Determining the feasibility of randomising children and young people to invasive and non-invasive urine sampling techniques (FROG)

A pragmatic multi centred randomised controlled feasibility trial and a mixed methods feasibility perspectives study

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Sponsor	Queen's University Belfast 63 University Road Belfast, BT7 1NN
Chief Investigator	Dr Thomas Waterfield Wellcome-Wolfson Institute for Experimental Medicine Queen's University Belfast 97 Lisburn Road Belfast, BT9 7BL Northern Ireland

PROTOCOL AUTHORISATION

Protocol Title	**Determining the feasibility of randomising children and young people to invasive and non-invasive urine sampling techniques**
Protocol Acronym (if applicable)	FROG
Protocol Number	B24/28
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A review of the protocol has been completed and is understood and approved by the following:

Chief Investigator	Signature	Date		

Statistician	Signature	Date	/	/

PROTOCOL AMENDMENT HISTORY

Amendment No.	Version	Date	Summary of Key Changes
1	2.0	07/02/2025	List of Abbreviations: Amended Study Acronym 1.0 Amended Study Title, updated Exclusions (WP1) 2.0 Amended Study Team (Coinvestigators) 6.0 Instated capital letters for sampling method acronyms 7.3.2 Parents to complete for infants (<4 years) 8.3.2 Updated Exclusions 9.3 Anonymised data recorded up to the point of withdrawal will be included in the study 10.1 Instated capital letters for sampling method acronyms; Included detail on protocol in the case of discontinuance of a sampling method 10.2.1 Removed stratification in sequence generation

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation/ Acronym	Full Wording
AE	Adverse Event
AR	Adverse Reaction
BHSCT	Belfast Health and Social Care Trust
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTU	Clinical Trials Unit
DMEC	Data Monitoring and Ethics Committee
DMP	Data Management Plan
EDs	Emergency Departments
FROG	Feasibility of Randomising to invasive and non-invasive urine samplinG
GCP	Good Clinical Practice
GP	General Practitioner
HTA	Health Technology Assessment
HRA	Health Research Authority
IB	Investigator's Brochure
ICH	International Conference of Harmonisation
IMP	Investigational Medicinal Product
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention to Treat
MHRA	Medicine and Healthcare Products Regulatory Agency
ModRUM	Modular Resource Use Measure
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NICTU	Northern Ireland Clinical Trials Unit
NIHR	National Institute for Health Research
PI	Principal Investigator
PIS	Patient Information Sheet
PPIE	Patient and Public Involvement and Engagement
RA	Research Assistant
RCT	Randomised Controlled Trial
RD	Risk Difference
R&D	Research & Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SPA	Suprapubic Aspiration
SUDS	Subjective Units of Distress Scale
SUSAR	Suspected Unexpected Serious Adverse Reaction

SWAT	Study Within a Trial
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
TUBC	Transurethral Bladder Catheterisation

1 STUDY SUMMARY

Scientific title	Determining the feasibility of randomising children and young people to invasive and non-invasive urine sampling techniques (FROG): A pragmatic multi centred randomised controlled feasibility trial and a mixed methods feasibility perspectives study.
Public title	Determining the feasibility of randomising children and young people to invasive and non-invasive urine sampling techniques (FROG).
Health condition(s) or problem(s) studied	Urinary tract infections
Study Design	Mixed methods feasibility study
Study Aim and Objectives	**Aim:** To conduct a study of feasibility to assess which participants and interventions should be included in a subsequent randomised controlled trial, explore potential barriers to recruitment and determine the feasibility of randomisation to invasive versus non-invasive urine testing. **Objectives** 1. To determine the number of potential participants with suspected UTI presenting to a range of clinical settings, including emergency care, inpatients, and outpatients. 2. To conduct a quantitative assessment of the ability to screen, recruit and randomise children and young people to one of three interventions (CCU, SPA and TUBC). 3. To explore the views of parents, children, young people, and clinicians on the acceptability of different collection methods, and the appropriate population for inclusion in a future study. 4. To identify potential barriers to recruitment and consent. 5. To establish the most appropriate design, including important patient centred outcomes, for use in a future study. 6. To perform a cost analysis of the three urine collection methods to inform the resource planning and design of a future cost-effectiveness study.
Study Interventions	Invasive Trans-Urethral Bladder Catheterisation (TUBC) or Invasive Suprapubic Aspiration (SPA) or Non-invasive Clean Catch Urine (CCU)

Primary Outcome	**Work Package 1** **Randomised Controlled Feasibility Trial** The proportion of participants who are offered to take part in the study who consent to randomisation.
Secondary Outcomes	**Work Package 1** **Randomised Controlled Feasibility Trial** 1. Age, gender, ethnicity and basic demographic data of participants who consent 2. Proportion of presenting patients who are judged unsuitable for the study 3. Proportion of participants who consent to randomisation to CCU, TUBC or SPA 4. Proportion of participants who consent to randomisation to CCU or TUBC only 5. Proportion of participants who consent to randomisation to CCU or SPA only 6. Proportion of participants in each randomised group who received the allocated intervention 7. Rates of contamination by urine collection method 8. Safety as defined as the incidence of adverse events 9. Time to collect urine sample 10. Pain score associated with urine sampling 11. Final diagnosis of confirmed UTI 12. Resource use and costs
Key Inclusion and Exclusion Criteria	**Work Package 1** **Randomised Controlled Feasibility Trial** **Inclusion criteria** 1. Child under 16 years of age at presentation. 2. Requiring urine testing for suspected UTI. 3. Cannot provide a mid-stream urine sample (are not toilet trained). **Exclusion criteria** 1. A clinical need to collect an immediate invasive urine sample without delay 2. Participants where both methods of invasive urine sampling are deemed inappropriate by the treating clinician or are unavailable. 3. Children sedated or admitted to intensive care units at the time of screening 4. Language issues (not overcome with use of translators and available translated information sheets). 5. Parent or legal representative unavailable to provide informed consent. 6. Consent declined.

	Work Package 2 – mixed methods feasibility study **AND** **Work Package 3 – consensus meeting** **Inclusion criteria** **Parents and Children** 1. Parents/guardians of children (0 to under 16 years) and children (aged 7 to under 16 years) who are approached to participate in WP1 including those who decline randomisation. **OR** 2. Parents/guardians of children (0 to under 16 years) and children (aged 7 to under 16 years) who have required urine testing in hospital setting for suspected UTI in the last three years. **Healthcare Practitioners** 3. Healthcare practitioners (doctors, nurses, research staff and Allied Health professionals) involved in recruitment to the FROG feasibility trial (WP1). **OR** 4. UK healthcare practitioners (doctors, nurses, research staff and Allied Health Professionals) not involved in recruitment, screening or conduct of the FROG feasibility trial (WP1) **Exclusion criteria** **Parents and Children** 1. Language issues (not overcome with use of translators and available translated information sheets). 2. Declined consent.
Countries of Recruitment	United Kingdom
Study Setting	Paediatric
Target Sample Size (WP1 - randomised controlled feasibility trial)	100
Target Sample Size (WP2 – mixed methods perspectives feasibility study)	Questionnaires: approx. 50 parents/guardians Interviews: 25-35 participants (~15-20 parents and ~10-15 children) Focus groups: 5 (5-8 healthcare practitioners)
Target Sample Size (WP3 – consensus meeting)	40 stakeholders
Study Duration	18 months

Funder Statement
This study is funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) Programme (Project Reference NIHR 156005). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

2 STUDY TEAM

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3 ROLES AND RESPONSIBILITIES

3.1 Funder

The National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) Programme is providing the research costs to the FROG study (Reference NIHR156005), as the result of a commissioned call (HTA 22/96). Further details can be found at www.fundingawards.nihr.ac.uk/award/NIHR156005 and the formal Funder Statement can be found in Section 1, Study Summary. The funder has no role in the study design, data acquisition, analysis and interpretation, or manuscript preparation.

3.2 Sponsor

The Queen's University Belfast (QUB) will act as Sponsor for the study and the Chief Investigator (CI) will take overall responsibility for the conduct of the trial. Separate agreements will be put in place between the Sponsor and each organisation undertaking Sponsor-delegated duties in relation to the management of the study. The Sponsor will have no role in the collection, analysis, and interpretation of data, writing of the report, and the decision to submit the report for publication.

3.3 Trial Oversight Committees

3.3.1 Trial Management Group (TMG)

A Trial Management Group (TMG) will be established and Chaired by the CI. It will comprise the CI, representatives from the Clinical Trials Unit (CTU), a patient representative and co-investigators who provide trial specific expertise. The TMG will meet face to face or by teleconference on a monthly basis, and will communicate between times via telephone and email as needed. The roles and responsibilities of the TMG will be detailed in the TMG Charter. Meetings will be formally minuted and a list of actions recorded and stored in the Trial Master File (TMF). All day-to-day activity will be managed by the Trial Manager, in consultation with the CI as needed, providing a streamlined approach for handling enquiries regarding the trial and disseminating communications.

3.3.2 Trial Steering Committee (TSC)

A Trial Steering Committee (TSC) will be convened to provide oversight with respect to the conduct of the study on behalf of the Funder and Sponsor. An independent chair will lead the TSC, with at least 75% independent membership. The TSC will include the CI, a patient representative, trialists and experienced paediatric emergency consultants. The membership, the role of the TSC and the frequency of meetings will be listed in the TSC Charter. The TSC, in the development of this protocol and throughout the trial, will take responsibility for monitoring and guiding overall progress, scientific standards, operational delivery and protecting the rights and safety of trial participants. Meetings will be formally minuted and stored in the TMF. On occasion, observers may be invited and in attendance at TSC meetings, such as the Sponsor or Funder representatives or the Trial Manager to provide input on behalf of the CTU.

3.3.3 Data Monitoring and Ethics Committee (DMEC)

An independent Data Monitoring and Ethics Committee (DMEC) will be convened, comprising two independent clinicians with experience in undertaking clinical trials in paediatrics, an independent expert in evidence synthesis and an independent statistician. The DMEC's overarching responsibility is to safeguard the interests of trial participants, in particular with regard to safety, and assist and advise the TSC so as to protect the validity and credibility of the trial. The membership, the role of the

DMEC and the frequency of meetings will be listed in the DMEC Charter. Meetings will be formally minuted and stored in the TMF. Following recommendations from the DMEC, the TSC will decide what actions, if any, are required. It will be the responsibility of the TSC to inform the Sponsor if concerns exist about participant safety, following which the Sponsor will take appropriate action.

If a trial extension and/or funding is required above the level originally requested, the independent DMEC may be asked by the CI, TSC, Sponsor or Funder to provide advice and, where appropriate, information on the data gathered to date in a way that will not compromise the trial.

3.3.4 User Involvement or Any Other Relevant Committees

Patient and Public Involvement (PPI) groups in Northern Ireland, Liverpool (Generation R) and via the GAPRUKI network contributed to the preparation of the study grant application. Eighty individuals including children, young people, and adults were involved through a mixture of virtual meetings (n=3) and surveys (n=2). The three work packages were designed with consideration of the PPI survey results and discussions.

One of the co-investigators will coordinate PPI activity including liaison with PPI groups from charitable organisations and primary schools.

A PPI competition will be held for children to design a study logo and develop the trial identity which will then be created by professional graphic designers. This approach has been used in several HTA trials delivered by members of our research team.

This study is dependent on high-quality information being presented to families in a clear and efficient way. The PPI group will contribute to the development of all participant information resources, the interpretation of results, report writing and dissemination of study results and findings.

A PPI representative will be invited to participate in TMG meetings and there will be a PPI representative on the TSC. PPI representatives will be invited to participate in other relevant meetings and the consensus meeting (Work Package 3 – see section 15) to ensure that the research is relevant to patients.

We will make sure that they are adequately trained and supported for this role. We will ensure family-friendly flexibility in meeting scheduling, including both face-to-face and virtual attendance options.

Support & training
PPI members will be offered training including the Northern Ireland Public Health Agency Research and Development PPI workshops. The following resources and documents will also be used to guide PPI:

1. HRA Best Practice Principles for Public Involvement
2. National Standards for PPI
3. The Northern Ireland Engage Website and Resources

All members of the PPI group and PPI representatives will receive reimbursement of expenses, in line with NIHR Centre for Engagement and Dissemination recommendations. All PPI representatives involved in the study management groups will be acknowledged for their contributions. The Guidance for Reporting Involvement of Patients and the Public, Version 2 (GRIPP2 checklists) [1] will be used for reporting on patient and public involvement (PPI) in research publications.

4 BACKGROUND AND RATIONALE

4.1 Background Information

Urinary tract infections (UTI) are the second most common serious bacterial infection in children and are responsible for large numbers of presentations to primary and secondary care [2]. By the age of 16, 1 in 10 girls and 1 in 30 boys will have had a UTI [3]. Features of a UTI include non-specific symptoms such as fever, vomiting, abdominal pain, and lethargy [4, 5]. When healthcare practitioners are unsure if an infant, child, or young person has a UTI they perform a urine test. The results of this test determine if they receive antibiotic treatment and follow up. Prompt treatment of UTI is important to prevent complications such as sepsis and renal scarring [6]. The National Institute for Health and Care Excellence (NICE) published guidance on the diagnosis and management of UTI in the UK in July 2022 (NG224) [4]. NICE advise that healthcare practitioners "use a clean catch method of urine collection wherever possible" and that where this isn't possible, they "use other non-invasive methods such as urine collection pads". NICE explicitly advises against any invasive urine testing such as trans-urethral bladder catheter (TUBC) samples or suprapubic aspirates (SPA) except for when "it is not possible or practical to collect urine by non-invasive methods".

The advantage of the non-invasive approach for urine collection is that these methods are painless and can be conducted in primary care settings. Unfortunately, non-invasive urine collection methods such as clean catch urine (CCU) and the use of urine pads are complicated by high rates of bacterial contamination and the samples are time consuming to collect.

This was exemplified by three UK studies including 1093 participants aged under two years of age reporting that 26% to 36% of CCU samples were contaminated [5-8]. This contrasts with much lower rates of reported contamination for TUBC (12%) and SPA (1%) [5].

Bacterial contamination results in poorer antimicrobial stewardship and antimicrobial resistance. Antimicrobial resistance (AMR) has been highlighted by the World Health Organisation as one of the greatest threats facing humanity [9]. In children, UTI are primarily caused by the bacteria E.coli.

Traditionally, E.coli UTI could be easily treated with the oral antibiotic Trimethoprim but, over time, E.coli has evolved and 30% of E.coli UTIs in England are now resistant to Trimethoprim and 10% are resistant to Cefalexin [4, 9]. The best approach to combating AMR in this setting is to reduce the unnecessary use of antibiotics. However, when healthcare practitioners rely on non-invasive urine sampling to diagnose UTI, antibiotic prescribing rates are increased, because of false positive urine test and culture results from contaminated samples. Bacterial contamination also impacts patients and families through the prescription of unnecessary follow up, painful investigations, and admission to hospital even though they do not have a UTI.

In older children (those typically over three months of age), the treatment of a suspected UTI is with oral antibiotics. In children under three months of age with a suspected UTI, standard clinical practice is to complete a septic screen with blood tests and a lumbar puncture and admit to hospital for broad-spectrum parenteral antibiotics [3].

All children less than six months of age with a UTI require follow up and a renal ultrasound scan, and those with "atypical" infections caused by bacteria other than E.coli require additional invasive tests of renal function [3]. False positive results from urine culture that are due to contamination in this setting lead to increased numbers of painful procedures for the child and higher healthcare costs.

4.2 Rationale for the Study

Internationally, the approach to urine collection varies. For example, in Europe and North America, national guidelines typically favour invasive urine collection methods [10- 14], given their advantage of much lower rates of bacterial contamination [15-18]. A UK based study is required to determine which invasive or non-invasive urine sampling infants, children, and young people should be offered. However, it is not clear if potential participants could be recruited to a randomised controlled trial (RCT) comparing the various urine collection methods and a feasibility study is required to determine if a definitive RCT would be possible and, if so, to inform its design.

5 STUDY AIM AND OBJECTIVES

5.1 Study Aim

To conduct a study of feasibility to assess which participants and interventions should be included in a subsequent randomised controlled trial, explore potential barriers to recruitment and determine the feasibility of randomisation to invasive versus non-invasive urine testing.

5.2 Study Objectives

1. To determine the number of potential participants with suspected UTI presenting to a range of clinical settings, including emergency care, inpatients, and outpatients.
2. To conduct a quantitative assessment of the ability to screen, recruit and randomise children and young people to one of three interventions (CCU, SPA and TUBC).
3. To explore the views of parents, children, young people, and clinicians on the acceptability of different collection methods, and the appropriate population for inclusion in a future study.
4. To identify potential barriers to recruitment and consent.
5. To establish the most appropriate design, including important patient centred outcomes, for use in a future study.
6. To perform a cost analysis of the three urine collection methods to inform the resource planning and design of a future cost-effectiveness analysis.

6 STUDY DESIGN

6.1 Study Design

This is a mixed methods feasibility study including three work packages, outlined below (Figure 1).

Work Package 1 (WP1) is a pragmatic multicentre randomised controlled feasibility trial (n = 100) to assess the feasibility of randomising children to invasive and non-invasive urine sampling (Section 7-14). The CONSORT diagram depicting an overview of the feasibility trial is presented in Figure 2. Table 1 depicts WP1 in terms of population, intervention, and outcome (PIO).

Population	Neonates, Infants and young people (aged 1 day – 15 yrs.)
Interventions	Invasive Trans-urethral Bladder Catheterisation (TUBC) or Invasive Suprapubic Aspiration (SPA) or Non-invasive Clean Catch Urine (CCU)
Outcome	Proportion of participants (parents/guardians and children) who are approached to take part in the study who consent to randomisation

Table 1: PIO terms

Work Package 2 (WP2) is a mixed methods study including questionnaire, interviews and focus groups to explore parent/guardian, children's and healthcare professional's views and acceptability of the proposed study and sampling methods (Section 15).

Work Package 3 (WP3) is a stakeholder consensus meeting to describe a final definitive study design (Section 16).

Figure 1: A mixed methods feasibility study involving three linked work packages

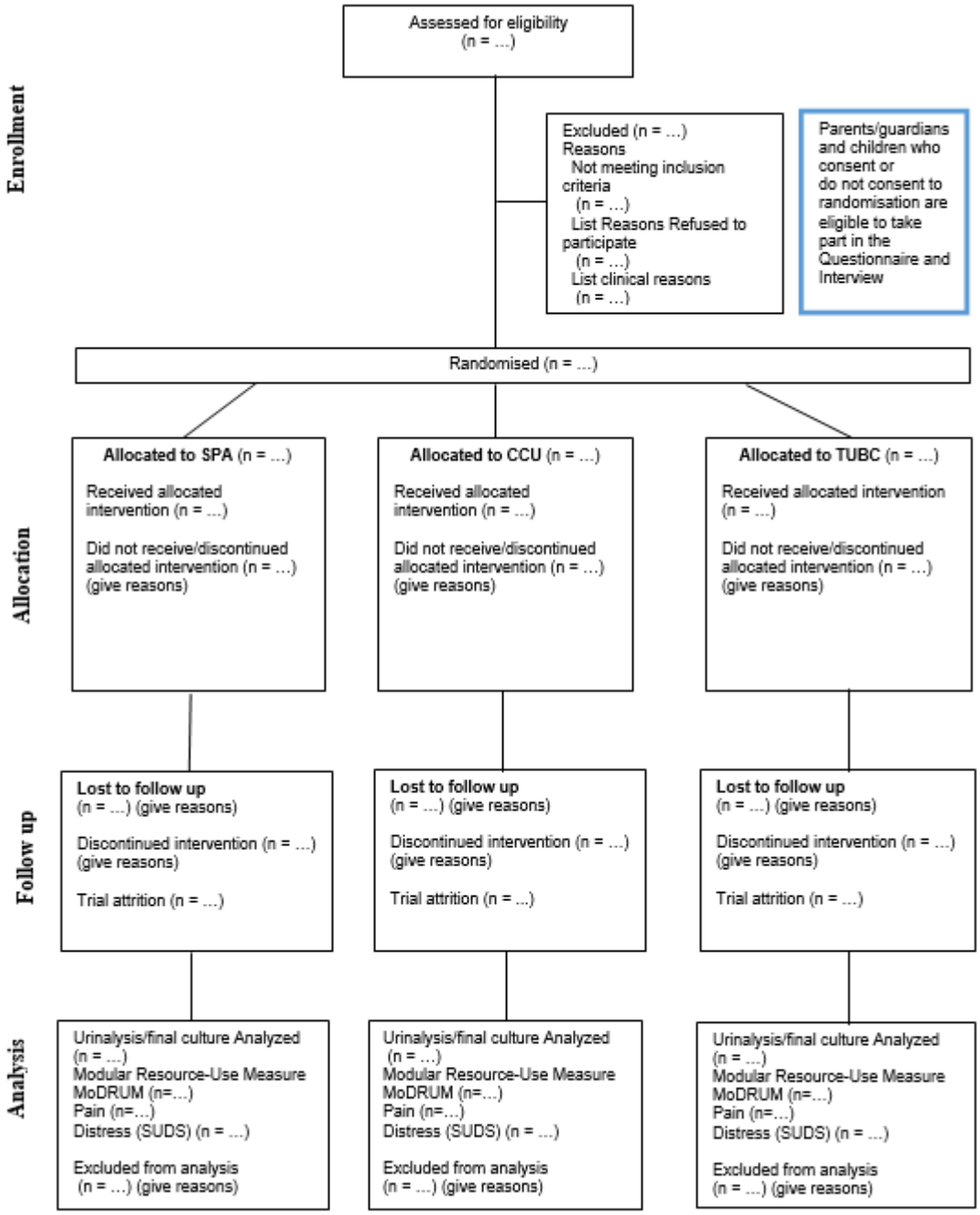

Figure 2: CONSORT diagram depicting participant flow through WP1 (randomisation)

6.2 Study Timelines

The overall duration of the study is 18 months. Details of specific trial tasks and planned timelines are presented in Table 2.

Table 2. Study timeline and key tasks

Milestones	Pre		Set Up				RCT Recruitment (WP1) & Qualitative										WP3	Analysis &	
Grant Year			Year 1												Year 2				
Grant Quarter			Q1			Q2			Q3			Q4			Q1			Q2	
Calendar Year							2025												2026
Calendar Month	Jul-24	Aug-24	Sep-24	Oct-24	Nov-24	Dec-24	Jan-25	Feb-25	Mar-25	Apr-25	May-25	Jun-25	Jul-25	Aug-25	Sep-25	Oct-25	Nov-25	Dec-25	Jan-26	Feb-26
Project Month	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Trial Set Up	x	x	x	x	x	x														
Trial Staff Recruitment	x	x	x	x	x	x														
Protocol Development	x	x	x	x	x	x														
REC Approval			x	x	x	x														
HRA Approval			x	x	x	x														
R&D Approval			x	x	x	x														
Site Set Up and Training			x	x	x	x														
RCT Feasiblity Study (WP1)							x	x	x	x	x	x								
Sites Initiated/Open to Recruitment							4	6	6	6	6	6								
Patient Recruitment/Month/Site							3	3	3	3	3	3								
Patient Recruitment/Month							12	18	18	18	18	16								
Patient Recruitment Cumulative							12	30	48	66	84	100								
Mixed Methods Qualitative Study (WP2)								x	x	x	x	x	x	x	x	x				
Data Collection/Cleaning							x	x	x	x	x	x	x	x	x	x				
Stakeholder Meeting (WP3)																	x			
TMG Meetings	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
DMEC Meetings					x					x				x						x
PPI Advisory Group				x					x				x							x
Site Closure																	x	x	x	x
Statistical Analysis															x	x	x	x	x	x
Health Economics Analysis															x	x	x	x	x	x
Reporting and Dissemination																			x	x

6.3 End of Study

The trial will end when all participants have completed follow-up for WP1, WP2 and the WP3 consensus meeting has been conducted. The trial will be stopped early if:

- Mandated by the Research Ethics Committee
- Mandated by the Sponsor e.g. following recommendations from the DMEC
- Funding ceases

The REC that originally gave a favourable opinion of the trial will be notified in writing if the trial has been concluded or stopped early.

7 WORK PACKAGE 1 – FEASIBILITY TRIAL OUTCOMES and OUTCOME MEASURES

7.1 Primary Outcome

The primary outcome is the proportion of participants who are offered the study who consent to randomisation.

7.2 Secondary Outcomes

1. Age, gender, ethnicity and basic demographic data of participants who consent
2. Proportion of presenting patients who are judged unsuitable for the study
3. Proportion of participants who consent to randomisation to CCU, TUBC or SPA
4. Proportion of participants who consent to randomisation to CCU or TUBC only
5. Proportion of participants who consent to randomisation to CCU or SPA only
6. Proportion of participants in each randomised group who received the allocated intervention
7. Rates of contamination by urine collection method^
8. Safety as defined as the incidence of adverse events
9. Time to collect urine sample
10. Pain score associated with urine sampling
11. Final diagnosis of UTI*
12. Resource use and costs

*The final urine culture will be used to determine if the child had a true urinary tract infection or contamination. UTI is defined as greater than 100 000 CFU/ml of a single organism from a single clean urine (clean catch, suprapubic aspiration, urethral catheter specimen) and the presence of pyuria (≥5 white cells per high-power field in centrifuged urine or ≥10 white cells per mm^3 in un-centrifuged urine) on laboratory microscopy [19].

^Contamination is defined as greater than 100 000 CFU/ml of either a single organism without pyuria or mixed bacterial growth. This is based on previous published definitions of UTI [19].

7.3 Outcome Measures

7.3.1 Modular Resource Use Measure (ModRUM)

A version of the ModRUM [20] adapted for completion by a parent/guardian and approved of by the ModRUM developers will be used. The ModRUM is a validated, concise, generic, measure designed to collect self-report data on the healthcare services people use in UK-based studies. The measure contains a set of core modules that can be expanded to ask participants for additional details by substituting 'core' questions for 'depth' questions.

7.3.2 Subjective Units of Distress Scale (SUDS)

Subjective Units of Distress Scale (SUDS) [21] is a validated visual analogue Likert scale ranging from 0 to 10 measuring the intensity of distress experienced by an individual. Respondents provide a self-report of where on the scale they feel with 0 being no distress and 10 being highly distressed. The scale can be used to measure range of emotions from anxiety to emotional disturbance and negative internal experiences such as anger, agitation, stress and painful feelings. SUDS is validated for children over 3 years. We will also ask parents to complete for infants (<4 years).

7.3.3 Pain Score Associated with Urine Sampling

The Pain Rating Scale Wong-Baker FACES® for children over 3 years old [22] will be used. Originally published in Whaley & Wong's Nursing Care of Infants and Children, this is an analogue faces scale that allows children over 3 years old to rate their level of pain and hence aid their communication about their pain. The child is asked to choose the face that best depicts their experienced pain. A rating of 0 for no pain to 10 the worst pain is self-administered or aided by an adult for children who cannot read.

The FLACC Behavioural pain scale (for young infants) [23] will be used. Face, legs, activity, cry and consolability are the five domains for assessing pain using the FLACC scale. An overall assessment score is rated on a scale of 0 - 10 as follows:

0 = Relaxed and comfortable, 1-3 = Mild discomfort, 4-6 = Moderate pain, 7-10 = Severe discomfort/pain

Categories	0	1	2
Face	No particular expression or smile	Occasional grimace or frown; withdrawn, disinterested	Frequent to constant frown, clenched jaw, quivering chin
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid, or jerking
Cry	No cry (awake or asleep)	Moans or whimpers, occasional complaint	Crying steadily, screams or sobs; frequent complaint
Consolability	Content, relaxed	Reassured by occasional touching, hugging, or being talked to; distractible	Difficult to console or comfort
Each category is scored on the 0-2 scale, which results in a total score of 0-10. **0:** Relaxed and comfortable **1-3:** Mild discomfort **4-6:** Moderate pain **7-10:** Sever discomfort or pain or both			

8 WORK PACKAGE 1 – FEASIBILITY TRIAL SETTING AND PARTICIPANT ELIGIBILITY CRITERIA

8.1 Trial Setting

The randomised controlled feasibility trial will be conducted in a minimum of six paediatric hospital settings from across the UK including EDs, assessment units, inpatient wards, and outpatient clinics. Neonatal units will be excluded from recruitment.

8.2 Trial Population

Participants will be screened from attendances to paediatric EDs, assessment units, inpatient wards, and outpatient clinics at recruiting sites. All participants who meet the study inclusion criteria will be entered into a screening log. If the participant is not recruited the reason will be recorded. This information is required to ensure the study can be reported in keeping with Consolidated Standards of Reporting Trials (Consort) extension to randomised pilot and feasibility trials [24] guidelines (www.consort-statement.org). The trial protocol is in alignment with the SPIRIT guidelines for protocols [25].

8.3 Eligibility Criteria

Participants will be assessed using the inclusion and exclusion criteria set out below. Eligibility to participate in the trial will be confirmed by a physician who is named on the Delegation Log. The medical care given to, and medical decisions made on behalf of, trial participants will be the responsibility of an appropriately qualified treating physician. Participants will be eligible to participate in the study in accordance with the following criteria:

8.3.1 Inclusion Criteria

1. Child under 16 years of age at presentation.
2. Requiring urine testing for suspected UTI.
3. Cannot provide a mid-stream urine sample (are not toilet trained).

8.3.2 Exclusion Criteria

1. A clinical need to collect an immediate invasive urine sample without delay
2. Participants where both methods of invasive urine sampling are deemed inappropriate by the treating clinician or are unavailable.
3. Children sedated or admitted to intensive care units at the time of screening
4. Language issues (not overcome with use of translators and available translated information sheets).
5. Parent or legal representative unavailable to provide informed consent.
6. Consent declined.

8.4 Co-enrolment Guidelines

Participants in the FROG study may be eligible for co-enrolment in other studies, and this will be decided on a case-by-case basis by the Trial Management Group. Participants enrolled in other observational studies and clinical trials of investigational medicinal products (CTIMPS) are potential candidates for this study. Co-enrolment with other studies should be documented in the Case Report Form (CRF).

9 WORK PACKAGE 1 – FEASIBILITY TRIAL SCREENING, CONSENT and RECRUITMENT

9.1 Screening Procedure

Participants will be screened from attendances to paediatric EDs, assessment units, inpatient wards, and outpatient clinics at recruiting sites. Eligible participants will then be discussed with their clinical team to confirm agreement with trial enrolment.

The outcome of the screening process including reasons for the non-enrolment of potentially eligible participants will be recorded on the FROG study screening database. The PI or designee will be required to submit screening data to the CTU weekly. Screening data will be used to monitor trial recruitment and provide feedback to sites. The collection of accurate screening data is also required to meet CONSORT 2010 extension pilot/feasibility trial reporting guidelines [24]. A minimal dataset will also be recorded for eligible and non-recruited participants which will include age, ethnicity and sex.

9.2 Informed Consent Procedure

A member of the clinical team will initially approach the adult(s) with parental legal/responsibility or legal guardian(s) of the child (participant). Where both parents have parental responsibility it is important they are both supportive of the child participating in the research. Where the mother is under 16, grandparents will be involved in decision making (GCP, 2024).

If the family is interested, they will be introduced to a member of the research team who will verbally explain the aims and objectives of the research, trial procedures, the invasive and non-invasive sampling techniques and data collection (including health resource questionnaire). In addition they will advise interested families about the questionnaire and interviews as part of WP2 (see section 15).

An age appropriate verbal explanation will also be provided to the child at their level of understanding.

Families will then be presented with the parent/guardian participant information leaflet to read, along with a QR code to access the explainer video footage.

Children will be presented with a participant information sheet to read at their level of understanding. Children who are under five years old will also be presented with a study colouring in page and crayons

Parents/guardians and children will then be given an opportunity to ask any questions they may have relating to the research.

Families will have a period of approximately one hour to decide whether they would like to consent to take part in WP1.

- Parents/guardians and children may decide not to consent to randomisation. The child will then receive standard care as determined by the local team.

- Parents/guardians and children/ young people who do not consent/assent to randomisation will be registered in the automated web based system.

- Parents/guardians and children (over 5 years) who consent to randomisation and Parents/guardians and children (over 5 years) who do not consent to randomisation are eligible to participate in the questionnaires (pain and distress scales, health resource use, acceptability) and/or interview components of feasibility WP2 (see section 15). The views of parents/guardians and children (over 7 years) who decline to be randomised will provide important insight for this feasibility study.

If the parent or guardian verbally consents to taking part in any of these aspects of the research (data collection (only) or data collection and randomisation (WP1) and/or questionnaires and/or interview (WP2)), they will be presented with a consent form.

Children over 5 years of age will be provided with an assent form to complete, dependent on their level of understanding and Gillick competency.

A member of the research team will talk through the consent and assent form(s) with the parent/guardian and the child and explain or answer any further questions they may have before completing.

All children's wishes will be taken into account regardless of age during the decision making process, and before consent is given (GCP, 2024). If assent is not received from a child, documentation of "very

clear compelling reasons as to why the child has been included in the study without their wishes must be established in advance" (GCP, 2024) of the sampling procedures. Practical implications of involving a child who does not wish to participate in terms of receipt of study procedures/processes against their will and compliance will be fully considered.

An appropriately trained doctor or nurse may take consent. The person taking informed consent must be GCP trained, suitably qualified and experienced, and have been delegated this duty on the delegation log. Appropriate signatures and dates must be obtained on the informed consent documentation prior to randomisation, and collection of trial data.

The Principal Investigator (PI) (or designee) is responsible for ensuring that informed consent for trial participation is given for each participant by their parent/guardian. If no consent is given the participant cannot be enrolled into the trial.

9.3 Withdrawal of Consent

The parent/guardian or child may withdraw consent from the study at any time without detriment. If consent is withdrawn this will be documented in the participant's medical notes and in the CRF. If the parent/guardian or child declines on-going participation, anonymised data recorded up to the point of withdrawal will be included in the study analysis.

10 WORK PACKAGE 1 – FEASABILITY TRIAL INTERVENTIONS and INTERVENTION ALLOCATION

10.1 Trial Interventions

Eligible participants who consent to be randomised will be asigned to one of the interventions

- Invasive Trans-Urethral Bladder Catheterisation (TUBC) or
- Invasive Suprapubic Aspiration (SPA) or
- Non-invasive Clean Catch Urine (CCU)

Invasive urine sampling is defined as either trans-urethral bladder catheterisation (TUBC) or suprapubic aspiration (SPA) (Figure 3). TUBC involves passing a flexible catheter into the bladder via the urethra. SPA involves placing a needle through the skin of the abdomen directly into the bladder. Non-invasive urine collection involves catching a urine sample in a small dish. The non-invasive clean catch urine sample can be performed with and without bladder stimulation (typically the use of cold/damp gauze on the abdomen to promote micturition). Sites will follow local policies and procedures for urine sampling collection.

If either of the invasive urine methods is contra-indicated for a particular participant (or if it is unavailable), it will be excluded from the randomisation. Therefore, the participant can still be randomised if at least one of the invasive urine sampling methods is deemed appropriate.

In the event that a sampling method has been discontinued, an alternative and clinically appropriate sampling method will be administered to the child. This will be assessed on a case by case basis and clear reporting will reflect clinical reasoning in the child's clinical notes and database.

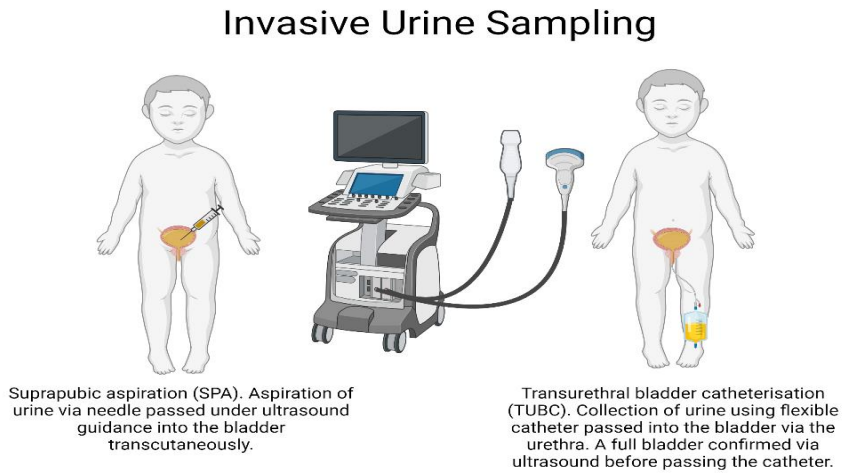

Figure 3: Visual summary depicting invasive urine sampling methods.

10.2 Assignment of Intervention

10.2.1 Sequence Generation

Participants will be recruited and randomised using an automated web-based system via randomly permuted blocks in a 1:1:1 ratio for CCU versus TUBC versus SPA. If either of the invasive urine methods is contra-indicated for a particular participant (or if it is unavailable), it will be excluded from the randomisation. Therefore, the participant can still be included if at least one of the invasive urine sampling methods is deemed appropriate. The advantage of this approach is that it allows for recruitment and randomisation in the event that one of the interventions is either unavailable or unsuitable. If one of the invasive methods is to be excluded they will be randomised in a 1:1 ratio to an invasive method or CCU.

10.2.2 Allocation Concealment Mechanism

The randomisation sequence will be held by the third party supplier providing the automated randomisation system, it will not be accessed by the trial statistician nor those who enrol or assign interventions

10.2.3 Allocation Implementation

After informed consent, patients will be recruited and randomised via an automated web-based system. Sites will be provided with trial specific randomisation guidelines. Randomisation will be completed by an appropriately trained and delegated member of the research team. Each patient will be allocated their own unique Participant Study Number during the recruitment/randomisation process, which will be used throughout the study for participant identification on all data collection forms and questionnaires. An entry will be recorded in the patients' medical notes noting enrolment into the study.

10.3 Blinding

Parents/guardians, participants and investigators will not be blinded to the urine sampling method used. This reflects the pragmatic design focused on the feasibility of conducting a larger study.

10.4 Trial Intervention Adherence

We will collect data to confirm participants received the allocated urine sample collection method, including if the allocated intervention was discontinued (with reasons why).

11 WORK PACKAGE 1 – FEASIBILITY TRIAL SCHEDULE of ASSESSMENTS

11.1 Participant Assessments

The frequency of assessments and follow up are detailed in the schedule of assessments (Table 3). The schedule defines the timing of assessments (with windows) necessary for data collection. Participants will be followed until 3 to 6 months dependent on when they were recruited. Figure 4 depicts the participant journey through the study.

Table 3: Schedule of Assessments

Day/Time point	Screening	Baseline Approx. 1 Hour	Approx. 2-4 Hours	Within 24 Hours of Urine Sample Collection	24 – 72 Hours After Sample Collection	Follow Up 3 to 6 Months (+/- 14 days)
At Hospital/Remote	Hospital	Hospital	Hospital	Hospital/Remote	Hospital/Remote	Remote
Eligibility	x					
Demographics	x					
Urine Sampling Methods	x					
Consent (WP1)		x				
Admission Details		x				
Medical History		x				
Symptoms		x				
Physical Examination		x				
Full Blood Count (including CRP, Creatinine, Electrolytes)		x				
Antibiotic Administration		x		x	x	x
Randomisation		x				
Urine Sample Collection			x			
Pain Scores Pain Rating Scale Wong-Baker FACES® (children over 3) **OR** FLACC Behavioural pain scale (infants)			x			
Distress Scale (SUDS)			x			
Urinalysis Results			x	x		
Urine Culture Results				x	x	
Hospital Discharge				x	x	x
Readmission (due to UTI or complication of procedure)					x	x
Imaging procedures						x
Adverse Events/ Serious Adverse Events		x	x	x		
Health Resource Use Questionnaire (ModRUM)						x
Consent (WP2) Questionnaire		x				
WP2 Questionnaire (completed by parent/guardian)		x				
Consent (WP2) Interview		x				
WP2 Participant Contact Details		x				

*Participants recruited in months 5-8 of the study should have these data collected up to 6 months post-randomisation. All other participants should have these data collected at month 13 (i.e. their follow-up periods will be less than 6 months and variable).The NICTU will flag to site when each participant should be followed up.

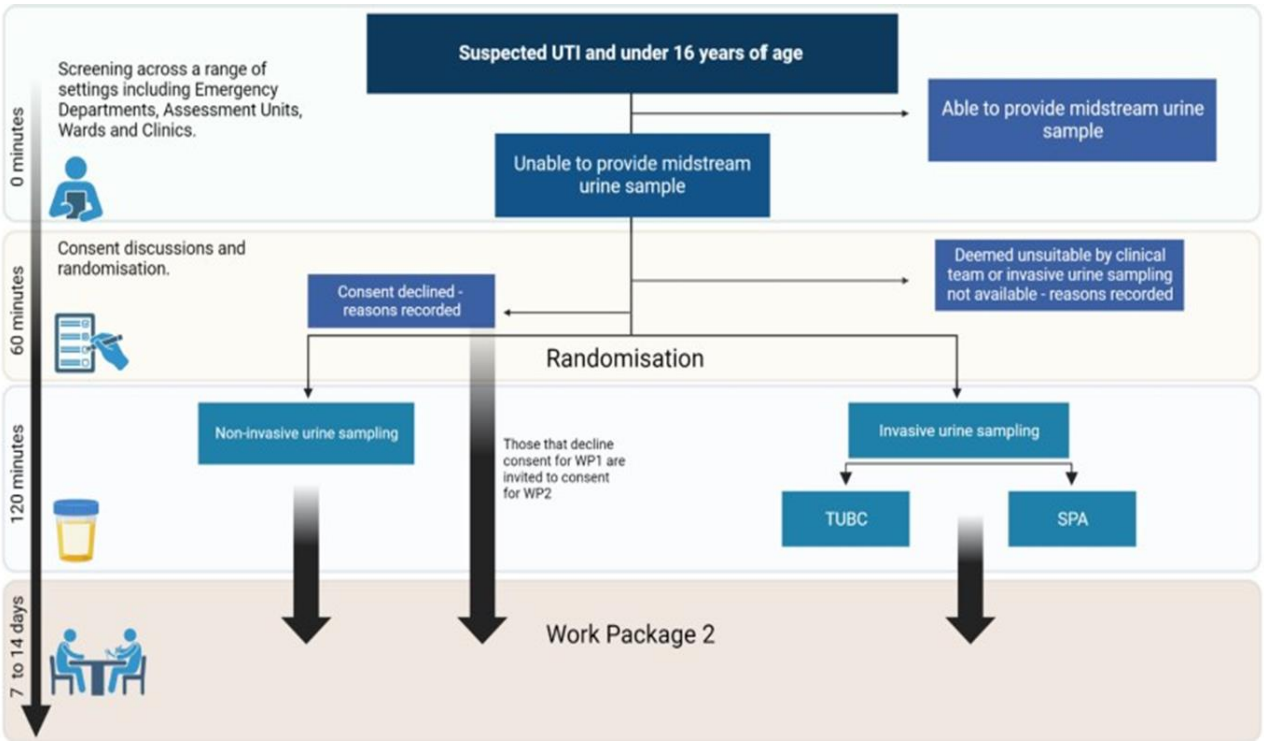

Figure 4: Participant Journey

11.2 Distress Guide

Play therapists (when available) will support parents/guardians and children to minimise distress and anxiety specific to the child's needs as part of standard care. A distress guide will be provided to sites that can be used alongside local procedures to safeguard the physical and emotional wellbeing of the child. Participants who may be in immediate danger throughout the trial will be monitored for safety and referred for additional care as required. An invitation to take part in the research may open a conversation of disclosure. If the participant discloses detail of life experiences that put the participant in immediate risk of danger, including early warning score, a member of the research team will refer the patient to the relevant services in accordance with local safeguarding and policy guidelines.

12 WORK PACKAGE 1 – SAFETY REPORTING

12.1 Terms and Definitions

Adverse event (AE) reporting will follow the Health Research Authority (HRA) guidelines on safety reporting in non CTIMP studies.

An **adverse event (AE)** is defined as any untoward medical occurrence in a participant in a research study, including occurrences which are not necessarily related to the administration of any of the research procedures.

An **adverse reaction (AR)** is defined as an AE that is deemed to be possibly, probably or definitely related (see Table 4, Section 12.3, below) to the study procedures (e.g. obtaining the urine sample via CCU, SPA or TUBC). If serious, as per the definition below, it would be considered a **serious adverse reaction (SAR).**

A serious adverse event (or reaction) (SAE/SAR) is defined as an untoward medical occurrence that:

- results in death
- is life-threatening
- requires hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity; or
- consists of a congenital anomaly or birth defect; or
- is otherwise considered medically significant by the investigator

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

12.2 Adverse Event Recording and Reporting

The AE reporting period for the trial begins upon consent and ends 24 hrs following the urine sampling procedure.

The PI or designee should record all directly observed AEs and all AEs spontaneously reported by the parent/guardian or child.

This paediatric population may experience a range of AEs such as common cold or other common childhood illnesses. Symptoms that are due to an alternative emergent condition (e.g. upper respiratory tract infection or other viral illness) **should not be** reported as an AE, unless the event is considered by the PI or designee to be associated with the study intervention/procedures or unexpectedly severe or frequent.

Symptoms of UTI (including fever, vomiting, abdominal pain) **should not be** reported as adverse events unless believed to be related to the study intervention/procedures. Events that are collected as outcomes for the FROG feasibility trial **do not** need to be reported as AEs, including pain and distress.

Complications of the study intervention/procedures (CCU, SPA and TUBC) **should be** reported as AEs. All other events deemed to be related and/or serious **should be** reported accordingly.

ARs are to be reported on the Adverse Event Form within the eCRF.
SAEs/SARs are to be reported on the Serious Adverse Event Form. SAEs/SARs should be reported to the NICTU by email (clinicaltrials@nictu.hscni.net) and within 24 hours of the investigator becoming aware of the event. The site should not wait until all information about the event is available before notifying the NICTU of the SAE. The NICTU will acknowledge receipt of the SAE Form by email. Information not available at the time of the initial report must be sought and submitted to the NICTU as it becomes available. The NICTU will notify the CI of all SAEs reported.

All reportable events as outlined above, should be followed until they are resolved. If the event has not been resolved within 28 days of the urine sampling procedure this will be recorded as ongoing.

An SAE occurring to a research participant will be reported to the main REC if the event was:
a) Related (i.e. SAR): that is, it resulted from any of the study interventions/ procedures, and
b) Unexpected: that is, the type of event is not listed in the protocol (section 12.6) as an expected occurrence.

Reports of related and unexpected SAEs will be submitted to REC within 15 days of the NICTU becoming aware of the event, using the SAE report form for non-CTIMPs published on the HRA website.

12.3 Assessment of Causality

The PI or designee should make an assessment of causality i.e. the extent to which it is believed that the event may be related to any of the research procedures (Table 4).

Table 4. Categories of Causality for Adverse Events

Category	Definition
Definitely*	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
Probably*	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.
Possibly*	There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of a research procedure). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant events).
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of a research procedure). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatments).
Not Related	There is no evidence of any causal relationship.
Not Assessable	Unable to assess on information available.

* Where an event is assessed as possibly, probably or definitely related, the event is an AR.

12.4 Assessment of Severity

The PI or designee should make an assessment of severity according to the following categories (Table 5).

Table 5. Categories of Severity for Adverse Events

Category (Severity)	Definition
Mild (Grade 1)	The adverse event is easily tolerated by the trial participant, causing minimal discomfort and not interfering with every day activities.
Moderate (Grade 2)	The adverse event is sufficiently discomforting to interfere with normal everyday activities.
Severe (Grade 3)	The adverse event prevents normal everyday activities.
Life Threatening (Grade 4)	The adverse event has life threatening consequences; urgent intervention indicated.
Death (Grade 5)	The adverse event results in death.

12.5 Assessment of Seriousness

The PI or designee should make an assessment of seriousness i.e. does the event fulfil any of the following criteria:

- Resulted in death
- Is life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Is any other important medical event(s) that carries a real, not hypothetical, risk of one of the outcomes above

12.6 Assessment of Expectedness

The PI or designee should make an assessment of expectedness for ARs or SARs. Events which are expected as a result of the research procedures include, bladder injury, urethral injury, frank haematuria and minor injury/irritation to external genitalia. ARs/SARs may be classed as either expected or unexpected as per Table 6.

Table 6. Categories of Expectedness for Adverse Reactions (ARs)/Serious Adverse Reactions (SARs)

Expectedness	Definition
Expected	The AR/SAR is listed in the protocol (section 12.6) as an expected AR
Unexpected	The AR/SAR is not listed in the protocol (section 12.6) as an AR.

12.7 Recording and Reporting of Urgent Safety Measures

If the PI, designee, or a member of study staff become aware of information that necessitates an immediate change in study procedure (i.e. urgent safety measure) to protect clinical trial participants from any immediate hazard, they should report the urgent safety measure immediately to the NICTU by phone and follow this up in an email to clinicaltrials@nictu.hscni.net

The NICTU will report the urgent safety measure immediately to the CI and the Sponsor and will liaise with the Sponsor and site to implement immediate procedures to eliminate any hazard. The NICTU will report any urgent safety measure to the REC within 3 days of becoming aware of the urgent safety measure. The PI or designee should respond to queries from the NICTU immediately to ensure the adherence to these reporting requirements.

13 WORK PACKAGE 1 – FEASIBILITY TRIAL DATA COLLECTION and MONITORING

13.1 Data Collection

To ensure accurate, complete, and reliable data are collected, the CTU will provide training to site staff. All data for an individual participant will be collected and recorded in source documents and transferred onto a bespoke, web-based, electronic CRF for the study. A data dictionary, record of automatic and manual data queries, and a full audit trail, will ensure data captured are consistent, reliable, and fully compliant with GCP and any other relevant regulatory requirements.

For routinely collected clinical data the NHS record will be the source document. Participant identification on the CRF will be through their unique participant study number, allocated at the time of randomisation. Data will be collected and recorded on the electronic CRF by the PI or designee as per the CRF submission guidelines.

13.2 Data Quality

The CTU will provide training to site staff on trial processes and procedures including CRF completion and data collection. Source data verification (SDV) will be completed by the CTU and will check the accuracy of entries on the electronic CRF against the source documents and adherence to the protocol. The extent of SDV to be completed is detailed in the Monitoring Plan.

Quality control is implemented by the CTU in the form of Standard Operating Procedures (SOPs), which encompass aspects of the clinical data management process, and ensure standardisation and adherence to International Conference of Harmonisation Good Clinical Practice (ICH GCP) guidelines and regulatory requirements.

Data validation will be implemented and discrepancy reports will be generated following data entry to identify discrepancies such as out of range, inconsistencies or protocol deviations based on data validation checks programmed in the clinical trial database.

A DMEC will be convened for the study to carry out reviews of the study data at staged intervals during the study.

13.3 Data Management

Following the entry of participant data into the study database, the data will be processed as per the CTU SOPs and the study specific Data Management Plan (DMP). Data queries will be generated electronically for site staff to clarify data or provide missing information, with the expectations that these queries will be completed within 14 days of receipt. All queries will be responded and amended within the study database.

13.4 Data Access

The agreement with each PI will include permission for trial related monitoring, audits, ethics committee review and regulatory inspections, by providing direct access to source data and trial related documentation. Each participant's confidentiality will be maintained and their identity will not be made publicly available, to the extent permitted by the applicable laws and regulations.

13.5 Monitoring Arrangements

The CTU will be responsible for trial monitoring. The frequency and type of monitoring (on site and/or remote) will be detailed in the monitoring plan and agreed by the Sponsor.

Before the trial starts at a participating site, training will take place to ensure that site staff are fully aware of the trial protocol and procedures. Checks will take place to ensure all relevant essential documents and trial supplies are in place. Monitoring during the trial will check the accuracy of data entered into the CRF against source documents, adherence to the protocol, procedures and GCP, and the progress of participant recruitment and follow up.

The PI or designee should ensure that the monitor can access all trial related documents (including source documents) that are required to facilitate the monitoring process. The extent of source data verification (SDV) will be documented in the monitoring plan.

14 WORK PACKAGE 1 - FEASIBILITY TRIAL STATISTICAL CONSIDERATIONS

14.1 Sample Size

Information will be recorded on all presenting patients who are assessed for eligibility for the study. Those who are judged suitable by the relevant clinician will be offered participation in the study with a target of 100 potential participants to be randomised. The target of 100 participants is based on experience with other NIHR feasibility studies that the study team have been involved with (PICNIC [27], FEVER [28], FiSH [29]) and based on the need to recruit enough participants to ensure that there is sufficient information to address the study aims and numbers of consenters and decliners who register interest in an interview for WP2 sampling.

14.2 Data Analysis

14.2.1 Analysis Population

Trial results will be reported in accordance with Consolidated Standards of Reporting Trials guidance (CONSORT). The analysis population is all those who are offered the study as the primary outcome is the proportion of participants who are offered the study who consent to randomisation.

14.2.2 Statistical Methods

As this is a feasibility study, analysis will be descriptive in nature. We will describe baseline characteristics and outcomes using suitable measures of central tendencies; means and medians with the associated standard deviations/interquartile ranges for continuous data; and frequencies and proportions for categorical data. A sensitivity analysis will be performed to determine numbers of children perceived to be at higher risk, the reasoning as to why they were higher risk (e.g. age, fever, signs of sepsis, symptoms) and the proportion of higher and lower risk children successfully recruited and randomised in WP1. Further details and a full description of the analyses will be given in the Statistical Analysis Plan.

14.2.3 Health Economics Analysis

A detailed costing analysis will be performed of the different methods of urine collection in children up to the point of achieving a definitive sample from a hospital perspective. We will prospectively collect the resource use associated with the staff time (nursing and medical) and equipment for each method in a sub sample of episodes from each site. We will aim to obtain two resource use descriptions for each urine sample method from each of the sites over the recruitment window, equating to 36 descriptions in total. Some sites may recruit better than others, and the 100 recruitment target may not be achieved, however we will endeavour to ensure that the descriptions collected are representative of the different types of recruiting sites (i.e. paediatric emergency departments, paediatric outpatient clinics and inpatient wards). We will liaise with sites about data collection after they have successfully recruited at least one participant in each arm.

Since misdiagnoses (e.g. false positives) due to e.g. contamination could lead to unnecessary repeat sampling, follow-up investigations, inappropriate antibiotic prescribing and imaging we will also pilot methods for collecting participants' health service use (primary and secondary care). The CRF will be

used to collect hospital resource use relating to the participants' presentation with a suspected UTI including follow-up investigations, imaging, prescribed medication and length of stay. A version of the Modular Resource-Use Measure (ModRUM) [20] adapted for completion by a parent/guardian will be used to collect healthcare resource use after the participants have left the hospital setting up to a maximum of 6 months post-randomisation. This questionnaire has adaptable sections in it to suit the needs of a study, and so by pilot testing it in FROG study we can assess what would be appropriate for a future cost-effectiveness analysis.

We will obtain feedback on the questions from parents/guardians at the end of the questionnaire. Questionnaires will be posted to parent/guardians by sites along with a pre-paid envelope to facilitate returns. We will collect as much health service use data as we can for each participant during the 10 month data collection window up to a maximum of 6 months post-randomisation. So for some participants the recall period for the ModRUM will be less than 6 months. This will help inform the design of a future cost-effectiveness analysis alongside a definitive trial in terms of e.g. selecting the most appropriate time horizon, and maximising data collection efficiency.

We will apply unit costs from publicly available sources (e.g. NHS Reference Costs, unit costs of health and social care) to the resource use where possible, and use other sources such as hospital costing departments and the literature when not. Costs will be presented in GBP£. We will include the costs associated with the initial sampling, any repeat sampling and any follow up investigations where appropriate to estimate the mean cost per definitive UTI diagnosis and follow standard reporting guidelines [19]. Sensitivity analyses will be performed to explore impact on the cost estimates of variations in key parameters e.g. time estimates, staff grade.

An important consideration of feasibility is the level of staff expertise and resources that would need to be available at recruitment sites in a future RCT to be able to deliver both invasive and non-invasive methods. The potential impact on the workforce may well be considered a barrier for sites to participate in a future trial, therefore our detailed costing analysis will quantify this impact for data synthesis enabling more informed discussions with stakeholders as part of WP3 (see section 16).

15 WORK PACKAGE 2 – EMBEDDED MIXED METHODS PERSPECTIVES STUDY INVOLVING PARENTS, CHILDREN, YOUNG PEOPLE AND HEALTHCARE PRACTITIONERS

15.1 Study Design

The FROG study will include an embedded mixed methods work package to explore the perspectives of parents, children, young people, and healthcare practitioners about the proposed trial. This research will involve questionnaires and interviews with parents and children as well as focus groups and interviews with healthcare practitioners. An exploration of topics will provide qualitative and quantitative insight into the acceptability of different sampling collection methods, the population for inclusion in a future study (Objective 3), potential barriers to recruitment and consent (Objective 4), and important patient centred outcomes for use in a future trial (Objective 5).

15.2 Population: Parents and Children

15.2.1 Eligibility Criteria

Inclusion Criteria:

- Parents/guardians of children (0 to under 16 years) and children (aged 7 to under 16 years) who are approached to participate in WP1 including those who decline randomisation.
  OR
- Parents/guardians of children (0 to under 16 years) and children (aged 7 to under 16 years) who have required urine testing in hospital setting for suspected UTI in the last three years.

Exclusion Criteria:

- Language issues (not overcome with use of translators and available translated information sheets)
- Declined consent

15.2.2 Recruitment and Sampling

Recruitment Route 1: Hospital Sites

As described in section 9.2, at participating sites, practitioners will provide all parents (including guardians) with study information. Study information will include details of the perspectives study element and they will be asked to complete a brief questionnaire following the study recruitment discussion and sampling method. They will also be invited to take part in an interview with a researcher from the University of Liverpool at a later date. If both parents are present, both will be asked to consent and complete a questionnaire. Completed questionnaires will be placed in a stamped self-addressed envelope and given to a member of the research team at the clinical site who will return to the FROG study team (e.g. within 12 hours) via post to the University of Liverpool. Child assent and parental consent will also be sought for children to take part in an individual or joint interview with parents if the child is deemed well enough to broach the study at that point in time. Based on previous studies in similar settings, we anticipate receiving approximately 50 completed questionnaires.

Recruitment Route 2: Social Media

To ensure sample diversity, including parents and children from varied geographic populations and ethnicities, we will use tailored advertising through social media platforms and email to relevant charities.

The Research assistant will contact gatekeepers (e.g. charity leads/Chief Executive Officers) of support groups for parents/legal representatives whose children have required urine testing for suspected UTI in the last three years. The RA will post with tagging or ask the gatekeeper to post the FROG recruitment advert on the support group's website and/or social media pages (e.g. Facebook, X, Instagram and Tik Tok). The advert will include a description of the purpose of the study and what is involved. The advert will also contain information and contact details for parents and children to register their interest in taking part via email.

The Research assistant will send an age and language-appropriate Participant Information Sheet, check eligibility and whether a translator will be required for the interview. Potential participants will

be asked to read the study information and ask any questions they may have before being sent a link by email to an online consent form to complete. An email or paper version can be sent on request if preferred (e.g. children).

We will purposively sample to ensure parents and children (aged 7 to under 16 years) reflect the various settings, ethnic diversity and representation of age ranges of infants, children and young people who would be eligible for a definitive study [27, 28, 29]. These details (if not already known through Work Package 1) will be collected at the point of screening to inform sampling.

15.2.3 Interview Procedures

The University of Liverpool team will contact parents and children to arrange an interview within one month of consent. Parents and children will be offered online or face to face (in the Northwest of England) interviews. All interviews requiring a translator will be conducted online via Microsoft Teams. Interviews will be conducted by the University of Liverpool research team. The Research assistant will check whether younger children wish to be interviewed alone or with a parent present. Interviews will be conducted using the age/level of understanding appropriate interview topic guide and in line with University of Liverpool's safeguarding policies and procedures for interviewing research participants.

Consent for audio recording of the interview by Dictaphone will be checked verbally before the interview commences. The topic guide has been informed by previous feasibility studies conducted in paediatric NHS settings. 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.

Interviewers will refer to the distress guide and any distress expressed by participants during the interviews will be managed with care and compassion. Participants will be free to decline to answer any questions that they do not wish to answer or to stop the interview at any point. Any such families will be supported in obtaining appropriate help.

We will interview approximately 25-35 participants (~15-20 parents and ~10-15 children) selected from the two recruitment routes. The final number will depend on the point of information power, which considers factors including quality of data and sample variance. All families who express an interest in taking part but are not selected for an interview will be contacted via telephone or email to thank them for their interest in the study.

15.3 Population: Healthcare Practitioners

15.3.1 Eligibility Criteria

Inclusion Criteria:

- Healthcare practitioners (doctors, nurses, research staff and Allied Health Professionals) involved in recruitment to the FROG feasibility trial (WP1)
- UK healthcare practitioners (doctors, nurses, research staff and Allied Health Professionals) not involved in recruitment, screening or conduct of the FROG feasibility trial (WP1)

Exclusion Criteria:

- None

15.3.2 Recruitment and Sampling

We will use social media advertising and send email invites through our PERUKI and GAPRUKI networks to invite UK healthcare practitioners to attend one of up to five online focus groups (mix of healthcare practitioners, approximately 6 to 8 in each group). For healthcare practitioners unable to attend the focus group, we will conduct up to ten telephone interviews. The Research assistant will send a Participant information sheet and provide an opportunity for questions. If they would like to participate, a link to an online consent form will be sent for completion prior to the focus group or interview as well as a list of potential outcomes to read before the focus group or interview.

15.3.3 Focus Group and Interview Procedures

Focus group or interview and topic guides will be informed by early parent/child interview findings to further explore study acceptability, feasibility, and design, including prioritised outcome measures. Clinical scenarios (vignettes) will be used to elicit views on optimal methods of urine collection by population and suitability for recruitment to a future study. Consent for audio recording of interviews will be checked verbally before the focus group or interview begins.

15.4 Data Analysis

Interviews and focus groups will be transcribed, checked and anonymised as the study progresses. QSR NVivo software will be used to assist in the organisation and indexing of qualitative data. Whilst thematic analysis will be informed by the constant comparison approach, 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 definitive RCT). Quantitative data from parent questionnaires will be analysed using SPSS software, and descriptive statistics and exact tests will be used, as appropriate. Data from each method will be analysed separately then synthesised through constant comparative analysis to assess Work Package 2 objectives using the Adapted Framework of Acceptability.

16 WORK PACKAGE 3 – CONSENSUS MEETING

16.1 Feasibility of a Future Trial

The final phase of the study will involve a face-to-face consensus meeting bringing together stakeholders from PERUKI, GAPRUKI, PPI (e.g. PPI members, parents from WP1/WP2 and children from WP1/WP2 if feasible), medical and nursing staff from general practice, ED, inpatient and outpatient settings.

The aim is to bring together key stakeholders to review all the data and seek consensus on whether or not a trial is feasible and acceptable to conduct. If it is deemed feasible, consensus will be sought on a non-invasive sampling arm, and one or two invasive sampling arms (TUBC and/or SPA) for use in a future comparative study.

16.1.2 Eligibility Criteria

Inclusion Criteria:

- Parents/guardians of children (0 to under 16 years) and children (aged 7 to under 16 years) who are approached to participate in WP1 including those who decline randomisation.
  OR

- Parents/guardians of children (0 to under 16 years) and children (aged 7 to under 16 years) who have required urine testing in hospital setting for suspected UTI in the last three years.
  OR
- Healthcare practitioners (doctors, nurses, research staff and Allied Health Professionals) involved in recruitment to the FROG feasibility trial (WP1)
  OR
- UK healthcare practitioners (doctors, nurses, research staff and Allied Health Professionals) not involved in recruitment, screening or conduct of the FROG feasibility trial (WP1)

Exclusion Criteria:

- Language issues (not overcome with use of translators and available translated information sheets)
- Declined consent

A matrix of 40 key stakeholders will be developed. This will include participants involved in WP1 and WP2 who registered their interest in participating in the consensus meeting, in addition to co-investigators, advisory group contacts and subject matter experts from literature review searches. Purposive sampling will be undertaken across fields of expertise and patient groups to help ensure the meeting attendees are representative of key stakeholder groups. This will involve an email invitation and parents/PPI partners who attend will be compensated for their time.

Informed consent will be sought from each participant before the meeting begins with an opportunity for questions. The meeting will begin with a presentation of empirical findings by Dr Tom Waterfield (TW) and Professor Kerry Woolfall (KW). Each aspect of the study including overall acceptability, design, interventions, population of inclusion and outcomes will be discussed in turn. Any areas of disagreement and study feasibility will be discussed and agreed about a potential study and clinical settings. The consensus opinion of relevant stakeholders on key preferred scenarios will then be sought. A voting system (e.g. Turning Point) will be used to help establish consensus if needed. At this stage, if deemed feasible, we will define a clinically valuable definitive trial. The progression criteria are outlined below in section 16.2.

16.2 Progression Criteria

Following WP3 a recommendation for progression to a definitive RCT will be based on the following criteria:

(a) Willingness and ability of health care professionals to screen and recruit eligible children during WP1 (objectives 1 and 2) – as evidenced by recruitment of at least 33% of eligible children.
(b) Mixed methods WP2 data on willingness to screen and recruit patients.
(c) Acceptability, or not, of the definitive study, including the invasive urine sampling intervention – to parents/guardians (objectives 3 and 4), to health care professionals as evidenced by WP2 data (mapped to the Theoretical Framework of Acceptability) and WP3 consensus data as well as expressions of interest for the definitive study.
(d) Development of recruitment and consenting procedures, with associated information materials, that are acceptable to children/parents/guardians based on qualitative insight from families in WP2 (objective 5).

(e) Selection of suitable patient-centred primary and secondary outcomes through consensus in WP3 (objective 5), resulting in a study design that addresses a clinically meaningful research question with adequate power.
(f) Evidence of an adequate number of eligible children to deliver the proposed definitive RCT within a reasonable timeframe (objective 1 and 2).

17 REGULATIONS, ETHICS AND GOVERNANCE

17.1 Regulatory and Ethical Approvals

The study and trial will comply with the principles of GCP and the requirements and standards set out in the UK policy framework for health and social care research. The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The protocol will be approved by a Research Ethics Committee (REC).

The trial protocol is prepared in compliance with the SPIRIT 2013 statement [17, 18] and the trial will be registered at https://www.isrctn.com/ before randomisation of the first participant.

17.2 Protocol Compliance

The investigators will conduct the study in compliance with the protocol given approval/favourable opinion by the REC. A protocol deviation is defined as an incident which deviates from the normal expectation of a particular part of the trial process. Any deviations from the protocol will be fully documented. A serious breach is defined as a deviation from the trial protocol or GCP which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the subjects of the trial; or
(b) the scientific value of the trial

The PI or designee is responsible for ensuring that any potential serious breaches are reported directly to the CTU within one working day using the dedicated email address (clinicaltrials@nictu.hscni.net). The CTU will notify the CI and Sponsor immediately to ensure adherence to reporting requirements to REC where a serious breach has occurred. Protocol compliance will be monitored by the CTU to ensure that the trial protocol is adhered to and that necessary paperwork (e.g. CRFs and participant consent forms) is being completed appropriately.

17.3 Protocol Amendments

investigators will conduct the study in compliance with the protocol given approval by the REC. Changes to the protocol may require ethics committee approval prior to implementation. The CTU in collaboration with the sponsor will submit all substantial protocol modifications to the REC for review in accordance with the governing regulations.

17.4 Good Clinical Practice

The trial will be carried out in accordance with the principles of the International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines (www.ich.org). All members of the trial team will be required to have completed GCP training.

17.5 Indemnity

QUB as Sponsor will provide indemnity for the management and design of the study. QUB will provide indemnity for negligent and non-negligent harms caused to participants by the design of the research protocol. The NHS/HSC indemnity scheme will apply with respect to clinical conduct and clinical negligence.

17.6 Participant Confidentiality

In order to maintain confidentiality, all CRFs, questionnaires, study reports and communication regarding the study will identify the participants by their unique participant study number. Participant confidentiality will be maintained at every stage and their identity will not be made publicly available, to the extent permitted by the applicable laws and regulations.

17.7 Record Retention

The site PI will be provided with an Investigator Site File (ISF) by the CTU and will maintain all trial records according to GCP and the applicable regulatory requirements. The PI is responsible for the archiving of essential documents at their sites in accordance with the requirements of the applicable regulatory requirements, Sponsor and local policies. The PI has a responsibility to allow Sponsor access to archived data and can be audited by the Sponsor on request. If the PI withdraws from the responsibility of keeping the trial records, custody must be transferred to a person willing to accept responsibility and this must be documented in writing to the CTU and Sponsor. Following confirmation from the Sponsor the CTU will notify the PI when they are no longer required to maintain the files.

The TMF will be held by the CTU and the essential documents that make up the TMF will be listed in a SOP. On completion of the trial, the TMF and study data (WP1) will be archived by the CTU according to the applicable regulatory requirements and as required by the QUB as Sponsor. University of Liverpool will hold and archive all essential documents and data for WP2 and WP3. The archiving period for the study will be 10 years.

17.8 Competing Interests

The research costs are funded by the NIHR Health Technology Assessment Programme. The CI and members of the TMG have no financial or non-financial competing interests and the members of the DMEC and TSC will be asked to confirm that they have no conflict of interest. In the event that a DMEC or TSC member reports a conflict of interest, advice will be sought from the Sponsor.

18 DISSEMINATION/PUBLICATIONS

18.1 Publication Policy

We will aim to publish the findings in high impact peer reviewed journals for wide dissemination. The NIHR Journals Library will help with dissemination of findings and will provide an important, permanent and comprehensive record of the study. Participants will be provided with a copy of the trial results and these will also be available on ISRCTN.

Findings will be presented at national and international conferences including annual meetings for the Royal College of Paediatrics and Child Health, Royal College of Emergency Medicine and the European

Society of Emergency Medicine. We will aim to access as wide an audience as possible, of professionals from the UK and around the world, as international interest is likely to be high.

The information is expected to be incorporated into BSAC and NICE guideline recommendations on the acceptability of invasive urine sampling methods to children and young people. Although only a feasibility study the results on acceptability of invasive urine sampling is likely to be of interest to policy makers in lieu of the definitive study.

18.2 Authorship Policy

Authorship will be determined according to the internationally agreed criteria for authorship (www.icmje.org).

18.3 Data Access/Sharing

Following publication of the primary and secondary outcomes there may be scope to conduct additional analyses on the data collected. In such instances formal requests for data will need to be made in writing to the CI via the CTU, who will discuss this with the Sponsor. The study will comply with the good practice principles for sharing individual participant data from publicly funded clinical trials [31, 32] and data sharing will be undertaken in accordance with the required regulatory requirements. In the event of publications arising from such analyses, those responsible will need to provide the CI with a copy of any intended manuscript for approval prior to submission.

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