



**S**torage, **TR**ansport & **I**ncubation for ***N****eisseria* ***G****onorrhoeae* **S**ampling

**A single-centre, controlled, prospective study to investigate the performance of the novel Sigma VCM diagnostic storage and transport kit compared to current standard methods to detect *Neisseria Gonorrhoeae***

**Version 2, dd 1 March 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, controlled, prospective study to investigate the performance of the novel Sigma VCM diagnostic storage and transport kit compared to current standard methods to detect *Neisseria Gonorrhoeae*. |
| **Short title** | STRINGS - Storage, Transport & Incubation for Neisseria Gonorrhoea Sampling |
| **IRAS number** | 243037 |
| **Device description** | Sigma VCM™ (MW911S, <http://www.mwe.co.uk/microbiology-lab-supplies/culture-swabs-liquid/sigma-vcm-mini-nasopharyngeal-mw911s/> ), small vial with 1.0ml medium, mini-tip Sigma swab.  Sigma-VCM® is compliant with CLSI’s M40-A standard for the recovery of viruses, and has been tested for chlamydia and mycoplasmas (including urea plasmas). Sigma-VCM® will also meet the requirements of M40-A for the recovery of *Neisseria Gonorrhoeae*, making it a suitable swab device for sexual health clinics. |
| **Study design** | Single-centre, controlled, prospective trial. Comparison of two sampling methods, and three different storage/transport options:  Phase A: 106 patients sampled via:   * Current practice, ie swab onto agar plate , pre-incubated or stored in fridge up to 48 hrs, before further incubation in microbiology lab * VCM kit, ie swab into VCM liquid medium, stored in *fridge* up to 48 hrs, before further incubation in microbiology lab   Phase B: 106 patients sampled via:   * Current practice, ie swab onto agar plate , pre-incubated or stored in fridge up to 48 hrs, before further incubation in microbiology lab * VCM kit, ie swab into VCM liquid medium, stored at *room temperature* up to 48 hrs, before further incubation in microbiology lab   Participants are recruited from sexual health clinics in Cumbria. |
| **Primary objective** | To determine detection rates for *N. Gonorrhoeae* using MW911S kit 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 plating, respectively, vs Sigma VCM.  To compare cost-effectiveness and potential benefits of using MW911S compared to current practices   * Storage (including time and temperature) * Transport * Incubation time * Costs |
| **Patient population and Intervention** | A total of 212 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 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. |
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| **Organisation where research will take place** | Cumbria Partnership 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): December 2018  Recruitment end date (last patient, single visit): September 2019  Study complete: November 2019 |
| **Protocol version, date** | Version 2, dd 1 March 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 transport system – Sigma VCM (product code MW911S, marketed by the company MWE) – compared to the current method of plating onto a solid growth medium to prepare, transport and detect Neisseria Gonorrhoea in sexual health clinics and to assess the potential cost-effectiveness and benefits in terms of storage, transport and incubation time.

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List of abbreviations and acronyms

ANOVA analysis of variance

HRA Health Research Authority

MWE Medical Wire

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

VCM virus – chlamydia - mycoplasma

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). Medical Wire (MWE) is specialised in the production of transport swabs and has developed a novel transport swab and liquid medium system, using Sigma VCM medium, which is suitable for viruses, chlamydia mycoplasma, ureaplasmas and fastidious bacteria such as *Neisseria gonorrhoeae* (Stuczen et al, 2011; Hague et al, 2011). The base medium allows survival and recovery of the target organisms whilst preventing the growth of most contaminating bacteria and fungi in the specimen.

This study aims to assess the accuracy of the novel Sigma VCM compared to the currently used method of direct plating onto agar to detect *Neisseria Gonorrhoeae* 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.

1. Investigational device

Medical Wire (MWE) is a medical device company specialised in the production of wire swabs and general laboratory components. MWE manufactures Transwab® products which comply with the CLSI standard M40-A for the quality control of microbiology specimen transport devices, are CE-marked and conform to the requirements of the European Medical Device Directive and In Vitro Medical Devices Directives. MW911S is one of the Transwab® products produced by MWE (figure 1). It is a small vial with 1.0ml Liquid Amies Transport Medium with a cellular foam bud (link: <http://www.mwe.co.uk/microbiology-lab-supplies/culture-swabs-liquid/sigma-vcm-mini-nasopharyngeal-mw911s/>). The Sigma VCM recovers viruses, chlamydia, mycoplasma, urea plasma and *Neisseria gonorrhoeae*. However, its performance for *N. Gonorrhoeae* has not been tested in a NHS clinical setting before.

Figure 1. Sigma MW911S

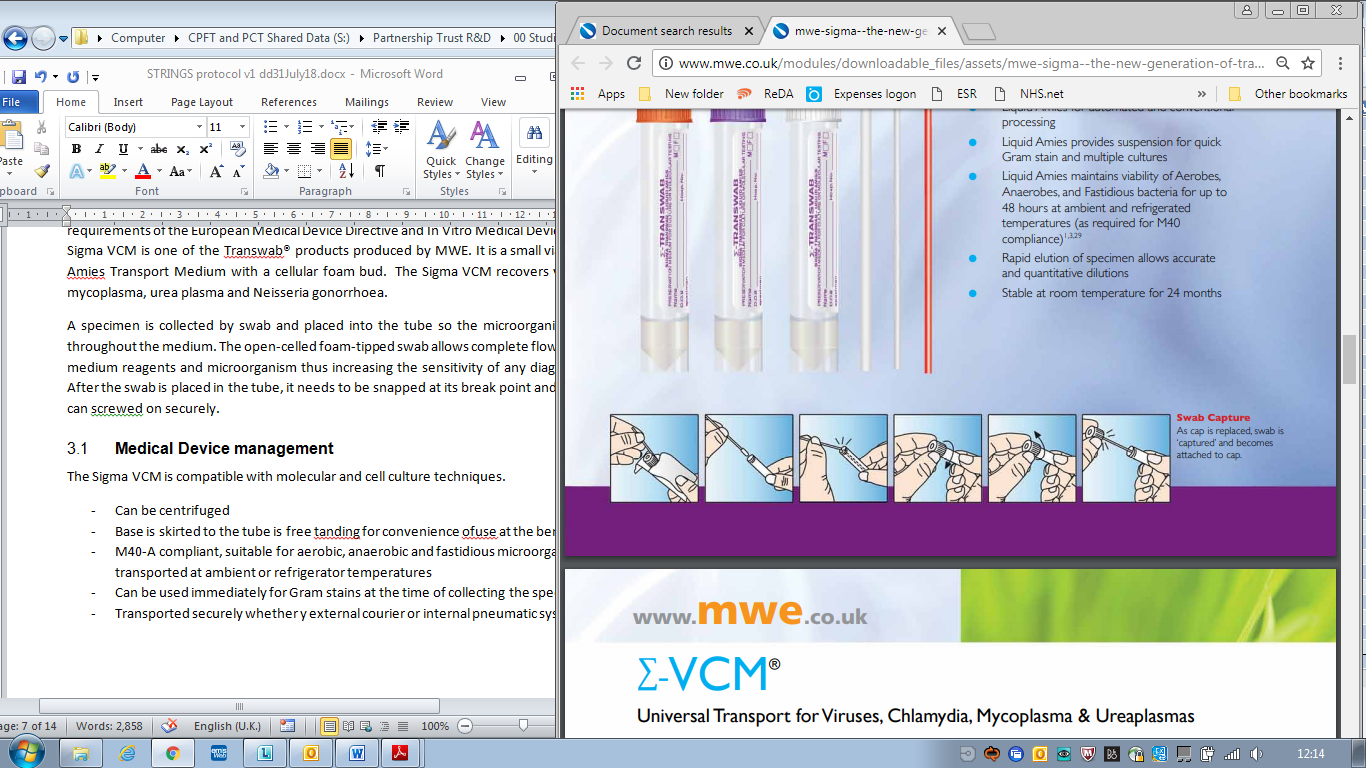


The open-celled foam-tipped swab is designed for optimum absorption and release and allows complete flow through the liquid medium reagents and microorganism thereby increasing the sensitivity of any diagnostic procedures. The VCM medium allows survival and recovery of the target organisms, while antimicrobials inhibit the growth of contaminating bacteria and fungi in the specimen. The VCM medium is compatible with molecular test system and the target organisms can be identified by culture of molecular techniques.

* 1. Medical Device management

A specimen is collected by swab and placed into the tube so the microorganisms are dispersed throughout the medium. After the swab is placed in the tube, it needs to be snapped at its break point and broken so the cap can be screwed on securely. The swab is ‘captured’ by the cap so that when the cap is removed, the swab is automatically removed with the cap (figure 2). The standard Sigma swab is suitable for general swab applications such as skin lesions, nose and throat whilst the mini-tip Sigma swab (used in this study) is suitable for nasopharyngeal and urethral sampling.

Figure 2. Swab capture



The Sigma VCM is suitable for aerobic, anaerobic and fastidious microorganisms and can be transported at ambient or refrigerator temperatures. The tubes can be transported securely whether by external courier or internal pneumatic system and the base is skirted so the tubes are free standing. The Sigma VCM can be used immediately for Gram stains at the time of collecting the specimen and is compatible with molecular and cell culture techniques.

1. Study hypothesis
   1. Primary objective

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

* 1. Secondary objective

To determine if there is a difference in performance of direct and indirect plating, respectively, vs Sigma VCM liquid transport medium.

To evaluate if storage temperature for Sigma VCM swab, before incubation at 37C in microbiology laboratory, affects performance.

To assess the cost-effectiveness and potential benefits of using Sigma VCM compared to current practices.

1. Study protocol
   1. Study design and timeline

This concerns a multi-centre, controlled prospective study conducted within one NHS Trust. The study will be carried out by NHS Cumbria Partnership NHS Foundation Trust staff. The study will take place at two Sexual Health clinics in Cumbria with support and oversight from research staff. Research delivery staff will be delegated to provide support with data collection and processing.

**Table 1. Anticipated timeline**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Month | Setup | Recruitment | Analysis | Finalise |
| Sep-18 | Submission for HRA approval |  |  |  |
| Oct-18 | NIHR portfolio adoption |  |  |  |
| Dec-18 | HRA and Trust approval | Start Recruitment |  |  |
| Sep-19 |  | Finish Recruitment |  |  |
| Oct-19 |  |  | Data collection complete; Analyse data |  |
| Nov-19 |  |  |  | Manuscript & report writing |

* 1. Participant identification and research setting

Participants will be recruited from sexual health clinics in Carlisle (Solway clinic) and Workington (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. 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 eligible patients will be invited to take part until the required numbers have been achieved.

* 1. 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.

* 1. Recruitment

Once a patient consented to the study a sample will be taken as part of normal clinical practice. This is a urine or urethral sample for man and a urine, 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 (Sigma VCM vs agar plating). The following baseline participant parameters will be collected from medical records:

* Demographics (including date of birth, gender,)
* Symptoms
* Sexual history (sexual orientation, number of contacts)
* Any previous STI episodes
* Contraception and condom use

During the recruitment process 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.

* 1. Storage, transport, incubation, and diagnostic procedures

The samples will be processed according to normal practice for the agar plates and additionally processed with the Sigma VCM. This translates as:

* Carlisle (direct plating): 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.
* Workington (indirect plating): plating onto agar plate in sexual health clinic but storage in fridge until collected by courier, and transferred (in CO2 in a gas jar) to Carlisle Infirmary microbiology/virology laboratory for incubation for 48 hrs, and NAAT/PCR in parallel.

The order of swab sampling will be as follows:

1. Swab for agar plate
2. Swab for MWE Sigma tube
3. Swab for molecular testing (if conducted)

The temperature of storage and time taken before the samples reach the microbiology laboratory will be recorded.

Two diagnostic approaches are taken, with the molecular testing being deemed the gold standard.

* 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).
* Microbiological and biochemical testing: growth of bacteria on a BC18 oxide medium agar plate for 48 hrs (once in the microbiology laboratory). 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.

Appendix 3 summarises what happens to the samples.

* 1. 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 Sigma VCM sampling 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.

* 1. Outcome measures
     1. Primary outcome measures

To determine the detection rates of the Sigma VCM compared to current (in)direct agar plating practise in Cumbrian sexual health clinics. The results from NAAT (PCR) will be used for primary outcome measure comparison. The results will be tabulated as follows:

**Table 2. Primary outcome measure: N Gonorrhoea detection levels**

|  |  |  |
| --- | --- | --- |
|  | NAAT result positive | NAAT result negative |
| (in)direct plating – combined results | n | N |
| Sigma VCM kit | n | N |

A separate 2x2 table will be produced for storage of MWE Sigma at either room temperature and in the fridge, both vs standard agar plating (which will be incubated at 37C instantly or first stored in the fridge) .

Phase A is standard swabbing with agar plates vs MWE Sigma tube stored in fridge.Phase B is standard swabbing with agar plates vs MWE Sigma tube stored at room temperature.

* + 1. Secondary outcome measures

The effect of either direct or indirect plating versus Sigma VCM will also be appraised. The results will be tabulated as follows:

**Table 2. Primary outcome measure: N Gonorrhoea detection levels**

|  |  |  |
| --- | --- | --- |
|  | NAAT result positive | NAAT result negative |
| indirect plating samples only | n | n |
| Sigma VCM kit (from patients whose samples are plated indirectly) | n | n |
|  | | |
| direct plating samples only | n | n |
| Sigma VCM kit (from patients whose samples are plated directly) | n | n |

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

This study also aims to assess the cost-effectiveness and potential benefits of using Sigma VCM 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)

1. Subjects
   1. Anticipated number of research subjects

Patients will be recruited from the adult (age 18+) 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 2. 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 actively select for patients with a higher chance of being diagnosed with Gonorrhoea, the sample size calculation will take into account 25% of patients actually carrying the infection.

The percentages for (in)direct plating are based on results obtained in the Cumbria sexual health clinics for patients who present with symptoms of Gonorrhoea infection. The proposed percentages for VCM are based on results obtained in a study supported by MWE using a different transport medium kit (Sigma Transwab MW177S/MW176S; see <http://www.mwe.co.uk/document-search-results/?productCodeFilter=MW176S&documentTypeFilter=5>). The detection rates are based on results to be obtained with NAAT techniques.

Ultimately the primary question is whether Sigma VCM is superior to (in)direct plating combined. A secondary question is whether one of indirect or direct plating is inferior to Sigma VCM.

Table 3. Sample size calculation

|  |  |  |  |
| --- | --- | --- | --- |
| **Sample Preparation /**  **/ Test outcome** | | Positive for Gonorrhoea (hypothetical) | Negative for Gonorrhoea (hypothetical) |
| Non-VCM (direct plating) | | 60% | 40% |
| VCM diagnostic storage medium kit | | 80% | 20% |
|  | | | |
|  | Power beta of 80%, Alpha p-value of 0.05, Effect size 0.5.  Sample size required if all participants carried Gonorrhoea but performance of different preparation techniques was as described above: 32. Since one patient provides two samples, this equates to 16 patients.  Total patients needed to take into account 15% actually being positive for Gonorrhoea:  (100/15) x 16 = 106  The study will be done with Sigma samples in the fridge (Phase A) or at room temperature (Phase B), and therefore the total sample size will be 212. | | |

* 1. Eligibility criteria

The criteria to enter the study are outlined here.

* + 1. Inclusion criteria
* 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

* + 1. Exclusion criteria
* Under the age of 18 years
* Unable to fully understand the consent process and provide informed consent due to either language barriers or mental capacity
* Rectal sampling
  1. 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.

1. Safety
   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 (in)direct plating and Sigma VCM medium. 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).

1. Statistical consideration and data analysis plan
   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)
  1. Primary outcome statistics

To determine the detection rates of the Sigma VCM compared to current practises, the following data will be collated:

* NAAT/PCR detection rates
* Microbiological culture and characterisation detection rates

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

* 1. Secondary outcome statistics

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

* NAAT/PCR detection rates
* Microbiological culture and characterisation detection rates

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

To assess the cost-effectiveness and potential benefits the following data will be collated:

* Storage requirements per method
* Transport requirements per method
* Incubation time per method
* Costs per method

Any difference in average cost of process the sample (agar plating vs VCM) 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 plating and VCM sampling methods:

* Dependent: detection of *N. Gonorrhoea* with NAAT/PCR, 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)

1. 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 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 (Medical Wire & Equipment) 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.

1. Goverance of study
   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

* 1. Sponsor & Indemnity

Cumbria Partnership NHS Trust is the sponsor of this study and therefore NHS indemnity applies for design, conduct and management of the study. MWE has provided a grant for this study by means of provision of Sigma VCM swab transport kit free of charge, to the value of £202.15.

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.

1. 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 sampling and transport method to get a patient sample to the laboratory 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, MWE diagnostics
* Presented on conferences and meetings

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Appendix 1. Neisseria gonorrhoea testing and diagnoses in Cumbria (2015-2018)

Site #1 and #2 will be recruiting sites for this present study

**1st August 2015-1st August 2016**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | GC testing / positive (male) | | GC testing / positive (female) | | GC testing / positive  (total) | |
| Site #1 | 1619 / 58 | **3.58%** | 1911 / 26 | **1.36%** | 3530 / 84 | **2.38%** |
| Site #2 | 1243 / 10 | **0.80%** | 1439 / 1 | **0.07%** | 2682 / 11 | **0.41%** |
| Site #3 | 783 / 13 | **1.66%** | 901 / 6 | **0.67%** | 1684 / 19 | **1.13%** |
| Site #4 | 475 / 11 | **2.32%** | 614 / 5 | **0.81%** | 1089 / 16 | **1.47%** |
| Total | 4120 / 92 | 2.23% | 4865 / 38 | 0.78% | 8985 / 130 | 1.45% |

**1st August 2016-1st August 2017**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | GC testing / positive (male) | | GC testing / positive (female) | | GC testing / positive  (total) | |
| Site #1 | 1648 / 57 | **3.46%** | 2186 / 31 | **1.42%** | 3834 / 88 | **2.30%** |
| Site #2 | 1073 / 13 | **1.21%** | 1571 / 3 | **0.19%** | 2644 / 16 | **0.61%** |
| Site #3 | 871 / 27 | **3.10%** | 1163 / 12 | **1.03%** | 2034 / 39 | **1.92%** |
| Site #4 | 480 / 13 | **2.71%** | 584 / 6 | **1.03%** | 1064 / 19 | **1.79%** |
| Total | 4072 / 110 | 2.70% | 5504 / 52 | 0.94% | 9576 / 162 | 1.69% |

**1st August 2017-1st August 2018**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | GC testing / positive (male) | | GC testing / positive (female) | | GC testing / positive  (total) | |
| Site #1 | 1218 / 71 | **5.83%** | 1382 / 38 | **2.75%** | 2600 / 109 | **4.19%** |
| Site #2 | 905 / 12 | **1.33%** | 1090 / 7 | **0.64%** | 1995 / 19 | **0.95%** |
| Site #3 | 757 / 29 | **3.83%** | 758 / 11 | **1.45%** | 1515 / 40 | **2.64%** |
| Site #4 | 473 / 21 | **4.44%** | 426 / 6 | **1.41%** | 899 / 27 | **3.01%** |
| Total | 3353 / 110 | 3.97% | 3656 / 52 | 1.70% | 7009 / 195 | 2.78% |

**Total over three years (1st August 2015 – 1st August 2018)**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | GC testing / positive (male) | | GC testing / positive (female) | | GC testing / positive  (total) | |
| Total | 1154 / 335 | 2.90% | 14025 / 152 | 1.08% | 25570 / 487 | 1.91% |

Appendix 2. Study participant Flowchart

Screening

Patient identified by clinical staff member at sexual health clinic

Consent requested to explain study

Patient ineligible

Patient declines to participate

Patient recruited into study

Patient identified by clinical staff member

Consent requested to explain study

Screening form completed

During baseline visit demographic data is obtained and the following baseline measures

* Demographics (including date of birth, gender)
* Symptoms
* Sexual history
* Previous STI episodes
* Contraception and condom use

Patient Information Sheet is provided to patient

Patients have sufficient time to consider the study and ask questions

Consent is obtained

One vaginal/cervix/urethral swab taken and processed according to local current methods (ie agar plating technique)

One vaginal/cervix/urethral swab taken and processed in Sigma VCM medium

Follow-up

Baseline

Recruitment

Screening

Screening

Consent process

Patient Information Sheet is provided to patient

Patients have sufficient time to consider the study and ask questions

Consent is obtained

Patient ineligible

Patient declines to participate

Patients are randomised

Samples send to the lab and processed according to normal standards

Results communicated to patient as per normal practice (Sigma VCM results can be used)

Test results recorded by research team

Appendix 3 – sample flowchart

Swab sample plated on agar plate

Sent directly to lab or first stored in fridge

Swab sample placed in Sigma VCM medium bottle.

Sent directly to lab or first stored in fridge (Phase A, first 120 patients) or stored at room temperature (Phase B, second 120 patients)

NAAT (PCR)

Euroclone dual test (chlamydia and N/Gonorrhoea): Real Time PCR DUPLICα® RealTime Neisseria gonorrhoeae and DUPLICα® RealTime Chlamydia trachomatis 2nd Generation Detection Kits (Euroclone®)

Microbiological and biochemical testing

48 hr incubation (once in the microbiology laboratory). Followed by oxidase test and Gram stain for positive colonies. Furthermore, a biochemical API NH test will be performed for confirmation

Results from this test used to compare positive / negative results for each sample kit