North Cumbria Integrated Care NHS Foundation Trust

GONDOLA, GONorrhoea DiagnOsis using Laboratory Assessment

A single-centre, prospective evaluative study to investigate the performance of the Bio Med InTray® GC (a sample collection, transport and culture in-vitro device), compared to current standard methods, to microbiologically detect *Neisseria Gonorrhoeae*

Version 4, dd 6 December 2019

Chief Investigator's Statement of Ownership and Content.

I, Dr Matt Phillips, confirm that this protocol is my work and is owned by me. The protocol conforms with standards outlined in the Declaration of Helsinki 1964.

Name (PRINT):_____

Signature:_____

Date: _____

RESEARCH PROTOCOL SUMMARY

TITLE	A single-centre, multi-clinic, prospective evaluative study to investigate the performance of the Bio Med InTray® GC (a sample collection, transport and culture in-vitro device), compared to current standard methods, to microbiologically detect Neisseria Gonorrhoeae
Short title	GONDOLA, GONorrhoea DiagnOsis using Laboratory Assessment
IRAS number	261500
Device description	BioMed's InTray™ GC is a microbiology sample collection, transport, and culture *in vitro* device allowing for simultaneous detection, and observation of *Neisseria gonorrhoeae.* The patented InTray™ system consists of an outer, re-sealable label with an optically clear, anti-fog window covering the media, which creates an airtight seal over the 2" diameter surface. The innovative design of the InTray™, with its unique, high-performance viewing window, can be placed directly under a microscope while remaining sealed removing the need to prepare slides or expose the sample post inoculation. The InTray™ GC system is equipped with a CO2 tablet, which is contained in a sealed inner chamber to prevent degradation during storage. Once the CO2 chamber is punctured and the InTray™ sealed; the tablet generates the required atmosphere of CO_2 gas, approximately 7%, to create the anaerobic environment needed for the growth of *N. gonorrhoeae*. The enriched medium in the InTray™ GC is selective in the growth of *Neisseria* species and inhibits the growth of fungi and other bacteria (including *C. albicans*, *E. coli*, *S. epidermis*, and *P. mirabilis)*.
Study design	Single-centre, controlled, prospective trial. Comparison of two sampling methods: - Current practice, i.e. swab onto agar plate , pre-incubated at 37◦C or stored at room temperature up to 48 hrs, before further incubation in microbiology lab - InTray™ GC device, i.e. swab onto InTray, induce anaerobic conditions, incubate up to 48 hrs in clinic at room temperature or 37◦C if available, before further incubation at 37◦C in microbiology lab Participants are recruited from sexual health clinics across Cumbria.
Primary objective	To determine detection rates for *N. Gonorrhoeae* using InTray™ GC device compared to current agar plating practice in Cumbrian sexual health clinics
Secondary objectives	To determine if there is a difference in performance of direct and

	indirect incubation of plates, respectively, for both standard agar plates and the InTray™ GC device. To compare cost-effectiveness and potential benefits of using InTray™ GC device compared to current practices - Storage - Transport - Incubation time - Costs
Patient population and Intervention	A total of 120 participants, attending Cumbrian sexual health clinics, aged sixteen or over and with capacity to provide written informed consent. Plus: • Presenting to sexual health clinic with symptom(s) of Neisseria Gonorrhoea (such as presence of urethral or vaginal discharge, dysuria, localised inflammation) that in the opinion of the treating clinician warrants microbiological investigation. AND/OR • Medical or sexual behaviour history (primarily proven positive *N. Gonorrhoea* infection of recent sexual partner) that warrants investigation *for N. Gonorrhoea* infection, due to significantly elevated risk of infection. **AND/OR** • Positive test for N Gonorrhoea by molecular testing (polymerase chain reaction) in the last two weeks and not yet treated with antibiotics Which therefore incorporates a population that would usually qualify for swab sampling for microbiological investigation
Sponsor	North Cumbria Integrated Care NHS Foundation Trust
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Organisation where research will take place	North Cumbria Integrated Care NHS Foundation Trust Sexual Health Clinics, c/o R&D department Cumwhinton Drive, Carlisle CA1 3SX
Planned timeline	Recruitment start date (first patient, single visit): 29 April 2019 Recruitment end date (last patient, single visit): 31 Aug 2020 Study complete: 30 Sep 2020
Protocol version, date	Version 4, dd 6 Dec 2019

LAY SUMMARY

The incidence of gonorrhoea is potentially underestimated because of suboptimal processing of samples, diagnosis methodology, case reporting and surveillance. Undetected or inadequately treated Gonorrhoea can cause serious reproductive health consequences and poses a threat to public health due to the emergence of drug-resistant strains; timely and accurate diagnosis is therefore essential. Despite high specificity tests available*, N. Gonorrhoeae* bacteria are technically difficult to preserve and recover from clinical specimens. Any delay in processing, transport and incubation of direct culture plates can significantly reduce the sensitivity of the test, resulting in false negative results and non-treatment. Novel swab transport systems have become increasingly important due their low cost, ease of use and the ability to maintain viability for aerobic, anaerobic and fastidious microorganisms – such as *N. gonorrhoeae* – over extended times. This may have benefits in clinic settings across the UK, particularly in rural settings where transport times to laboratories may be longer. This study aims to assess the performance of a novel swab incubation and transport system – BioMed's InTray™ GC – compared to the current method of plating onto a solid growth medium to prepare, transport and detect Neisseria Gonorrhoea in sexual health clinics. Further the objective is to assess the potential cost-effectiveness and benefits in terms of storage, transport and incubation time.

1. CONTENTS

LIST OF ABBREVIATIONS AND ACRONYMS

ANOVA	analysis of variance
HRA	Health Research Authority
NAAT	Nucleic Acid Amplification Tests
NHS	National Health Service
NIHR	National Institute for Health Research
NRES	National Research Ethics Service
N. gonorrhoea	Neisseria gonorrhoea
PCR	Polymerase Chain Reaction
PHE	Public Health England
SD	standard deviation
STI	sexually transmitted infection

1. INTRODUCTION

In 2017 there were approximately 422,000 diagnoses of sexually transmitted infections (STIs) in England of which 44,676 Gonorrhoea diagnoses (PHE, 2018). In Cumbria there were 130, 162 and 195 positive diagnosis of gonorrhoea in 2015-2016, 2016-2017 and 2017-2018 respectively (Appendix 1). Gonorrhoea, caused by the bacterium *Neisseria gonorrhoeae*, causes an infection of the lower genital tract and is often symptomatic in men (urethral discharge (80%) and /or dysuria (50%)) and in approximately half of women (vaginal discharge (50%)) (Bignell & Fitzgerald, 2011). Undetected or inadequately treated Gonorrhoea can cause serious reproductive health consequences such as epididymitis or prostatitis in men and pelvic inflammatory disease, infertility or ectopic pregnancy in women (PHE 2018; PHE 2014; Bignell & Fitzgerald, 2011; Sonnenberg et al, 2013; WHO, 2016). The incidence of gonorrhoea is underestimated because of suboptimal diagnosis, case reporting and surveillance (Unemo et al, 2012). Additionally, the emergence of drug resistance gonococcal strains have increased rapidly in recent years thereby reducing treatment options and causing a threat to public health (Sonnenberg et al, 2013). Routine test of care are widely recommended to slow the spread of resistance gonorrhoea (Bignell & Fitzgerald, 2011; Unemo et al, 2012).

Diagnosis of gonorrhoea is confirmed by the detection of *N. gonorrhoeae* at an infected site. The methods used to diagnose gonorrhoea are influenced by the clinical setting, storage and transport system to the laboratory (Bignell & Fitzgerald , 2011). A direct method to diagnose gonorrhoea in men with urethral discharge is with urethral swab specimen by microscopy (x1000) of Gram-stained genital specimens (sensitivity 90-95%) (Bignell & Fitzgeral 2011). This method, however, has poor sensitivity in women and asymptomatic men. Other diagnostic methods to detect *N. gonorrhoeae* include culture and Nucleic Acid Amplification Tests (NAATs). Culture offers a specific, sensitive and cheap method to detect *N. Gonorrhoeae* and the specimens used are urethral and cervix swabs.

NAATs are recommended for both symptomatic and asymptomatic infections in men and women and achieve high sensitivity (>90%)(PHE 2014; Bignell & Fitzgerald, 2011). Samples used include urine and urethral swabs for men and vaginal and cervix swabs for women. Urine samples for women are not optimal and achieve low sensitivity. An additional benefit of the NAATs is that it offers dual testing for Chlamydia on the same sample. Both culture and NAATs have the additional benefit of antimicrobial susceptibility testing allowing for early detection of antibiotic resistance.

Despite high specificity tests available, *N. Gonorrhoeae* bacteria are technically difficult to preserve and recover from clinical specimens (Thompson & French, 1999). In order to achieve effective laboratory diagnosis, the collection and transport of samples need to be optimal. Sub-optimal media conditions can reduce the sensitivity and the organism's fastidious nature makes it intolerant of delays in transport to laboratories (if transported in sub-optimal culture conditions). Any delay in processing, transport and incubation of direct culture plates can significantly reduce the sensitivity of the test, resulting in false negative results and non-treatment.

Although initially perceived less optimal for culture than direct plating, swab transport systems have become increasingly important due their low cost, ease of use and the ability to maintain viability for aerobic, anaerobic and fastidious microorganisms over extended times (Farhat et al, 2001; Gizzie & Adukwu, 2016). BioMed's InTray™ GC is a microbiology sample collection, transport, and culture *in vitro* device allowing for simultaneous detection, and observation of *Neisseria gonorrhoeae.* In this diagnostic kit, an optimised carbon dioxide concentration is generated to optimise the growth of *N. Gonorrhoeae* if present in the swab sample.

This study aims to assess the effectiveness of the novel InTray™ GC system compared to the currently used method of plating onto standard agar plates (which operate in an atmospheric 0.4% CO_2 environment), to detect *Neisseria Gonorrhoeae* microbiologically in sexual health clinics and to assess the potential cost-effectiveness and benefits in terms of storage, transport and incubation time. The results of this study can provide an incentive to reassess current methods used in order to improve quality of sampling and processing Neisseria gonorrhoea and ultimately improve services for patients.

2. INVESTIGATIONAL DEVICE

BioMed's InTray™ GC is a microbiology sample collection, transport, and culture in vitro device allowing for simultaneous detection, and observation of Neisseria gonorrhoeae. The patented InTray™ system consists of an outer, re-sealable label with an optically clear, anti-fog window covering the media, which creates an airtight seal over the 2" diameter surface. The innovative design of the InTray™, with its unique, high-performance viewing window, can be placed directly under a microscope while remaining sealed removing the need to prepare slides or expose the sample post inoculation.

The InTray™ GC system is equipped with a CO2 tablet, which is contained in a sealed inner chamber to prevent degradation during storage. Once the CO2 chamber is punctured and the InTray™ sealed; the tablet generates the required atmosphere of CO2 gas, approximately 7%, to create the anaerobic environment needed for the growth of N. gonorrhoeae. The enriched medium in the

InTray™ GC is selective in the growth of Neisseria species and inhibits the growth of fungi and other bacteria (including C. albicans, E. coli, S. epidermis, and P. mirabilis).

Figure 1. An opened and unopened version of the InTray™ GC system

2.1 Medical Device management

To inoculate the InTray™ GC, the lower right corner of the label adjacent to the clear window is pulled back until the protective seal is completely visible. The seal is removed by pulling the tab, and the seal is discarded – though the white filter strip over the vent hole is not removed. A small amount of specimen sample is obtained using a cotton swab or microbiology loop and placed on top of the agar. The 2" diameter well allows for a large enough surface area to streak for isolation. Specimens may include oral, vaginal, urethral and rectal swabs. To initiate the internal CO2 system, a small hole is made in the cover of the CO_2 tablet chamber, and then the InTray™ is resealed by returning the label to its original position so the optically clear anti-fog window covers the medium. The edges of the label are pressed against the plastic tray to ensure an airtight seal. Once sealed, the InTray™ GC is incubated for 24-48 hours at 37ºC.

3. STUDY HYPOTHESIS

3.1 Primary objective

To determine the microbiological detection rates of Gonorrhoea using InTray™ GC liquid transport medium compared to current practise (agar plating) in Cumbrian sexual health clinics

3.2 Secondary objective

To determine if there is a difference in performance of direct and indirect incubation of plated samples, within each diagnostic method group and for agar plates vs InTray™ GC respectively.

To assess the cost-effectiveness and potential benefits of using InTray™ GC compared to current practices.

4. STUDY PROTOCOL

4.1 Study design and timeline

This concerns a multi-clinic, prospective evaluative study conducted within one NHS Trust. The study will be carried out by NHS North Cumbria Integrated Care NHS Foundation Trust staff. It will take place at two Sexual Health clinics in Cumbria with support and oversight from research staff. Samples will be processed in the microbiology department of North Cumbria University Hospitals NHS Trust, and a service level agreement is in place for this. Research delivery staff will be delegated to provide support with data collection and processing.

Table 1. Anticipated timeline

Month	Setup	Recruitment	Analysis	Finalise
Feb-19	Submission for HRA approval			
Mar-19	NIHR portfolio adoption			
Mar-19	HRA and Trust approval			
Apr-19		Start recruitment		
Aug20		Finish Recruitment		
Sep-20			Data collection complete; Analyse data	
Sep-20				Manuscript & report writing
Sep-20				Study complete

4.2 Participant identification and research setting

Participants will be recruited from sexual health clinics in Carlisle (Solway clinic) and Workington/Whitehaven (Derwent clinic). Identification and screening for eligibility will be done by clinical staff supporting the study. The eligible patient population is defined in the Inclusion and Exclusion criteria section. When a patient is eligible the patient information sheet will be introduced and the study will be discussed in detail. The participant has the opportunity to ask any questions. If the participant is happy to take part and all questions have been answered the participants can be consented by the clinical or research team. If applicable, by virtue of healthcare staff not consenting patients, the direct clinical staff managing the patient will ask for verbal consent before a member of the research team discusses the study with the patient and performs the consent process. The direct healthcare team can also perform the consent process.

All clinically eligible patients will be invited to take part until the required numbers have been achieved.

4.3 Consent

Those eligible will be approached and provided with a patient information sheet (PIS) and consent form, which will be signed to indicate that informed consent has been given. Potential participants have the time to consider the PIS and have the opportunity to ask any questions. The minimum of 24 hours consideration time is not required if the patient understands the nature and aims of the study.

In the interest of performing the diagnostic test as soon as possible, it is desirable for patients to consent on the day of being approached.

Participants will receive no incentives and consent will be regarded as a process and not a one-off event. Participants are free to withdraw from the study at any time without the need to give any reasons for withdrawal. Their standard of care will not be affected by either declining to participate in the study or withdrawing during participation. Data collected up to the date of withdrawal will be retained for analysis.

4.4 Recruitment

Once a patient has given informed written consented to taking part in the study, a sample will be taken as part of normal clinical practice. These are urine, urethral or rectal sampling for man and a urine, rectal, urethral or vaginal/cervix swab for women. An additional swab might be taken for this study since two transport systems will be used and compared (InTray™ GC vs agar plating), though in practice is anticipated to be a rare occurrence. The following baseline participant parameters will be collected from medical records:

- Demographics (including date of birth, sex)
- Symptoms
- Sexual history (sexual orientation, number of contacts)
- Any previous STI episodes
- Contraception and condom use
- Type of swab (location)

During the recruitment process and whilst the study is live, the research team acts as a contact point and coordinator for patients requiring information and support. If concerns are raised on participants (mental) wellbeing based on the outcome of the assessments, referral of patients/families on to other professional agencies will be done as appropriate and according to the Trust guideline.

4.5 Storage, transport, incubation, and diagnostic procedures

The samples will be processed according to normal practice for the agar plates and – in parallel-processed with the InTray™ GC. This translates as:

- Carlisle (‘direct incubation’): plating onto agar plate in sexual health clinic and incubation at 37°C until collected by courier, and transferred (in individual sealed bags with CO2 generators) to Carlisle Infirmary microbiology/virology laboratory for further incubation for 48 hrs, and NAAT/PCR in parallel.
- Barrow, Kendal, Workington/Whitehaven (‘indirect incubation’): incubation in charcoal tube (Kendal/Barrow) or plating onto agar plate (Workington/Whitehaven) in sexual health clinic but storage at room temperature until collected by courier, and transferred (in CO_2 in a gas jar) to Carlisle Infirmary microbiology/virology laboratory for incubation for 48 hrs, and NAAT/PCR in parallel.

The time taken to reach the microbiology laboratory will be recorded.

Microbiology testing is the main diagnostic approach taken for this study, and this is what will be done upon arrival in the microbiology department as standard:

- Microbiological and biochemical testing: growth of bacteria on a BC18 oxide medium agar plate – or InTray™ GC - for 48 hrs. Followed by oxidase test and Gram stain for positive colonies. Furthermore, a biochemical API NH test will be performed for confirmation (see eg http://www.cantonhealth.org/pdf/400-001-06-13-A_API%20NH%20System%20BioMerieux%20Product%20Insert.pdf). Antibiotics sensitivity testing may be performed but is not part of the present study.

However, molecular testing through PCR is deemed the gold standard, and the following will be done separately from microbiology testing, using different swabs that do not form part of this study:

- Molecular testing: Euroclone dual testing kit for both *N. Gonorrhoeae* and Chlamydia (the latter is not part of this present study, but may be reported on by the treating sexual health clinician).

Appendix 3 summarises what happens to the samples.

4.6 Follow-up

When the lab results are available the clinical team will inform the patients as per normal practice. The clinical teams can utilise results from both the standard plating technique and the InTray™ GC incubation kit. Follow-up data collection will take place (e.g. tested negative/positive) and participants are discharged from the study. The test results will be obtained via sexual health medical record. Patients may be continued to be managed by the sexual health team beyond participation in the study.

4.7 Outcome measures

4.7.1 Primary outcome measures

To determine the detection rates of InTray™ GC compared to current (in)direct agar plate incubation practice in Cumbrian sexual health clinics. The results from NAAT (PCR) will be used for comparative purposes, but the primary outcome measure is the comparison of agar plating vs InTray™ GC. The results will be tabulated as follows:

Table 2. Primary outcome measure: N Gonorrhoea detection levels

	Incubation result positive for N Gonorrhoea	Incubation result negative for N Gonorrhoea
(in)direct agar plate incubation – combined results	n	N
InTray™ GC	n	N

4.7.2 Secondary outcome measures

The effect of either direct or indirect incubation will also be appraised. The results will be tabulated as follows:

Table 3. Secondary outcome measure: N Gonorrhoea detection levels

	Incubation result positive for N Gonorrhoea	Incubation result negative for N Gonorrhoea
indirect incubation of samples	n	n
InTray™ GC (indirect incubation, ie not instantly at 37◦C)	n	n
direct incubation of agar plate samples	n	n
InTray™ GC (direct incubation, ie not instantly at 37◦C)	n	n

Description of timeline for samples collected in sexual health clinics, in terms of time between a sample been taken from patient to arrival in microbiology department.

This study also aims to assess the cost-effectiveness and potential benefits of using Biomed InTray compared to current practices. The secondary outcome measures are:

- Storage requirements per method
- Transport requirements per method
- Incubation time per method
- Costs per method (including materials)

5. SUBJECTS

5.1 Anticipated number of research subjects

Patients will be recruited from the adult (age 16+) population routinely seen by the evaluating clinical staff members in the sexual health clinic.

The non-parametric Chi-squared test is used and 80% power and 5% significance is applied. A priori power calculations using GPower 3.1 software, result in the following sample size summarized in Table 4. The sample size calculation does not have to take into account any patient attrition rate (one-off visit, as part of standard clinic visit).

Although the study will involve patients with a higher chance of being diagnosed with Gonorrhoea, ie those who are symptomatic and therefore would benefit from *N Gonorrhoea* being diagnosed by

microbiological diagnosis, the sample size calculation will take into account 40% of patients actually carrying the infection.

The percentages for (in)direct incubation are loosely based on all-sample results obtained in the Cumbria sexual health clinics for patients who do and do not present with symptoms of Gonorrhoea infection. The detection rates are based on results to be obtained with microbiological techniques. Detection rates for InTray™ GC are purely hypothetical and therefore this present study will inform what the actual performance of this diagnostic kit is compared to standard practice. Since this study is not hypothesis-driven, the sample size is calculated purely to guide on the likely minimal number of patients' samples that should be included in the evaluation.

Ultimately the primary question is how the performance of InTray™ GC compares to standard agar plate incubation. A secondary question is how indirect incubation compares to direct incubation (in both the cases of using standard agar plates or InTray™ GC).

Table 4. Sample size calculation

Sample Preparation / / Test outcome	Positive for Gonorrhoea (hypothetical)	Negative for Gonorrhoea (hypothetical)
Direct and indirect plating combined	60%	40%
Biomed InTray™ GC	80%	20%
	Power beta of 80%, Alpha p-value of 0.05, Effect size of 0.4. Sample size required if all participants carried Gonorrhoea but performance of different preparation techniques was as described above: 48. Since one patient provides two samples, this equates to 24 patients. Total patients needed to take into account 40% actually being positive for Gonorrhoea by means of PCR /NAAT. Therefore , total sample size is (100/40) x 24 = 60 To allow sufficient power to calculate the above for direct and indirect plating separately, 2x 60 samples are required, meaning a total of 120 samples.	

5.2 Eligibility criteria (inclusion and exclusion criteria)

The study aims to be pragmatic in terms of inclusion of a relevant patient population that would usually qualify for swab sampling for microbiological investigation.

Therefore, this means the inclusion of a total of 120 participants, attending Cumbrian sexual health clinics, over the age of eighteen and with capacity to provide written informed consent. Plus:

- Presenting to sexual health clinic with symptom(s) of *Neisseria Gonorrhoeae* (i.e. presence of urethral or vaginal discharge and/or dysuria)

  OR

  Recent medical history and risk factors that in the opinion of the treating clinician warrants investigation *for N. Gonorrhoeae* infection

Patients are not allowed to be enrolled into another research study on diagnostics if they consent to take part in this study. This is to avoid patients being subjected to excessive swabbing.

5.3 Early withdrawal of subjects

Participants have the right to withdraw from the trial at any time and without giving any reason. If a patient withdraws from the trial, any and all information gathered prior to the withdrawal will be included in the analysis, though no further data collection will take place.

6. SAFETY

6.1 Potential risks & benefits to study participants

There may be a clinical benefit from taking part in this study, if the new diagnostic sample kit proves to be superior over the existing practice. However, this is not certain at present and the study is designed to determine if there is any statistically significant difference between agar plating and InTray™ GC . Participants cannot claim payments, reimbursements of expenses or any other benefit or incentives for taking part in this research.

There is no anticipated personal safety risk associated with taking part in this study. If the research team learns of important new information that might affect the patient's desire to remain in the study, he or she will be told. Appropriate precautions are in place to ensure medical and personal information is kept safe through adhering to appropriate governance regulations (see section 9).

7. STATISTICAL CONSIDERATION AND DATA ANALYSIS PLAN

7.1 Analysis of baseline characteristics

To determine the demographics and characteristics of the participants the following data will be collated:

- Age
- Sex
- Contraception methods (if any, including Condom use)
- Symptoms
- Sexual orientation
- Number of sexual contacts in the last 12 months

- Previous STI history (NG/CT/other)

7.2 Primary outcome statistics

To determine the detection rates of InTray™ GC compared to current practises, the following data will be collated:

- Microbiological culture and characterisation detection rates

Chi-squared test will be used to determine any difference in detection rates between using agar plating and InTray™ GC. If the incidence of one of the cells in the 2x2 table is low then Fisher exact test may be applied.

Since the same patient provides the two samples (one for agar plating and one for InTray™ GC) it can be argued that the data is paired. As such, McNemar's test will be applied too to determine any difference in detection rates between using agar plating and InTray™ GC.

7.3 Secondary outcome statistics

To determine the detection rates of the InTray™ GC compared to either of the two current plating practises (indirect and direct incubation plating respectively) ,the following data will be collated:

- Microbiological culture and characterisation detection rates

Chi-squared test will be used to determine any difference in detection rates between using agar plating and InTray™ GC.

The performance of both agar plating and InTray™ GC plating will also be compared in relation to NAAT/PCR detection rates for patients' who provided samples.

To assess the cost-effectiveness and potential benefits the following data will be collated for a cost-utilisation exercise:

- Storage requirements per method
- Transport requirements per method
- Incubation time per method
- Costs per method (cost of plates themselves, any difference in processing times for sexual health clinic staff and microbiology dept staff)

Any difference in average cost of process the sample (agar plating vs InTray™ GC) will be determined with student t-test or Mann-Whitney test, depending on whether data is distributed normally or not.

Multiple logistic regression analysis will be performed to determine if any patient or transport methods are interlinked - in terms of factors that may be associated with the detection of N Gonorrhoea. This results in the following analysis setup for both agar incubation and InTray™ GC methods:

- Dependent: detection of *N. Gonorrhoea* with microbiology, yes/no

- Variables: patient demographics (age, sex), patient circumstances (number of sexual contacts, sexual orientation, smoking, alcohol, contraception), clinical symptoms (discharge, other symptoms, history of infection)

8. DATA HANDLING AND MONITORING

Data arising from this study is confidential. Identifiable information can only be accessed by delegated members of the study team. Anyone in the research team who does not have a substantive contract with Cumbria Partnership NHS Trusts, or operational contract in the case of microbiology department staff at North Cumbria University hospitals NHS Trust, will need to apply for a letter of access via the NIHR research passport scheme, should they require access to identifiable study data.

Patient identifiable data will only be used within the Trust and by the core research team. All identifiable data is stored on password protected NHS computer systems. Anonymised data will be shared and stored using security-enabled systems such as password-protection and encryption of e-mails and files. The requirements of the Data Protection Act and NHS Code of Confidentiality will be followed at all times. All researchers will be fully trained in NHS Confidentiality and GCP.

All paper data will be held in secure locked environments in the office of the Research & Development department in the Carleton Clinic, Carlisle and Ann Burrow Thomas Health Centre, Workington, Cumbria Partnership. Data released (e.g. by publication) will contain no information that could lead to the identification of an individual participant. Upon completion of the study the site files will be archived for a period of 10 years in line with local archiving policy and procedures. Direct access to data only will be granted to authorised representatives from the sponsor / host institution, grant funder and medical device company (Biomed) and the regulatory authorities to permit trial-related monitoring, audits and inspections.

This investigator-initiated trial will be monitored in terms of conduct of the study by the in-house research team, led by Dr Matt Phillips, who will convene on a monthly basis in person or via phone/e-mail. A trial steering committee will not be convened for this trial. The study can be audited by the in-house R&D department as part of their rolling audit programme of sponsored and hosted research studies. As part of the research grant agreement, anonymised study data will be shared with Medical Wire & Equipment for review and for potential publication purposes. No identifiable data will be contained in any of this data.

9. GOVERANCE OF STUDY

9.1 Approvals

This study will be conducted in compliance with the protocol approved by the Health Research Authority, National Research Ethics Service, and local Trust R&D Approval, and according to Good Clinical Practice standards including the Declaration of Helsinki (1964, Amended Oct 2013). No deviation from the protocol will be implemented without the prior review and approval of the

aforementioned review bodies, except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported according to policies and procedures

9.2 Sponsor, Indemnity, and Funding

Cumbria Partnership NHS Trust is the sponsor of this study and therefore NHS indemnity applies for design, conduct and management of the study. Biomed diagnostics has provided a grant for this study by means of provision of InTray™ GC transport kit free of charge, to the value of £288. Furthermore, a £6700 grant has been obtained form the Academic Health Sciences Network North East and North Cumbria (AHSN NENC).

Patients will not be given financial incentives for taking part in the study. Travel expenses are not offered in this study since participants are by community nurses or in clinic as part of their normal care pathway.

10. PUBLICATION AND DATA-SHARING POLICY

The study will be registered on ISRCTN or Clinical Trials Gov website, in line with STARD guidelines (Cohen et al, 2016) on good practice in clinical diagnostic research. It should be noted that this study does not intend to ascertain the accuracy or performance of the diagnostic tests applied for Gonorrhoea testing. Only the relative performance concerning the sampling and transport method to get a patient sample to the laboratory, and hence the relative ability to recover bacteria, is appraised.

The results of this study will be disseminated through:

- Peer-reviewed manuscript in scientific journal
- Internal report to the funder of the trial, Biomed diagnostics
- Presented on conferences and meetings

11. REFERENCES

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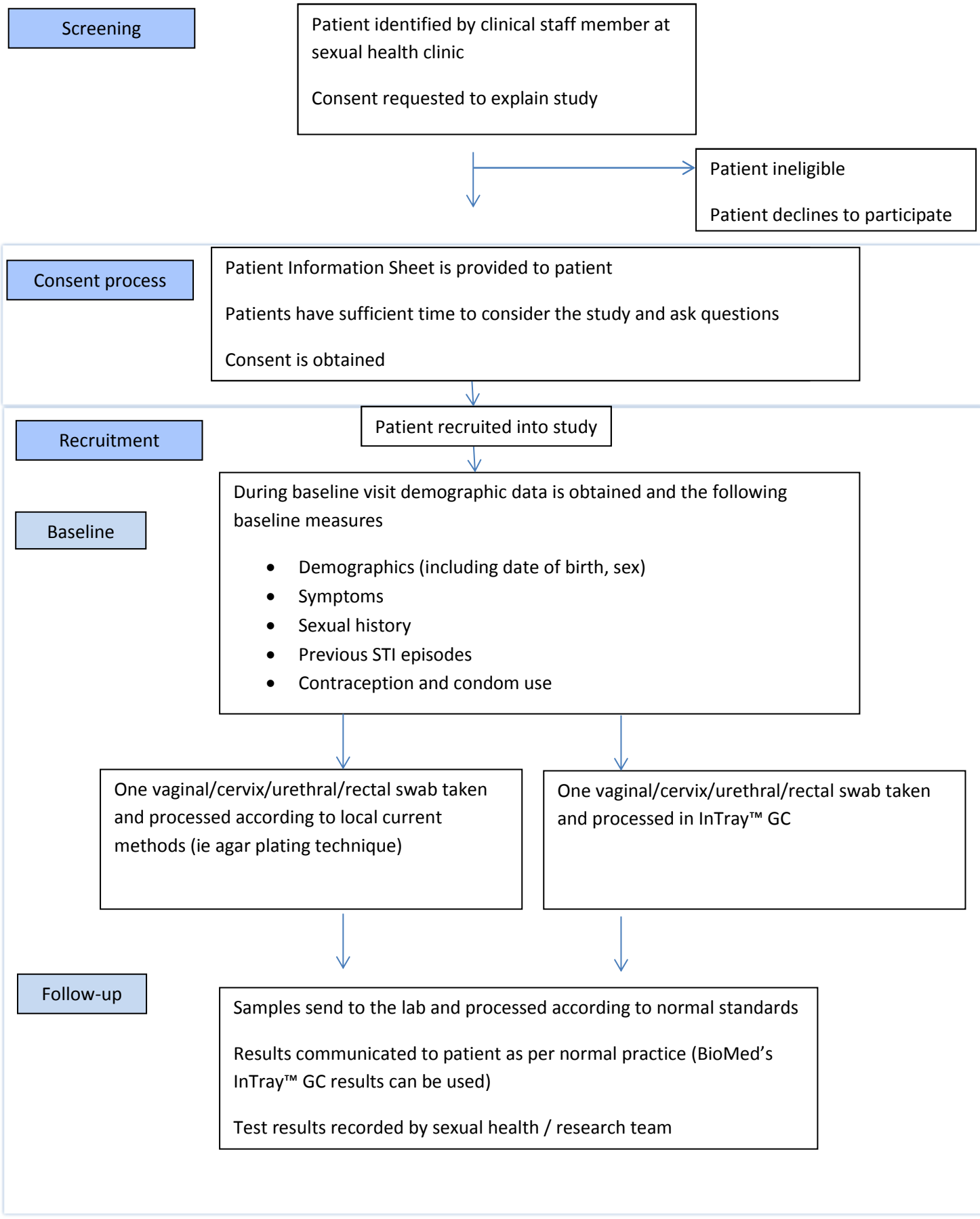
APPENDIX 1. NEISSERIA GONORRHOEA TESTING AND DIAGNOSES IN CUMBRIA (2015-2018)

Clinic location 1 in Cumbria (indirect incubation at 37◦C)					*Clinic location 2 in Cumbria (direct incubation at 37◦C)*			
Microbiology culture: Overall numbers	**total +ve**	**34**	**3.2%**		**Microbiology culture: Overall numbers**	**total +ve**	**144**	**9.4%**
	total samples	1068				total samples	1537	
NAAT: Overall numbers	total +ve	116	1.0%		NAAT: Overall numbers	total +ve	308	2.1%
	total samples	11105				total samples	14595	
percentage +NAAT also +culture			29%					47%

APPENDIX 2. STUDY PARTICIPANT FLOWCHART



APPENDIX 3 – SAMPLE FLOWCHART