University Hospitals Birmingham NHS
NHS Foundation Trust

The G-ToG Trial

G-ToG – Gentamicin in the Treatment of Gonorrhoea

A randomised controlled trial to compare the clinical effectiveness and safety of gentamicin and ceftriaxone in the treatment of gonorrhoea

CLINICAL TRIAL PROTOCOL

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VERSION CONTROL LOG

There have been no previous versions of this protocol.

PROTOCOL SIGNATURE SHEET

This protocol has been approved by:

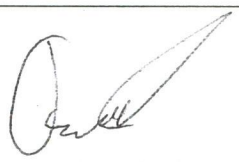
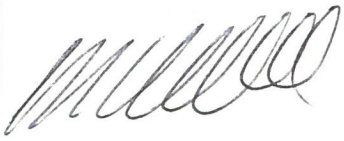
Name and role	Signature	Date
Professor Jonathan Ross **Chief Investigator**		25.7.14
Dr Chris Counsell **Sponsor Representative (Head of Research and Development (Governance))**		29th July 2014

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TABLE OF CONTENTS

SYNOPSIS

Title	A randomised controlled trial to compare the clinical effectiveness and safety of gentamicin and ceftriaxone in the treatment of gonorrhoea
Acronym	G-TOG
Short title	**G**entamicin in the **T**reatment **O**f **G**onorrhoea
Chief Investigator	Professor Jonathan Ross Professor of Sexual Health and HIV Department of GU Medicine University Hospitals Birmingham NHS Foundation Trust
Objectives	The primary objective of the study is to determine whether gentamicin is an acceptable alternative to ceftriaxone, in the treatment of gonorrhoea. This will be addressed by determining whether the rate of microbiological clearance of *Neisseria gonorrhoeae* in participants treated with gentamicin is non-inferior to the rate in participants treated with ceftriaxone.
Trial Configuration	Phase III, Multicentre, parallel group, investigator-blinded, non-inferiority randomised controlled trial
Setting	Sexual Health Clinics in the UK
Sample size estimate	Based on an efficacy rate of 96% for the ceftriaxone regimen which is consistent with previous trials, a total sample size of 646 for analysis (323 in each group) will achieve 90% power to detect non-inferiority with lower confidence interval for the absolute risk difference of 5%. The significance level is 0.025. To allow for a loss to follow-up rate of up to 10%, the study will recruit a total of 720 participants.
Number of participants	720 participants – 360 in each treatment group
Eligibility criteria	**Inclusion criteria** Individuals must meet ALL of the following to be included in the study • Individuals aged 16-70 years. • Diagnosis of uncomplicated untreated genital, pharyngeal or rectal gonorrhoea based on a positive gram stained smear on microscopy, or positive NAAT. • Written informed consent provided. **Exclusion criteria** Individuals will be excluded from the study if they meet ANY of the following • Known concurrent bacterial sexually transmitted infection (apart from chlamydia).

	• Known contra-indications or allergy to gentamicin, ceftriaxone, azithromycin or lidocaine. • Pregnant or breast-feeding. • Current clinical diagnosis of complicated gonorrhoea infections eg pelvic inflammatory disease, epididymo-orchitis. • Weight less than 40kg at the time of randomisation • Currently receiving or have received ceftriaxone or gentamicin within the preceding 28 days. • Previous participation in this study
Description of interventions	**Intervention**: Gentamicin (240mg) administered as an intramuscular injection. **Control:** Ceftriaxone (500mg) administered as an intramuscular injection. Additionally both groups will receive a single oral dose of azithromycin (1g).
Duration of study	Participants are asked to return to the clinic for a follow-up visit at 2 weeks. Each participant will remain in the study until this follow-up visit has been completed.
Randomisation and blinding	Participants will be randomised to a single IM injection of gentamicin with 1g oral azithromycin or to a single IM injection of ceftriaxone with 1g oral azithromycin. Participants will be randomised using a secure web based system. Participants, investigators and research staff assessing the participant at follow-up will be blinded to the treatment allocation.
Outcome measures	**Primary outcome measure.** The primary outcome measure is clearance of *N. gonorrhoeae* at all infected sites confirmed by a negative NAAT, two weeks post treatment (as recommended by the British Association for Sexual Health and HIV). The results from the AC NAAT will be considered primary. **Secondary outcome measures** Secondary outcomes are • clinical resolution of symptoms • frequency of nausea/vomiting, hearing loss, dizziness and rash. • frequency of other adverse events • tolerability of therapy • relationship between clinical effectiveness and MIC to inhibit *N. gonorrhoeae* growth • cost effectiveness

Statistical methods	The analysis and reporting of the trial will be in accordance with CONSORT guidelines. A full statistical analysis plan will be developed prior to completion of data collection. Continuous variables will be summarised in terms of the mean, standard deviation, median, lower and upper quartiles, minimum, maximum and number of observations. Categorical variables will be summarised in terms of frequency counts and percentages. Descriptive statistics of demographic and clinical measures will be used to compare balance between the randomised arms at baseline. The evaluation of the primary clinical outcome variable will be performed using a general linear model for binary outcome adjusted by clinic site. Gentamicin will be regarded as non-inferior if the lower 95% confidence limit for the risk difference in confirmed clearance is -5 percentage points or greater. Secondary outcomes will be similarly analysed using appropriate regression models dependent on data type (binary, continuous etc), adjusted for clinic site and baseline value of the outcome variable if collected. Safety and tolerability analysis will be of descriptive nature. Frequency counts and percentages of the per-specified main categories of side effects and AEs will be presented by treatment arm.

LIST OF ABBREVIATIONS & DEFINITIONS

Abbreviation	Definition
AC	Aptima Combo
ADR	Adverse Drug Reaction
AE	Adverse Event
AR	Adverse Reaction
BD	Becton Dickinson
DMC	Data Monitoring Committee
DMP	Data Management Plan
IM	Intra-muscular
IMP	Investigational Medicinal Product
NAAT	Nucleic acid amplification test
NIHR	National Institute for Health Research
RCT	Randomised Controlled Trial
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
STBRU	Sexually Transmitted Bacteria Reference Unit
SUSAR	Serious Unexpected Suspected Adverse Reaction
TSC	Trial Steering Committee
VAS	Visual Analogue Scale

1 BACKGROUND INFORMATION

N. gonorrhoeae readily develops resistance to antibiotic regimens. There are now high levels of resistance against penicillins, sulphonamides, tetracyclines and quinolones, all of which are no longer recommended for use. Current guidance from the British Association for Sexual Health and HIV is to treat with ceftriaxone (given with adjunctive azithromycin). Recent surveillance data show a reduction in sensitivity to ceftriaxone with an upward drift in the minimum inhibitory concentration [MIC] (13% with MIC over 0.03mg/l in 2010 cf. 1% in 2007) i.e. the proportion of cases which remain highly sensitive to ceftriaxone is decreasing over time[1]. Sporadic clinical failure of cephalosporins has been reported from Japan, Sweden, Spain and France [2] [3] [4] [5] [6]. The same reduction in antibiotic sensitivity was followed by widespread clinical failure within a few years for other antimicrobials (penicillin, tetracyclines and quinolones) used to treat gonorrhoea. Options to treat gonorrhoea are severely limited if cephalosporins become ineffective. With the exception of gentamicin, alternative agents have not been assessed in vivo (e.g. ertapenem, solithromycin)[7] [8] [9] [10], are reserved for specific infections (e.g. rifampicin for tuberculosis) [11] or have the potential to rapidly develop resistance (e.g. spectinomycin) [12].

The efficacy of gentamicin to treat gonorrhoea has been reported in small observational or controlled trials which date from the 1970s/80s, and all have a significant risk of bias [13] [14] [15] [16] [17] [18] [19] [20] [21] [22] Clinical and microbiological cure rates range from 65-100%. No adverse events were reported in these studies. No data are available on the efficacy of gentamicin when treating gonorrhoea in the pharynx or rectum, although antibiotics are sometimes less effective at these sites. A recent systematic review on gentamicin monotherapy found 3 studies (including 1 randomised controlled trial (RCT)) with cure rates of 91-95%, but the studies were small and had a significant risk of bias[23].

Gentamicin is usually bacteriocidal in action. Although the exact mechanism of action has not been fully elucidated, the drug appears to inhibit protein synthesis in susceptible bacteria by irreversibly binding to 30S ribosomal subunits. In general, gentamicin is active against many aerobic gram-negative bacteria and some aerobic gram-positive bacteria.

Ototoxicity and nephrotoxicity are the most common side effects associated with gentamicin therapy. Both effects are related to renal impairment and their frequency following a single dose of gentamicin is not known.

There have been rare reports of changes in electrolyte balance including hypocalcaemia and hypokalaemia caused by renal tubular dysfunction. Vestibular damage and ototoxicity may occur. This is usually reversible if observed promptly and the dose adjusted. Other adverse reactions associated with gentamicin therapy include nausea, vomiting, urticaria, reversible granulocytopenia, allergic contact sensitisation and neuromuscular blockade. There have been a few reports of anaphylactic reactions associated with gentamicin containing therapy.

Gentamicin 240mg will be given as a single intramuscular injection. In the published observational and controlled studies (including the three quoted in the Kirkcaldy systematic review[23]), 240mg was the most commonly chosen dose of gentamicin used (range 160mg-350mg) and no significant dose response effect is evident comparing across studies. Gentamicin has been used to treat gonorrhoea in Malawi for 20 years. A single 240mg i.m. dose was adopted there in 1993 as empirical therapy. In 2007 a survey confirmed continued susceptibility with all isolates having gentamicin MIC values of under 8 mg/l[24]. Slightly higher gentamicin MICs have recently been reported from a multinational European survey (MIC range 1 mg/l to 16 mg/l; modal MIC 8mg/l)[25].

The trial will be conducted in compliance with the protocol, GCP, ethics committee and MHRA requirements.

Gentamicin will be compared to ceftriaxone for the treatment of gonorrhoea. Participants will be randomised to receive either a single intramuscular injection of gentamicin (240mg) OR a single intramuscular injection of ceftriaxone (500mg). Additionally both groups will receive a single oral dose of azithromycin (1g).

The trial will recruit patients aged 16-70 years with a diagnosis of genital, pharyngeal and/or rectal gonorrhoea attending a participating sexual health clinic in the United Kingdom.

2 OBJECTIVES

2.1 Primary Objectives

The primary objective of the study is to determine whether gentamicin is an acceptable alternative to ceftriaxone, in the treatment of gonorrhoea. This will be addressed by determining whether the rate of microbiological clearance of *Neisseria gonorrhoeae* in participants treated with gentamicin is non-inferior to the clearance in participants treated with ceftriaxone.

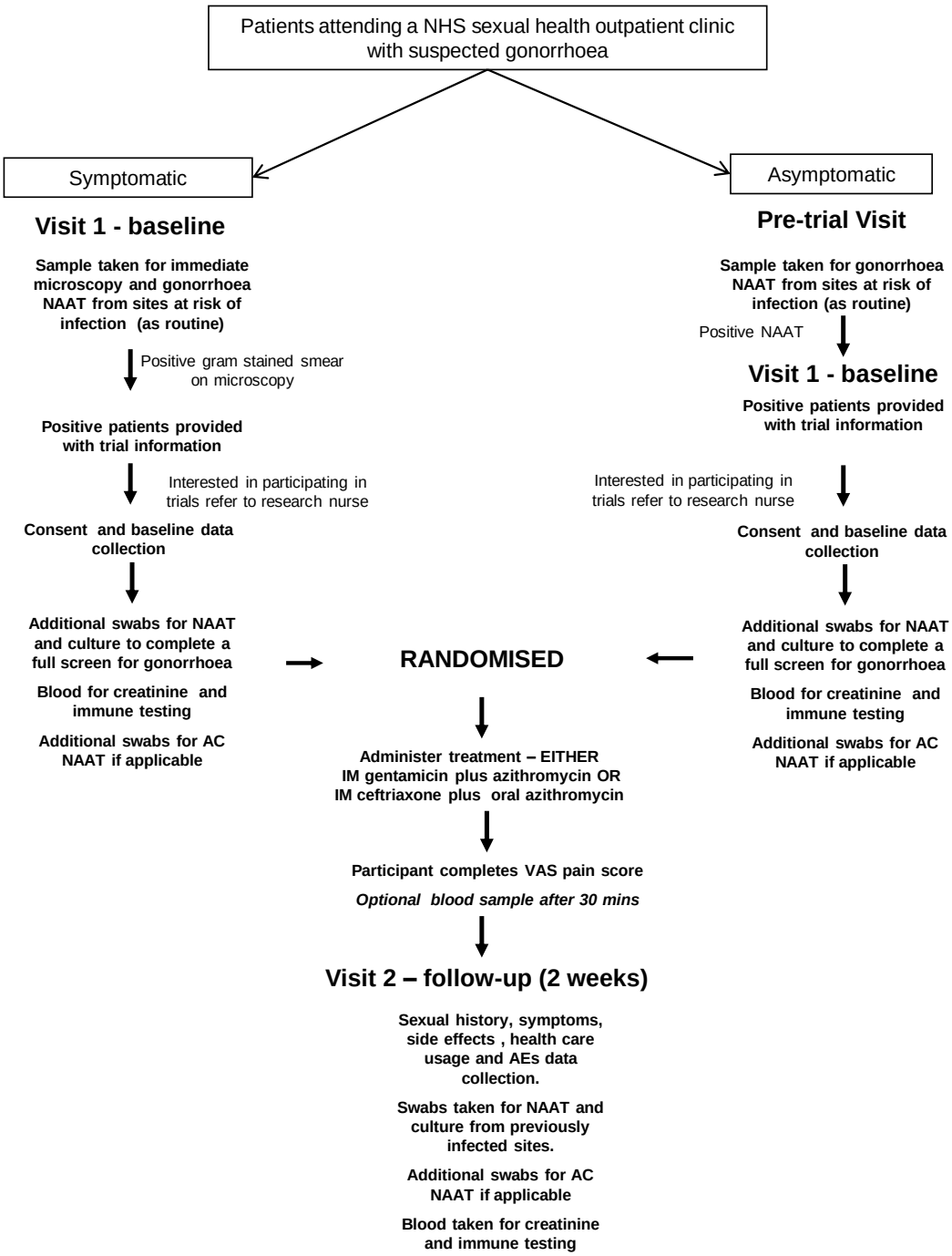
2.2 Secondary Objectives

Secondary objectives of the study are:

- To determine whether a single intramuscular dose of gentamicin is safe and well tolerated
- To determine whether a single intramuscular dose of gentamicin is cost effective to the NHS when used to treat gonorrhoea
- To determine the relationship between clinical effectiveness and the laboratory measurement of antibiotic effectiveness (the minimum inhibitory concentration (MIC) required to inhibit growth of *N. gonorrhoeae*)

3 TRIAL OVERVIEW

Figure 1



4 TRIAL DESIGN

4.1 Methodology

The study will be a multicentre, parallel group, blinded, randomised trial with equal allocation [1:1].

Patients with a provisional (indicated by a positive gram stain on microscopy) or confirmed (indicated by a positive nucleic acid amplification test (NAAT)) diagnosis of gonorrhoea will be approached by a member of the site research team to determine whether they are interested in participating in the study. They will be provided with written information about the study and the researcher will explain the study verbally to them and address any questions and concerns the patient may have. Due to the requirement for rapid treatment after diagnosis, patients will be asked to give their consent at the same clinic visit.

Diagnosis will be by a positive gram stained smear on microscopy for symptomatic patients, and by NAAT for asymptomatic patients or those negative on microscopy.

After informed consent baseline information will be collected. This will include demographic information, details of the participant's sexual history, and details of their symptoms. Additional swabs will be taken for NAAT and culture as required to complete a full sampling profile for each participant. Blood samples will also be taken to measure baseline creatinine levels and for storage for subsequent measurement of immune responses to gonorrhoea. Participants will then be randomised to receive either an intramuscular injection of gentamicin or an intramuscular injection of ceftriaxone. The participant will not be aware which treatment they have received. Staff administering the injections will be aware of which treatment the participant is receiving but will not be part of the trial research team and will be trained to ensure that this information is not provided to the participant or to any member of the research team assessing the participant. All participants will also receive an oral dose of azithromycin (standard treatment). Treatment will be given as soon as possible after randomisation. Following the injection, participants will be asked to rate how uncomfortable their injection was using a visual analogue scale (VAS).

Participants may also be asked to consent to provide a blood sample to be used in a separate sub study to determine the pharmacokinetics of gentamicin. This consent is optional and participants who do not consent are still eligible to participate in the main trial. If a participant consents to the sub-study, the blood sample will be taken 30 minutes after injection of study drug. To maintain blinding, all participants who consent to this sub-study will have the additional blood sample taken irrespective of their randomised treatment allocation.

Participants will be asked to return to clinic 2 weeks after their treatment for a follow-up visit. During this visit swabs from the previously infected sites will be taken for NAAT and culture to assess clearance of *N. gonorrhoeae*.

Blood samples will be taken to determine creatinine levels, and for storage for subsequent measurement of immune responses to gonorrhoea. In addition, all participants will also be asked about their sexual history, their symptoms and any side effects they may have experienced in the two weeks since they were treated.

The importance of attending the clinic for the 2 week follow-up visit will be emphasised to the participant and they will be reminded of their appointments using methods currently used in the individual clinics such as SMS messaging and telephone reminders.

Once the 2 week follow-up visit has been completed, this is considered to be the end of the study for the participant.

If results show that the participant still has gonorrhoea, they will be offered further investigation and treatment according to local guidelines. This will not be considered part of the study.

4.2 Target Number of participants

It is aimed that 720 participants are randomised into this trial – 360 into each treatment group.

4.3 Expected Duration of Study

It is expected that the study will be of 3 years' duration from the start of the study to the submission of the final report to NIHR. The recruitment period is planned to be 26 months.

4.4 Primary and Secondary Outcome Measures

Primary outcome measure.
The primary outcome measure is clearance of *N. gonorrhoeae* at all infected sites confirmed by a negative NAAT, two weeks post treatment (as recommended by the British Association for Sexual Health and HIV). The results from the AC NAAT will be considered primary.

Secondary outcome measures
Secondary outcomes are

- clinical resolution of symptoms
- frequency of nausea/vomiting, hearing loss, dizziness and rash.
- frequency of other adverse events
- tolerability of therapy
- relationship between clinical effectiveness and MIC to inhibit *N. gonorrhoeae* growth
- cost effectiveness

The NAAT is an automated laboratory test and therefore it is not subject to bias through knowledge of treatment allocation. The method of NAAT performed varies between centres, therefore for those centres where the AC NAAT method is not used by the local laboratory, additional swabs will be taken and sent for testing at a central laboratory using this method. This will ensure consistency in diagnosis and response for all participants for the ascertaining the primary end point of the study.

A doctor/nurse independent of the trial will administer the study drug and will therefore not be blinded to the treatment allocation. The participant and the physicians/nurses performing the initial and follow up assessment 2 weeks after treatment, and the laboratory staff performing microbiology analyses will be blinded to the treatment given in order to minimise any bias in the collection of outcome data.

5 ELIGIBILITY CRITERIA

5.1 Inclusion Criteria

Individuals must meet ALL of the following to be included in the study

- Individuals aged 16-70 years.
- Diagnosis of uncomplicated untreated genital, pharyngeal or rectal gonorrhoea based on a positive gram stained smear on microscopy, or positive NAAT.
- Written informed consent provided.

5.2 Exclusion Criteria

Individuals will be excluded from the study if they meet ANY of the following

- Known concurrent bacterial sexually transmitted infection (apart from chlamydia).
- Known contra-indications or allergy to gentamicin, ceftriaxone, azithromycin or lidocaine.
- Pregnant or breast-feeding.
- Current clinical diagnosis of complicated gonorrhoea infections eg pelvic inflammatory disease, epididymo-orchitis.
- Weight less than 40kg at the time of randomisation
- Currently receiving or have received ceftriaxone or gentamicin within the preceding 28 days.
- Previous participation in this study

6 ENROLMENT AND WITHDRAWAL

6.1 Screening

A screening log will be maintained at each site detailing the number of patients approached about the study and the number agreeing to participate.

6.2 Informed Consent and Participant Information

Participants who have a provisional or confirmed diagnosis of gonorrhoea will be asked if they are interested in participating in the study. If they indicate interest, an appropriately qualified member of the research team will provide them with a patient information leaflet, explain the background and aims of the study, and explain what will happen if they decide to participate in the study and what they can expect if they do not participate.

The participant will be given time for consideration and to ask questions. Consent will be requested during the same clinic visit due to the requirement for immediate treatment.

The decision regarding participation in the study is entirely voluntary. The investigator or their nominee shall emphasise to them that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled. No trial-specific interventions will be done before informed consent has been obtained.

Written consent will be sought by an appropriately qualified member of the research team (doctor or nurse).

<u>Optional consent</u>

Participants will be asked for separate consent to provide an additional blood sample 30 minutes after their injection to allow a pharmacokinetic analysis to be performed.

Sexual health clinics do not routinely inform patient's GPs of their attendance or treatments. Whilst GP information is usually requested, provision of this is not obligatory. Some clinics will specifically ask if contact with the GP can be made but no clinics will routinely write to the GP without permission. Patient surveys have shown that the majority of patients, when asked, do not wish their GPs to be informed of their attendance at the clinic. Patients frequently receive licensed medication at GU clinics without their GP being specifically informed. Therefore, participants will be asked to provide separate consent if they want their GP to be informed of their participation in the study.

Participants will also be asked if they would like to receive a summary of the results at the end of the study. If they consent to this, they will be asked to provide contact details which will be securely held independently of their study data. These details do not have to be their home address and could potentially be a work address or an e-mail address.

It will be made clear to potential participants that not consenting to have an additional blood sample at 30 mins, not wishing their GP to be informed of their participation or not wishing to provide a contact address to receive a summary of their results will not preclude participation in the trial.

The participant will receive a copy of their signed and dated form and the original will be retained in the Trial Master File. A second copy will be filed or scanned into the participant's medical notes and a signed and dated annotation made in the notes that informed consent was obtained for the trial.

The process for obtaining participant informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The investigator or their nominee and the participant or other legally authorised representative shall both sign and date the Consent Form before the person can participate in the study.

The investigator will inform the participant of any relevant information that becomes available during the course of the study, and will discuss with them, whether they wish to continue with the study. If applicable they will be asked to sign revised consent forms.

6.3 Subject Withdrawal

Participants can be discontinued at any part of the study at any point in the study. They may withdraw themselves or may be withdrawn by a physician.

Withdrawal from treatment
Given that there is only one dose of medication given and that this is administered in close proximity to randomisation, it is unlikely that a participant would withdraw their consent to treatment. If the participant did withdraw they would be treated according to their local clinical protocol. In line with the intention to treat principle, they would be asked to come back to clinic 2 weeks after to complete the study assessments.

Withdrawal from Follow-up
Participants will be encouraged to attend for their follow-up visit, 2 weeks after treatment. However, they are free to withdraw from the study and therefore the follow-up assessment. They will be asked their reason(s) for withdrawal but are not obliged to provide these. Unless a participant specifically asks, untested samples will be tested and included in the analyses.

6.4 Assessment of feasibility

Nine months after recruitment opens accrual will be reviewed by the TSC to determine whether the feasibility criteria have been met. The feasibility criteria will be agreed in advance by the TSC but are likely to include:

- If recruitment is below 80% of target at 9 months, effective and realistic strategies to increase recruitment and retention will be required in order for the study to proceed.
- If the study does proceed, there will be an additional assessment of recruitment.
- If the number of completed follow-up participants is below 50%, the study will be stopped.

The data monitoring committee will examine unblinded safety data to determine the on-going safety profile of gentamicin and can make recommendations about trial progression to the trial steering committee.

7 RANDOMISATION AND BLINDING

7.1 Randomisation

Participants will be assigned to treatment groups using a remote internet based randomisation system maintained by the Nottingham Clinical Trials Unit (NCTU). Access to the system will be granted by the NCTU in accordance with the responsibilities on the delegation log.

Once a patient has provided consent for trial participation an authorised member of the research team will log in to the secure randomisation system and register/randomise the participant. This will generate a prescription for "trial treatment" (the actual treatment will not be specified on this prescription), containing the participant's Trial Identification Number and a unique study drug identification code for the participant. This study drug identification code will be provided to the member of staff administering the study drug to the participant who will not be blinded to the treatment allocation.

The member of staff administering the study drug will log into a separate area of the randomisation system and enter the unique study drug identification code which will reveal the treatment (gentamicin or ceftriaxone) that the participant is to receive.

This two-step approach will maintain the blinding for members of the research team who may be involved in the assessment of the participant.

7.1.1 Randomisation schedule

The randomisation schedule is based on a computer generated pseudo-random code using random permuted blocks of randomly varying size, created by the Nottingham Clinical Trials Unit (NCTU) in accordance with their standard operating procedure (SOP) and held on a secure University of Nottingham server. The randomisation will be stratified by clinical centre.

The randomisation website will be accessed by means of a remote, internet-based randomisation system developed and maintained by the NCTU.

7.2 Blinding

Only the nurse/doctor administering the treatment will know what treatment the participant has been randomised to. The participant and staff involved in the care and assessment of the participant will not know what treatment they have been randomised to. This should ensure the minimisation of any bias in assessment due to knowledge of the treatment administered,

7.2.1 Maintenance of blinding

The study drugs are taken from routine clinic stock, therefore in order to maintain blinding, the study drug must be made up (see Section 8) in an area where the participants and staff involved in the care and assessment of the participant cannot see, and all packaging must be kept out of sight.

Members of the research team, and in particular the clinician who assesses the participant at their 2 week visit, should not have any knowledge of the treatment the participant has received to allow their assessment to be conducted in an unbiased manner.

The member of staff who administers the treatment will be unblinded and should not be involved in the assessment of participants.

Each site will have a procedure to ensure blinding within the trial.

The clinician who assesses the participant at their 2 week visit should not have any knowledge of the treatment the participant has received to allow their assessment to be conducted in an unbiased manner.

7.2.2 Unblinding

To maintain the overall quality and legitimacy of the clinical trial, blind break should only occur in exceptional circumstances when knowledge of the actual treatment is absolutely essential for further management of the patient. Investigators are encouraged to discuss with the Chief Investigator if he/she believes that unblinding is necessary.

It is unlikely that individual treatment allocations will have to be prematurely disclosed since the intervention is a single dose and there is no antidote to the intervention. However, there will be an electronic web-based system available 24 hours a day where authorised personnel are able to log in to determine what treatment a participant has received. This system will record who has broken the blind, when and for what reason. If emergency unblinding is deemed to be necessary, this system should be used.

The Investigator is encouraged to maintain the blind as far as possible.

If required, the data monitoring committee will review unblinded data to determine on-going safety and tolerability of the treatments.

8 STUDY TREATMENT

8.1 Treatment Arms

There are two treatment arms within the study:

- Gentamicin (240mg) administered as a single intramuscular injection.
- Ceftriaxone (500mg) administered as a single intramuscular injection.

Both groups will also receive azithromycin (1g) administered orally.

8.2 Control Group

The control group will be the group randomised to receive ceftriaxone. Both groups will also receive standard treatment with oral azithromycin (1g)

8.3 Description of Study IMP(s)

All treatments will use standard clinic stock. Any licensed brand may be used.

Gentamicin injection (gentamicin sulphate Ph Eur equivalent to 80mg/2ml Gentamicin base).

Ceftriaxone powder for solution for injection.

Azithromycin and the lidocaine used in the preparation of the ceftriaxone injection are not considered to be IMPs.

8.4 Preparation, Dosage and Administration

Participants will be randomised to receive either a single intramuscular injection (IM) of gentamicin (240mg) OR single IM injection of ceftriaxone (500mg). Additionally both groups will receive a single oral dose of azithromycin (1g).

The injections will be prepared, following the instructions in the relevant Summary of Product Characteristics (SMPC) by an unblinded nurse.

Ceftriaxone should be dissolved in 1% Lidocaine Injection BP according to the SMPC. The solution should be administered by deep intramuscular injection.

Gentamicin should be administered by deep intramuscular injection according to the SMPC.

Treatment should be given in clinic as soon as possible after randomisation.

The batch number(s) and manufacturer(s) of all the products administered and the date of administration should be recorded on the form provided through the electronic randomisation system.

8.5 Dose Modification

No dose modifications are expected in this trial.

8.6 Dispensing and IMP accountability

An authorised, unblinded member of staff will log onto the randomisation system to determine what treatment has been allocated to the participant.

The treatment(s) will then be collected from a secure storage area and will be prepared out of sight of both the participant and any blinded members of the research team. This will minimise the potential for unblinding of the study drug

The batch numbers, manufacturers and date of administration of all products administered will be recorded on forms provided by the electronic randomisation system.

There will be no requirements for IMP accountability logs since the treatments are taken from clinic stock and batch numbers are being recorded.

8.7 Selection and Timing of dose

Gentamicin will be administered as a single IM injection (240mg) and ceftriaxone will be administered as a single IM injection (500mg). Azithromycin will be provided as a single oral dose (1g). The order of administration will be according to local protocol or participant preference.

8.8 Prior and Concomitant Therapy

Participants should not be currently receiving or have received gentamicin or ceftriaxone within 28 days of randomisation.

Participants currently receiving medication which is contraindicated for use with gentamicin, ceftriaxone, azithromycin or lidocaine, should not be included in the study.

8.9 Continuation of treatment or therapy

Study treatment is given only on one occasion. There is no requirement for any additional study treatment. If results show that the participant still has gonorrhoea, they will be offered further investigation and treatment according to local guidelines. This will not be considered part of the study.

9 PROCEDURES AND ASSESSMENTS

9.1 Overview

A summary of trial assessments is shown in Table 1 below.

Table 1. Table of assessments

	Pre-trial[1]	Baseline	End of study (2 weeks)
		Visit 1	Visit 2
Before trial (routine care – not part of trial)			
NAAT swabs	X		
Microscopy swab	X[2]		
Patients with a positive diagnosis given information about trial		X	
Trial			
Informed consent		X	
Baseline information (demography, eligibility)		X	
Pregnancy test (females)		X	
Symptom assessment		X	X
Sexual history		X	X
NAAT swabs		X[3,4]	X[5]
Microscopy and culture swabs		X[4]	X[5]
Blood sample for creatinine and immune response measurement		X	X
Randomisation		X	
Administration of treatment		X	
VAS score for injection site pain		X	X
Optional blood sample for pharmacokinetic measures		X[6]	
Health Utility questions			X
Side effects/toxicity questions[7]			X
Collection of adverse events			X
Serious adverse events			X

[1]Pre-trial will be the same day as Visit 1 for symptomatic patients and approx. 2 weeks before Visit 1 for asymptomatic patients.
[2]Only for symptomatic patients
[3] Duplicate swabs required for patients in the centres which do not perform Aptima Combo NAAT testing.
[4]To complete full test screen.

- Heterosexual men – NAAT from urethra (or urine); culture from urethra
- Men who have sex with men – NAAT from urethra (or urine), pharynx and rectum. Culture from urethra, pharynx and rectum.
- Women – NAAT from vagina, pharynx and rectum. Culture from cervix, pharynx and rectum.

[5]Only from previously infected sites
[6]30 mins after injection
[7]Questionnaire specific to known side effects

9.2 Pre-trial

Prior to being considered for entry into the trial, potential participants will undergo any diagnostics assessments in accordance with routine local clinical practice.

Routine local procedure is usually as follows:

Symptomatic patients
If the patient is symptomatic, a sample is taken for immediate microscopy and gonorrhoea NAAT from sites at risk of infection based on the patient's sexual history (urethra [or urine for men], cervix, pharynx, rectum), according to local practice. Where clinically indicated, microscopy is also performed on samples from the urethra and/or cervix (and optionally from the rectum following proctoscopy).

Symptomatic patients will be asked to wait in clinic for the results of their microscopy.

Asymptomatic patients
If the patient is asymptomatic samples are usually taken for gonorrhoea NAAT from sites at risk of infection according to local practice. No sample is required for immediate microscopy.

Asymptomatic patients will be contacted if they have a positive NAAT test result, and asked to return to clinic after their positive test results are available.

9.3 Baseline assessments (Visit 1)

If a symptomatic patient shows gram positive diplococci on microscopy of a stained smear, they are assumed to have gonorrhoea and therefore require treatment. The baseline visit (visit 1) for symptomatic patients is the same as their pre-trial visit, as they are tested and diagnosed at that visit.

For asymptomatic patients that are found to be positive for gonorrhoea, visit 1 will take place approximately two weeks after the pre-trial clinic visit when the patient is recalled to clinic after their test result is available (as per routine standard practice).

Once informed consent has been obtained (see section 6.2) the following trial-specific assessments are required:

9.3.1 Pregnancy test

A pregnancy test must be performed for female patients of child bearing potential where there is a risk that they could be pregnant. Any patients with a positive pregnancy test will be excluded from entering the trial.

9.3.2 Collection of baseline information, sexual history and symptom assessment

Baseline and sexual history information will be taken from the patient and their symptoms assessed during visit 1.

9.3.3 Swabs

In all centres, participants will have additional swabs taken, if required, so that a full sampling profile is obtained for both NAAT and culture. The routine swabs taken pre-trial will contribute to the full sampling profile ie swabs are only required from those sites from which samples have not already been taken prior to entry into the trial. All samples will be analysed locally.

A full sampling profile is defined as

- Heterosexual men – NAAT and culture testing from urethra (for NAAT a urine sample can be taken as an alternative to urethra)
- Men who have sex with men – NAAT and culture testing from urethra, pharynx and rectum (for NAAT a urine sample can be taken as an alternative to urethra)
- Women – NAAT and culture testing from cervix, pharynx and rectum (for NAAT a vaginal sample can be taken as an alternative to cervix).

Asymptomatic patients only: Participants will undergo the same study procedures as the symptomatic patients after diagnosis with the exception that a full sampling profile for NAAT and culture for the local lab will be taken ie the routine swabs taken for diagnosis (at the pre-trial visit) will be taken again, in addition to the swabs required to make up the full sampling profile. This will indicate if there has been further infection since initial testing.

In centres which do not perform Aptima Combo (AC) NAAT testing, in addition to the swabs for local testing and culture, a separate full sampling profile will be taken post-randomisation for AC NAAT testing at a central laboratory (*Sexually Transmitted Bacteria Reference Unit (STBRU), Public Health England).*

Where possible, swabs should be taken in the following sequence: swabs for AC NAAT, swabs for BD NAAT (where applicable), swabs for culture.

9.3.4 Blood sample for creatinine and immune response measurement

If a blood sample for routine STI screening has not already been taken, two additional blood samples will be taken when it is - an extra 2-3ml to have the creatinine level measured, and 28mls for storage to measure the immune response to gonorrhoea infection (20mls serum plus 8mls EDTA). If the routine blood sample has been taken prior to informed consent, then an additional venepuncture will be performed to collect samples for baseline creatinine level and to measure immune response.

9.3.5 Randomisation and administration of treatment

The participant will then be randomised to receive either a single IM injection of gentamicin or a single IM injection of ceftriaxone. They will also receive an oral dose of azithromycin. See section 7 for further details on randomising a patient.

9.3.6 VAS score for injection site pain

The participant will be asked to assess the discomfort associated with their injection using a visual analogue scale (VAS).

9.3.7 Optional blood sample for pharmacokinetic sub-study

If the participant had consented to provide an additional blood sample for further investigation including pharmacokinetic assessment, a 10ml clotted blood sample will be taken 30 minutes after their injection.

9.4 Follow-up (Visit 2)

All participants would be asked to return to clinic a minimum of 2 weeks after treatment.

All participants will have swabs taken for NAAT and culture from all previously infected sites. In addition, swabs from the urethra and cervix will be taken for microscopy, if they were previously infected.

In addition, in centres which do not perform AC NAAT, swabs will be taken from all previously infected sites for AC NAAT at the STBRU. These swabs are additional to those taken for local NAAT testing.

Participants will have their symptoms assessed and sexual history since their last visit recorded. They will also be asked about specific known side effects and whether they have experienced any other adverse events. They will also be asked some short questions about any additional health resource use. Participants will be asked to complete a VAS indicating the pain they experienced from their previous injection.

Participants will have a 2-3ml blood sample taken for creatinine measurement and blood sampling for storage to measure immune response to gonorrhoea infection (28ml - 20ml serum plus 8ml EDTA).

Participants will be given the results of the microscopy in accordance with standard local practice and therefore they will be aware of whether their gonorrhoea has been cleared.

This would denote the end of the trial for the participant.

9.5 Sample analysis, storage and transport.

Details of sample analysis, storage and transport are provided in the trial manual.

10 CLINICAL AND LABORATORY ASSESSMENTS

10.1 Clinical Assessments

Clinical assessments - baseline
Participants will have their symptoms assessed at baseline.

Clinical assessments – follow-up
Participants will have their symptoms assessed at the 2 week follow-up visit.
They will also be asked about any side effects and adverse events, and about health resource use.

10.2 Laboratory assessments

Table 2 provides a summary of the laboratory samples to be taken.

Table 2 Laboratory samples

	Symptomatic	Asymptomatic	All
	Visit 1	**Visit 1**	**Visit 2**
PRE-TRIAL			
Routine swabs for microscopy	✓		
Routine swabs for local NAAT	✓	✓	
Routine swabs for local culture	✓	✓	
AFTER CONSENT			
Swabs			
Additional swabs to make up full sampling profile for local NAAT	✓		
Additional swabs to make up full sampling profile for local culture	✓		
Full sampling profile for local NAAT		✓	
Full sampling profile for local culture		✓	
Full sampling profile for AC NAAT at STBRU (for centres who do not perform AC NAAT)	✓	✓	
Swabs from infected sites for microscopy			✓
Swabs from infected sites for NAAT			✓
Swabs from infected sites for local culture			✓
Swabs from infected sites for AC NAAT at STBRU (for centres who do not perform AC NAAT)			✓
Blood			
2-3ml for creatinine levels	✓	✓	✓
28ml for storage for immune study	✓	✓	✓
10ml for pharmacokinetic analysis (optional)	✓	✓	

Routine samples should be analysed in local laboratories according to local practice.

The clinical management of the participant will be based on the results of local laboratory testing.

Additional samples to make up the full sampling profile for local NAAT and local culture will be analysed in local laboratories according to local practice.

For centres who do not perform AC NAAT, additional samples must be shipped to STBRU using materials provided by STBRU. Details instructions are provided in the Trial Manual.

For all centres, any positive cultures must be shipped to STBRU using materials provided by STBRU. Detailed instructions are provided in the Trial Manual.

Blood samples taken for the immune response study and any blood samples taken for the optional pharmacokinetic study will be sent to the University of Birmingham for preparation, storage and analyses. Detailed instructions are provided in the Trial Manual.

The results of testing by the STBRU will be transferred directly to the NCTU. Participating centres will not be provided with copies of these results.

Full details of the laboratory assessments will be provided in the trial laboratory manual. This will include details of sample preparation, storage and transfer requirements.

11 Assessment of Efficacy

Efficacy will be measured primarily by clearance of *N. gonorrhoeae* at the infected site(s), two weeks post-treatment. Clearance will be defined as a negative NAAT (Aptima Combo) at all infected sites.

12 ASSESSMENT OF SAFETY

12.1 Definitions

12.1.1 Adverse Event (AE)

Any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. Not all adverse events are adverse reactions but all adverse reactions are adverse events.

12.1.2 Adverse Drug Reaction (ADR) to an Investigational Medicinal Product (IMP)

An Adverse Drug Reaction is any untoward and unintended response in a participant to an IMP which is related to any dose administered to that participant. Any adverse event judged by either the reporting Investigator or Sponsor as having causal relationship to an IMP qualifies as an ADR.

All adverse reactions are adverse events.

12.1.3 Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose:

- Results in death
- Is life threatening,
- Requires inpatient hospitalisation or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect`

'Important medical events' may also be considered serious if they jeopardise the patient or require an intervention to prevent one of the above consequences.

The term 'life-threatening' in the definition of serious refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Hospitalisations for pre-planned procedures do not require reporting as an SAE, unless the condition worsens.

12.1.4 Serious Adverse Reaction

An Adverse Reaction which also meets the definition of a Serious Adverse Event.

12.1.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SUSAR is a serious ADR where the reaction to an IMP that is not consistent with the applicable product information highlighted in the Investigators brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product. For this trial, the Summary of Product Characteristics (SPC) will be the reference document.

12.2 Reporting Requirements and Procedure

The collection and reporting of Adverse Events (AEs) will be in accordance with the Medicines for Human Use Clinical Trials Regulations 2004 and it's subsequent amendments.

All medical occurrences which meet the definition of an AE that occur during the trial will be recorded. All adverse events must be assessed for seriousness and causality.

The following methods will be used to collect adverse events in this trial:

12.2.1 Adverse Events

1) **AEs which are pre-specified outcomes of the trial.**
   The following AEs are pre-specified outcomes for the trial: nausea, vomiting, hearing problems, dizziness and rash.

   These adverse events will be collected on the eCRF following targeted questioning by a member of the research team during the follow-up visit at two weeks.

   Any of the above events which meet the definition of serious will also require reporting on a serious adverse event form (see section 12.2.2)

   Creatinine levels will be collected at baseline and at the 2 week follow-up visit. If changes in these levels are of clinical concern, they should be reported as AEs.

2) **Other Adverse Events**
   Participants will be asked at their two week follow-up visit whether they have experienced any other adverse events. All adverse events experienced by the patient (apart from those specified above which are pre-specified outcomes for the trial) must be recorded on the Adverse Event eCRF at the two week follow-up visit.

   Injection site pain should not be recorded as an Adverse Event. This is captured elsewhere on the eCRF.

   Any events which meet the definition of serious will also require reporting on a serious adverse event form (see section 12.2.2)

12.2.2 Serious Adverse Events

Participants will be asked to contact the research team at site immediately in the event of any serious adverse event and will also be asked at their follow-up visit if they have experienced any adverse events.

The Investigator must report any AEs that meet the definition of a serious adverse event (SAE). Serious Adverse Events must be reported to the Nottingham Clinical Trials Unit within 24 hours of becoming aware of the SAE.

The Investigator must assess the seriousness and causality of all AEs experienced by the patient.

Further instructions on reporting SAEs are contained in the Trial Manual.

12.2.3 Assessment of expectedness

Upon receipt by the NCTU, the Chief Investigator will assess all serious adverse events for expectedness in relation to the Reference Safety Information.

12.3 Follow-up of serious adverse events

Serious adverse events will be monitored until resolution or stabilisation.

12.4 Reporting Period

Details of all AEs will be documented and reported from the date of consent until completion of the follow-up visit at two-weeks. If a patient fails to return to clinic for their follow-up visit despite reminders, adverse event data will be assumed to be lost to follow up and missing at random.

12.5 Pregnancy

Pregnant patients are excluded from entering the trial. All women will have a pregnancy test prior to administration of the study drug. Given that the study drug is a single dose and the half-lives of gentamicin and ceftriaxone are about 2-3 hours and 8 hours, respectively there will be negligible risk after 24 hours, thus no specific pregnancy monitoring is deemed necessary in this study.

Participants are advised to avoid sexual intercourse for 7 days and until their sexual partner has also been evaluated and tested negative or received treatment.

12.6 Reporting to Sponsor, MHRA and Ethics Committee

The Nottingham Clinical Trials Unit will report all serious adverse events to the Sponsor within 24 hours of the event being reported.

The Nottingham Clinical Trials Unit will produce an annual report which includes a listing of all serious adverse reactions (SARs) and a summary report of the patients' safety and submit this within the required timeframes. A copy of the annual safety report will also be sent by Nottingham Clinical Trials Unit to the Sponsor.

Any SUSARs that occur during the course of the trial will be reported by the NCTU within the required timeframes to the MHRA and REC. The Sponsor will be notified by NCTU within 24

hours of becoming aware of a SUSAR and sent a copy of the report submitted to the MHRA/REC.

The Nottingham Clinical Trials Unit will also notify investigators at all trial sites of any SUSARs that occur after the Sponsor has been informed.

13 TRIAL CLOSURE

Planned trial closure will be when all randomised participants have had their follow up visit (Visit 2) and all data associated with that visit has been recorded on the database.

The Chief Investigator may stop the trial or terminate one or more centres if new information becomes available causing major safety concerns or if there are issues with trial conduct.

If recruitment and/or retention fail to reach the rates predicted, despite implementation of improvement strategies, the trial may be terminated.

14 STATISTICAL CONSIDERATIONS

The analysis and reporting of the trial will be in accordance with CONSORT guidelines. A full statistical analysis plan will be developed prior to completion of data collection.

14.1 Sample size

Based on an efficacy rate of 96% for the ceftriaxone regimen which is consistent with previous trials, a total sample size of 646 for analysis (323 in each group) will achieve 90% power to detect non-inferiority with lower confidence limit for the absolute risk difference of 5%. The significance level is 0.025. To allow for a loss to follow-up rate of up to 10%, the study will recruit a total of 720 participants. A 5% lower confidence interval was acceptable to 17 of 24 sexual health patients whose opinion was sought, and provides a realistic recruitment target.

14.2 Statistical Analysis

Continuous variables will be summarised in terms of the mean, standard deviation, median, lower and upper quartiles, minimum, maximum and number of observations. Categorical variables will be summarised in terms of frequency counts and percentages. Descriptive statistics of demographic and clinical measures will be used to compare balance between the randomised arms at baseline.

The primary approach to between-group comparative analyses will be by intention-to-treat without imputation of missing outcome data. Sensitivity analyses will be conducted to investigate the impact of missing primary outcome data, using simple and multiple imputation. Due to both interventions being single dose administered immediately following randomisation, non-adherence with treatment allocation is expected to be negligible. Therefore additional sensitivity analyses that aim to estimate treatment effect among those who have adhered with allocation are not expected to be required.

The evaluation of the primary clinical outcome variable will be performed using a general linear model for binary outcome adjusted by clinic site. The primary efficacy parameter

comparing gentamicin with ceftriaxone will be the risk difference in the proportion of participants clear of infection at two weeks follow up along with the 95% confidence interval. Gentamicin will be regarded as non-inferior if the lower 95% confidence limit for the risk difference in confirmed clearance is -5 percentage points or greater.

Secondary outcomes will be similarly analysed using appropriate regression models dependent on data type (binary, continuous etc), adjusted for clinic site and baseline value of the outcome variable if collected.

We are interested in whether treatment efficacy differs by site of infection. Participants may have infection at multiple sites, and up to seven different combinations of 1/2/3 sites are possible. For each of the three infection sites, we will separately estimate clearance by treatment arm along with 95% confidence intervals, rather than formally fit an interaction term for different combinations of infection site in the regression model. Any suggestion of a differential effect according to infected site would require confirmation in future research.

Safety and tolerability analysis will be of descriptive nature. Frequency counts and percentages of the per-specified main categories of side effects and AEs will be presented by treatment arm.

No formal interim analyses are planned for this trial.

15 DATA HANDLING AND RECORD KEEPING

15.1 Data Handling and Record Keeping

Each participant will be assigned a trial identity code number, allocated at randomisation, for use on eCRFs, other trial documents and the electronic database. The documents and database will also use their initials (of first and last names separated by a hyphen or a middle name initial when available) and date of birth (dd/mmm/yyyy).

eCRFs will be treated as confidential and held securely in accordance with regulations. The investigator will make a separate confidential record of the participant's name, date of birth, local hospital number or NHS number, and Participant Trial Number (the Trial Recruitment Log), to permit identification of all participants enrolled in the trial, in accordance with regulatory requirements and for follow-up as required.

eCRFs shall be restricted to those personnel approved by the Chief or local Principal Investigator and recorded on the 'Trial Delegation Log.'

The Principal Investigator or designee shall electronically complete a declaration ensuring accuracy of data recorded in the eCRF.

Details about data handling will be specified in the Data Management Plan (DMP). This will include the agreed validation specification which will validate data for consistency and integrity as it is entered. Additional manual and electronic reviews may also be conducted and data queries may arise from such reviews.

Data will be held on clinical trial dedicated servers. These servers are located within a managed data centre that is managed/monitored 24/7. Security is both physical (secure limited access) and electronic (behind firewalls, access via user accounts (user name and password), restricted access – e.g. site user only have access to their sites data, and by user type/role). All access and data transactions are logged in a full audit trail.

Participants data are frozen on an ongoing basis once they are deemed to have a complete set of data that has passed data validation checks (i.e. there are no data queries outstanding). Once all participant data have been frozen, the trial database is locked (set to read only). This is done prior to the final analysis.

15.2 Direct Access to Source Data/Documentation

Source documents shall be filed at the investigator's site and may include but are not limited to, consent forms, current medical records, laboratory results and pharmacy records. Only trial staff as listed on the Delegation Log shall have access to trial documentation other than the regulatory requirements listed below.

The eCRF and all source documents, including progress notes and copies of laboratory and medical test results shall made be available at all times for review by the Chief Investigator, Sponsor's designee and inspection by relevant regulatory authorities (MHRA).

16 TRIAL ORGANISATIONAL STRUCTURE

16.1 Sponsor

The trial is sponsored by University Hospitals Birmingham NHS Trust.

16.2 Coordinating Centre

The trial is co-ordinated by the Nottingham Clinical Trials Unit (NCTU).

16.3 Trial Management Group (TMG)

The Trial Management Group (TMG) will be responsible for day-to-day management of the trial. Membership includes the CI, the Trial Manager and at least one other member of the NCTU. The TMG will be responsible for ensuring project milestones are achieved. The TMG will meet regularly throughout the duration of the trial.

16.4 Trial Steering Committee (TSC)

A Trial Steering Committee (TSC) has been established which includes an independent chair, independent and non-independent members and patient representatives. A minimum of 75% of the members will be independent. The TSC will meet to discuss and agree the protocol, and it will approve the Statistical Analysis Plan before the trial data are unblinded.

16.5 Data Monitoring Committee (DMC)

An independent Data Monitoring Committee (DMC) will be established and will operate in accordance with a trial specific Charter agreed with the TSC. It will be fully independent and will consist of a chair, expert statistician and a minimum of one independent clinician. They will have access to unblinded data if necessary. The DMC will review all Serious Adverse Events.

17 HEALTH ECONOMICS

The economic analysis will compare the costs associated with the current standard treatment, ceftriaxone, with those of the proposed alternative treatment, gentamicin, in the treatment of gonorrhoea. Given that the primary objective of the trial is to determine non-inferiority of gentamicin, the economic analysis will focus on establishing whether the use of gentamicin rather than ceftriaxone is cost-neutral in the treatment of gonorrhoea. This will involve the examination of costs and resource use to determine whether there are any differences between the two treatments.

The economic evaluation will adopt the perspective of the health service (NHS), and data on resource use and costs will be collected prospectively within the study. Resource use data will be collected via a nurse / assessor completed form and will include questions on drug use, GP or other clinic visits etc. For a small random subset of patients in both arms of the trial we will collect information on the length of consultation required for delivery of the treatment therapy. This will be for the purpose of validation only, to confirm that the delivery of the treatment and length of consultation is not relevant to the drug being administered. Unit cost estimates will be applied to resource use data to generate individual level cost estimates. The sources of unit costs will include routine or published literature (e.g. PSSRU Unit costs of Health and Social Care).

The results will be reported in terms of the cost per patient successfully treated (measured in terms of microbial clearance of *Neisseria gonorrhoeae*). We will carry out a range of sensitivity analyses to explore the robustness of these results to plausible variations in key assumptions, and to consider the broader issue of the generalisability of the results.

18 QUALITY CONTROL AND QUALITY ASSURANCE

18.1 Trial Conduct

Trial conduct will be subject to systems audit of the Trial Master File for inclusion of essential documents such as permissions to conduct the trial, Trial Delegation Log, CVs of trial staff and training received, local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, correct randomisation, timeliness of visits) and adverse event recording and reporting.

18.2 Monitoring

Monitoring of trial data shall be in accordance with the trial monitoring plan and may include confirmation of informed consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation in accordance with the monitoring plan.

Entries on CRFs will be verified by inspection against the source data. A sample of CRFs will be checked on a regular basis for verification of all entries made. In addition the subsequent capture of the data on the trial database will be checked. Where corrections are required these will carry a full audit trail and justification.

Trial data and evidence of monitoring and systems audits will be made available for inspection by the regulatory authority as required.

18.3 Notification of Serious Breaches

Sites should report any trial-related serious breaches of GCP and/or the trial protocol to the NCTU. The NCTU will report any serious breaches of GCP and the protocol to the MHRA within 7 days of becoming aware of the breach. The Sponsor will be notified by the NCTU of any serious breaches immediately after becoming aware of them.

18.4 Record Retention and Archiving

In compliance with the ICH/GCP guidelines, regulations and in accordance with University Hospitals Birmingham NHS Foundation Trust policy, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 15 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The Trial Master File, trial documents and database will be held at the Nottingham Clinical Trial Unit, University of Nottingham on behalf of the Sponsor. They shall be finally archived at secure archive facilities at the University of Nottingham.

18.5 Discontinuation of the trial by the Sponsor

The Sponsor reserves the right to discontinue this trial at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice from the Trial Steering Committee and Data Monitoring Committee as appropriate in making this decision.

18.6 Statement of Confidentiality

Individual participant medical information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted in this protocol.

Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

Data generated as a result of this trial will be available for inspection on request by University Hospitals Birmingham NHS Foundation Trust, the REC, local R&D Departments and the regulatory authorities.

19 ETHICS AND REGULATORY

The trial will not be initiated before the protocol, informed consent forms and participant and GP information sheets have received approval / favourable opinion from the Medicines and Healthcare products Regulatory Agency (MHRA), Research Ethics Committee (REC), and the respective National Health Service (NHS) Research & Development (R&D) department. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant and GP information sheets (if appropriate) have been reviewed and received approval / favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the MHRA, R&D and REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 2013; the principles of Good Clinical Practice, in accordance with the Medicines for Human Use Regulations, Statutory Instrument 2004, 1031 and its subsequent amendments and the Department of Health Research Governance Framework for Health and Social care, 2005.

20 SPONSORSHIP, FINANCE AND INSURANCE

20.1 Sponsorship

University Hospitals Birmingham NHS Foundation Trust will act as the main sponsor for the trial. Delegated responsibilities will be assigned to the NHS trusts taking part and to the NCTU.

20.2 Insurance and Indemnity

Insurance and indemnity for trial participants and trial staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but trial participants may have recourse through the NHS complaints procedures.

20.3 Funding source

This study is funded by NIHR.

20.4 Participant stipends and payments

Participants will not be paid to participate in the trial. However, at the end of their follow up visit they will be provided with £15 of vouchers to compensate for the additional time spent at clinic to participate in the study.

21 PUBLICATION POLICY

The dissemination of the proposed research findings will be via a published HTA monograph, research papers for publication in peer reviewed journals, presentation at medical conferences and communication of our findings to groups involved in guideline development.

Study participants will be asked whether or not they would like to receive a summary of the research findings, and invited to leave contact details (eg home or work address or e-mail address)by which we can contact them with the research summary at the end of the project.

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