Sarah Boulby. Case report form and consent forms in box on ward 1

ICG dose:
<2 years 0.2 mg/kg Max 1.25 mg
>2 years 2.5 mg
NB do NOT reconstitute in NaCl, use water or dextrose

2.5 MG for all children > 2 yrs Oct 2024 (1 ml of 25mg in 10mls)

Side effects to be aware of:
Nausea
Vomiting
Hot flush
Itchy Skin
Severe adverse reaction: Anaphylaxis (risk 1/40000)

Appendix 4. Summary of Product Characteristics ICG

This can be found at:

https://mhraproductsprod.blob.core.windows.net/docs-20200128/587f5400e93d096fc30f5e0e44e23ec99caa8b2b

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Appendix 5. ICG in Torsion Study-Wide Adverse Events (AE) Log Template
Project: Is ICG imaging safe and accurate to predict testicular torsion?
Purpose: This template provides a recommended structure for recording and tracking adverse events for the above research study
Audience/User: Caroline MacDonald, PI Sheffield Children's NHS Foundation Trust

STUDY NUMBER SCH 2769 IRAS 2769 **March 2023 v2**
Study/Protocol ID: _ IRAS 2769 Site Name/Number:_SCNFT PI:Caroline MacDonald

Study-wide Adverse Event (AE) Log Template

This log is cumulative and captures adverse events (including serious adverse events) of all participants throughout the study. Each subject should be asked about the presence/absence of AEs at every study visit.

Severity	Study Intervention Relationship	Action Taken Regarding Study Participation	Outcome of AE	Expected	Serious Adverse Event (SAE)
1 = Mild 2 = Moderate 3 = Severe	1= Not related 2 = Unlikely related 3 = Possibly related 4 = Probably related 5 = Definitely related	1 = None 2 = Study intervention modification 3 = Study intervention discontinued 4 = Concomitant medication administered 5 = Subject withdrawn from study 6 = Hospitalization 7 = Other	1 = Resolved 2 = Recovered with sequelae 3 = Ongoing/Continuing treatment 4 = Condition worsening 5 = Death 6 = Unknown	1 = Yes 2 = No (AE is not listed as side effect in Investigator's Brochure, package insert, or as a characteristic of the study condition)	1 = Yes (complete SAE Form) 2 = No

Subject #	Adverse Event Description	Start Date	Stop Date	Severity	Relationship	Action Taken	Outcome	Expected	SAE	Investigator Initials & Date

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Subject #	Adverse Event Description	Start Date	Stop Date	Severity	Relationship	Action Taken	Outcome	Expected	SAE	Investigator Initials & Date

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