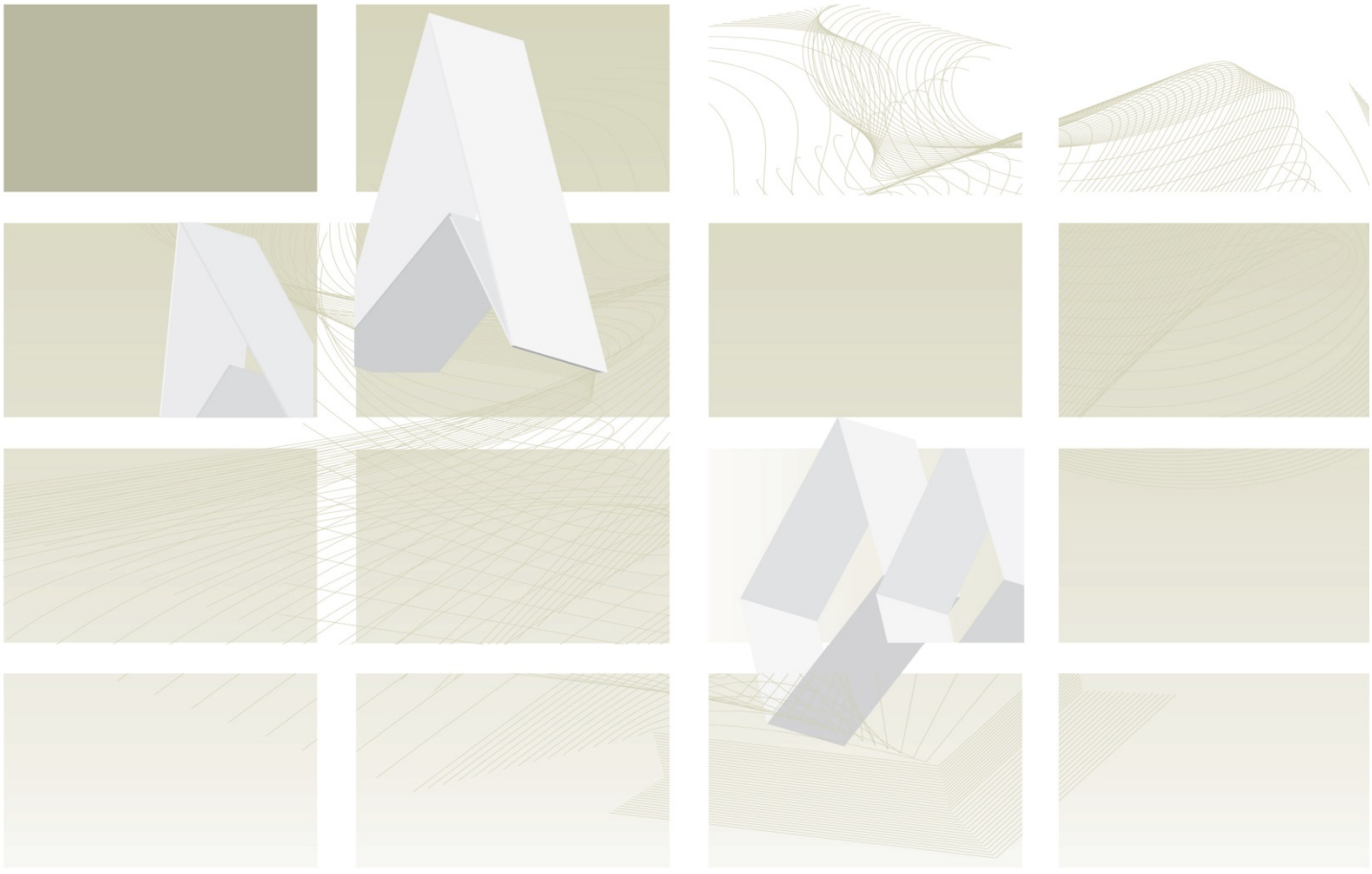
Public Health England

NHS

UK Standards for Microbiology Investigations

Review of users' comments received by
Working group for microbiology standards in clinical virology/serology

V 37 *Chlamydia trachomatis* infection – testing by Nucleic Acid Amplification Tests (NAAT)



NICE accredited
www.nice.org.uk/accreditation

"NICE has renewed accreditation of the process used by **Public Health England (PHE)** to produce **UK Standards for Microbiology Investigations**. The renewed accreditation is valid until **30 June 2021** and applies to guidance produced using the processes described in **UK standards for microbiology investigations (UKSMIs) Development process, S9365', 2016**. The original accreditation term began in **July 2011.**"

Recommendations are listed as ACCEPT/ PARTIAL ACCEPT/DEFER/ NONE or PENDING

Consultation: 16/05/2016 – 31/05/2016

Version of document consulted on: V 37dn+

Proposal for changes

Comment number	1		
Date received	20/05/2016	**Lab name**	Bristol Public Health Laboratory
Section	CT NAAT		
Comment			
An observation and suggestion rather than a request for change, and one that cuts across all diagnostics. The exceptionalism of medico-legal samples is mentioned in the document but the rationale is far from rigorous. I suspect the issues are one of possible legal sanction for an individual and reputation for a laboratory, but it is worth noting that laboratories standard practice should be good enough for patient care, which is the primary aim of diagnostics relevant to UK SMI. Add to the discussion that many legal cases do not come to light until many months, if not years, after the sample date. Finally, there is a standard for forensic testing (17025) that I know Bristol PHL has agreed not to work towards, and I suggest that another note indicating that known medico-legal samples should be processed in such an environment, or at least have an agreement with the sender how they will be handled.			
Recommended action	**NONE** The UK SMI refers to the Royal College of Pathologists Medicolegal guidelines which are appropriate for this document. The information is however welcome.		

Comment number	2		
Date received	30/05/2016	**Lab name**	British Association for Sexual Health and HIV
Section	All		
Comment			
Thank you for the opportunity for BASHH to comment on this consultation. We have taken advice from the BASHH special interest group and this is a summary of their comments. General comments There are 4 main areas of concern 1. The large section on pooling implies this is a recommended method It is not clear how well validated pooling of samples is for testing with commercial NAATs, with possible changes in sensitivity and specificity and the section implies that it is to be encouraged. It is also not clear whether commercial assays are licensed for use with multiple samples.			

2. Table 2 is misleading

   Table 2 could be a very useful table but it is not clear which tests, and what generation of some of the tests, are being quoted or whether they are single or dual NAATs. Using published data for sensitivity and specificity does risk giving misleading results as it will be dependent on the population tested and the prevalence of the infection, manufacturer's quoted values is safer.

3. The section on POCT needs updating

   The section on POCTs needs updating with recent references and there needs to be a definition of a POCT versus a rapid test. The GeneXpert rapid test has had comparable performance to lab-based NAATs – whether it is a POCT is a matter of debate. The Atlas io platform for CT is now CE-marked, with 2 conference abstracts reporting the test's performance (Pearce et al, ISSTDR 2015, abstract 07.03; Cousins et al. ESCR 2016, Abstract No. 0127). Another PCR-based test in development is being reported at ESCR (Harding-Esch et al. ESCR, Abstract No. 0032). The following papers are a bit more up-to-date than reference 22 on the state of STI POCTs: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4065592/, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3635142/ and http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4204237/

4. The European guidelines of 2010 (reference 10) have been revised and published in 2015 but not referenced.

   The European guidelines have been updated and the text should be checked to ensure comparability with the new guidelines

Specific comments

a. *Neisseria gonorrhoeae* should be spelt correctly throughout the text.

b. Page 9: NAATs for medico-legal cases: perhaps important to clarify that a positive NAAT in these situations should be confirmed by using a NAAT with a different target (as per BASHH guidelines). It is mentioned under the Confirmation and Medico-legal sections later, but repetition here would be good.

c. Page 9: It is important to clarify what is meant by "rapid tests", and based on what criteria these are not recommended; it says "EIA and rapid tests are not recommended." The Cepheid GeneXpert is promoted as a rapid test (90 minute turnaround time), and is used as the reference NAAT in a number of clinics.

d. Page 9: Screening: '3-6 month' should read '3-6 months'.

e. Page 10: Endocervical swabs have been shown to be less sensitive than vulvo-vaginal swabs and must be taken by a healthcare worker – this should be referenced

f. In men, first void urine has been shown to be more sensitive than urethral sampling and is the sample type of choice, this should also be referenced

g. Page 10: Sample types: The large section on pooling is a concern and question whether this is a method that should be encouraged, particularly when most labs are using dual tests these days? Certainly from a laboratory perspective pooling extracts can be a recipe for disaster outside of the blood service who are obviously very well versed in it. It would be good to mention that it has been looked at clinically (with references) but does suffer from a lack of sensitivity. Equivalent lab data may not be available.

h. Page 10: It would be helpful to have a reference to back up the statement "however, pooled samples may not be appropriate if using a dual *Neisseria gonorrhoeae/Chlamydia trachomatis* NAAT."

i. Page 10: If this type of pooling is carried out and is sent for LGV diagnosis to the reference laboratory, the method of pooling used should be stated on the referral paperwork. "Have pooled samples for LGV testing been validated at STBRU? There should be a reference

j. Page 11: Laboratory tests: the use of the term 'POCT' should be clarified.

k. Page 11: "Nucleic Acid Amplification Technique (NAAT) " should be "Nucleic Acid Amplification Test"

l. Page 11: Table 2. Estimates of sensitivities and specificities for diagnostic tests for *C. trachomatis* in urogenital specimens14. Misleading table – What is meant by SDA test? Does this mean the first or second generation test by BD? Further information is required? Also PCR is a very general term? Which PCR? Either requires more information or should be removed.

m. Page 12: As per national and international guidelines, for infections where the PPV of a test is less than 90%, and for specimens from extra-genital sites (eg rectal swabs), confirmatory testing, = where is the evidence base for this statement?

n. Page 13: It should be "but for best practice" not "but for best practise"

o. Page 13: NAAT inhibition: Can we not now say that use of an inhibition control is essential? Anyone not using one is at a massive legal risk as well as it being exceptionally poor practice. It should be essential.

p. Definitions – invalid is not always the same as inhibitory. Invalid may indicate a sample process error rather than the presence of inhibitors. This should be clarified and potentially added to the flow chart later in the document.

q. Page 15: Test flow chart legend: should this mention 'equivocal/indeterminate' results?

r. Test flow chart legend: e) line 4 – 'platform i used' should read 'platform is used'.

s. Page 16: "which platform is used for screening"

t. Page 16: "In populations with low prevalence it is still necessary to confirm" – what is the definition of "low prevalence"?

Recommended action	General Comments 1. **ACCEPT** Reference to pooled samples removed from the document. The following text has been added to the scope: *'This SMI does not cover the testing of pooled samples or the use of point of care tests (POCT).'* 2. **ACCEPT** It was agreed that the table should be removed, however the reference should be kept within the document. Text updated to:

	'Varying sensitivities and specificities for diagnostic tests in urogenital specimens have been demonstrated in clinical trial data, package inserts and published papers.' 3. **ACCEPT** It was agreed that the section on POCT should be removed as it is outside of the scope of this SMI. Information on rapid tests will be included. The following text has been added to the scope: *'This SMI does not cover the testing of pooled samples or the use of point of care tests (POCT).'* 4. **ACCEPT** The document has been reviewed again the 2015 guidelines and reference within the document has been updated accordingly. Specific Comments a. **ACCEPT** Text updated. b. **ACCEPT** Text updated. c. **ACCEPT** Text clarified with regards to rapid tests. d. **ACCEPT** Text updated. e. **ACCEPT** BASHH (2015) UK national guideline for the management of infection with *Chlamydia trachomatis* included. f. **ACCEPT** BASHH (2015) UK national guideline for the management of infection with *Chlamydia trachomatis* included. g. **ACCEPT** The section on pooling samples has been removed from the document. h. **NONE** Section on pooled samples has been removed. i. **NONE** Section on pooled samples has been removed. j. **NONE** The section on POCT has been removed from the

	document. k. **ACCEPT** Text updated. l. **ACCEPT** The group agreed that the table should be removed and the reference kept within the document. m. **PARTIAL ACCEPT** The sentence has been rephrased to remove PPV from the document. n. **ACCEPT** Text updated. o. **NONE** Inhibition controls are not available for all commercial NAAT platforms. BASHH (2015) UK national guideline for the management of infection with *Chlamydia trachomatis.* p. **ACCEPT** Invalid and its meaning has been included in the document. q. **NONE** Equivocal and indeterminate results were previously included in the algorithm; however, it was felt that these should be reported following local protocol. r. **ACCEPT** Sentence rewritten: *'the platform that has been used for screening'* s. **ACCEPT** Sentence rewritten as above. t. **ACCEPT** This term has been removed from the document.

Comment number	3		
Date received	31/05/2016	**Lab name**	PHE - AMRHAI
Section	Throughout		
Comment			
We are very sorry but we received this document last minute therefore have put some comments on the attached document. a. **Type of specimens:** Not sure pooled samples should be listed here as they are			

not a preferred sample type b. **Introduction - Risk factors for *C. trachomatis*:** Make clear these are non-LGV risk factors as LGV risk factors very different. c. **Introduction - Laboratory Diagnosis (Confirmation *C. trachomatis*):** Please check as reference 23 may now be superseded by ref 3. d. **Introduction - Laboratory Diagnosis (Confirmation *C. trachomatis*):** Please make clear that STBRU can only accept a pooled sample from the same patient e. **Introduction - Laboratory Diagnosis (Confirmation Lymphogranuloma venereum):** Please clarify - Only if LGV is suspected, not for all CT rectal pos in women f. **Introduction - Persistent Infection:** STBRU currently has a Chlamydia culture service for samples from patients who consistently fail treatment – it may be worth mentioning here. However this service is currently under-review. g. **Footnote g:** This is a bit non-descript, could use more detail as to when labs should send to reference laboratory.	
Recommended action	a. **ACCEPT** It was agreed that pooled samples should be removed from the document. b. **ACCEPT** Text updated. c. **ACCEPT** Up to date reference has now been included. d. **NONE** Pooled samples have been removed from the document. e. **ACCEPT** Text updated. f. **NONE** A note will be added to the document record to review the status of this service for inclusion at the document's next review. g. **PARTIAL ACCEPT** It was agreed that footnote g should be removed and replaced with footnote f to avoid duplication.

Comment number	4		
Date received	31/05/2016	**Lab name**	National Chlamydia Screening Programme

Section	All
Comment	

Scope of document

a. Do pooled samples referred to samples from multiple sites on one individual or samples tested in one batch from multiple individuals. Would benefit from clarification of what pooled samples refers to.

b. "Send samples to the sexually transmitted bacteria reference unit (STBRU), or a local laboratory with validated test for diagnosis"

   This is a point about process and should be separate.

Introduction

c. "*Chlamydia trachomatis* infection is the most frequently reported bacterial, sexually transmitted infection in the UK, particularly in young adults"

   It is also the most prevalent rather than reported and could reference the NATSAL paper.

   Sonnenberg P, Clifton S, Beddows S, Field N, Soldan K, Tanton C et al. Prevalence, risk factors, and uptake of interventions for sexually transmitted infections in Britain: findings from the National Surveys of Sexual Attitudes and Lifestyles (Natsal). Lancet 2013; 382(9907):1795-1806.

d. "This SMI covers the detection of urogenital *C. trachomatis* infection, but does not differentiate between LGV and non-LGV serovars"

   Given that LGV testing is a specialist procedure and samples are sent to the STBRU for diagnosis (not reference) I think LGV warrants a separate section.

e. "Risk factors for *C. trachomatis* infection include <25 years of age, a new sexual partner or more than one sexual partner in the past year and inconsistent use of condoms"

   I think the document would be clearer if there was less epi and more clinical guidance ie CT (non-LGV) is tested for in asymptomatic and symptomatic individuals and is most prevalent in heterosexuals under 25.

   CT-LGV is tested for in symptomatic individuals and is most prevalent in MSM.

   Test for each as per BASHH clinical guidance.

Screening

f. "Patients should be tested where there are symptoms or signs suggestive of chlamydial infection, in patients with reactive arthritis who are sexually active, in parents of children with chlamydial conjunctivitis/pneumonia and in egg and semen donors, or on request"

   I don't think it's necessary to give indications for testing in the SMI guide targeting lab staff, particularly as this is a lab standard for the whole of the UK. I would say that testing indications are locally determined and can include asymptomatic testing. I would also make a point to say that any testing in populations with low positivity will result in a lower positive predictive value and local labs should be evaluating testing to ensure that where necessary confirmatory testing is available.

g. "In England, routine screening is recommended in all sexually active men and

women between the ages of 16 and 25 annually, or sooner if there has been a change of partner"

Should be 15 and 24. Suggest also to reference most recent NCSP standards document.

h. "Repeat testing should be carried out 3-6 months following the completion of treatment in those diagnosed with chlamydial infection who are under 25 years old"

Note this is the BASHH guideline; NCSP recommends re-testing at around 3 months.

i. "Routine screening is not recommended in pregnant women unless from high prevalence populations; however, screening is recommended for those seeking termination of a pregnancy"

Note to say that those in NCSP screening age group would still be indicated for screening.

Laboratory diagnosis

j. "EIA and rapid tests are not recommended"

It would be helpful for readers for recommendations to be highlighted as a bullet.

Laboratory diagnosis – sample types

k. "The recommended sample type for women is a vulvo-vaginal swab which may be self-collected and submitted by post"

given this is only the recommended swab for women with a vaginal test it would be advisable to simplify this first paragraph to state:

"Sample type is dependent upon suspected locus of infection, gender and sexual orientation – see table/BASHH guidance"

Additional notes in the table could be used to highlight specific details such as

- rectal samples may be taken by patient, HC worker or during proctoscopy.

then add clear recommendations for each

- Testing algorithms for extra genital samples should be evaluated locally.
- Endocervical swabs should only be taken by HCW
- first catch urine in women has lower sensitivity and should not be used
- Pooled samples…
- LGV samples…
- dual samples…

l. I think "submitted by post" warrants its own declaration – the NCSP providers do thousands of tests through post and it would be good to set out what, if anything, is known on the time samples will still be viable for. What swab types and mediums they need contained in and what impact if any this has on accuracy.

m. "Endocervical swabs have been shown to be less sensitive than vulvo-vaginal swabs"

Needs a reference.

n. "In men, first void urine has been shown to be more sensitive than urethral sampling and is the sample type of choice"

   Needs a reference.

o. "Pooling of samples may be undertaken; however, pooled samples may not be appropriate if using a dual *Neisseria gonorrhoea*/*Chlamydia trachomatis* NAAT"

   Needs a reference – as we are not aware of guidance suggesting that pooled sampling can be undertaken without local validation.

p. "If this type of pooling is carried out and is sent for LGV diagnosis to the reference laboratory, the method of pooling used should be stated on the referral paperwork"

   Advise a separate LGV section for clarity.

Laboratory diagnosis – laboratory tests

q. "Dual NAAT for *C. trachomatis* and *Neisseria gonorrhoea* are available and are used in many laboratories in the UK"

   This requires a separate subsection which points to existing PHE guidance and comments on the low PPV in low prevalence populations – ie warning against widespread testing without good reason and the need for verification using separate targets.

r. "Table 2. Estimates of sensitivities and specificities for diagnostic tests for *C. trachomatis* in urogenital specimens"

   This is a moderately old table and not necessarily based on systematic review or including most up to date papers, so while useful it is hard to know for sure how accurate the ranges are, particularly in light of newer test platforms. Suggest not to include and just make a clear statement to say which specimen types and platforms are acceptable.

s. "Postal test-kits (PTK) have also been trialled as a form of sample collection for home-based screening" – add "and are widely used in England".

t. "Assessment of these strategies in terms of test and cost effectiveness is ongoing"

   This method is used widely in England. I'm not sure of which assessment this refers to.

Laboratory diagnosis – point of care testing (POCT)

u. "POCTs using NAAT are currently under development"

   A recommendation which explicitly states the need for comparable accuracy before use should be included as the risks of using low accuracy tests in low prevalence populations are high (outreach and GPs may find these tests appealing but have much lower positivity when testing their populations) ie "POCTs should be evaluated and shown to have comparable accuracy."

Laboratory diagnosis – confirmation – *C. trachomatis*

v. Delete "as per national and international guidelines" and reference new guidelines http://www.bashh.org/documents/UK%20guideline%20for%20the%20 management%20of%20%20Chlamydia%20trachomatis%20(8-06-

15%20v4)%20submitted%20to%20IJSA.pdf

w. "specimens from extra-genital sites (eg rectal swabs)"

IUSTI guidelines state that confirmatory assay "may be appropriate" and 2015 BASHH do not recommend confirmatory assay. Is there a particular reference to point to the low accuracy of NAATs in extra genital sites?

x. "Samples for *C. trachomatis* confirmation can be sent to the sexually transmitted bacteria reference unit (STBRU)"

Given other labs will provide this service will PHE be criticised for advocating the use of a service we charge for? We suggest that this sentence be removed and separate out LGV to separate section.

Laboratory diagnosis – confirmation – Lymphogranuloma venereum

y. "LGV testing is recommended in ~~those~~ MSM with proctitis and in patients who are HIV positive MSM, with or without symptoms, who have *C. trachomatis* infection at any site"

As per most recent BASHH guidance.

Window period and test of cure

z. "In addition, it is recommended in some cases of rectal infection depending on treatment type"

Please identify treatments in question.

Persistent infection

aa. Change "rounds of therapy" to "full courses of appropriate antimicrobial therapy".

Medicolegal cases

bb. Change "reproducibility" to "accurate result".

Footnotes

cc. A statement or a footnote on the importance of positive predictive values is essential – particularly in light of the increasing use of dual NAATs for NG/CT.

dd. Footnote e: Change "platform" to "target"

ee. Footnote e: Typo – "which platform i"

ff. Footnote g: please clarify purpose – "…confirmation of inhibitory result" or "for testing of sample with reference assay"

Notification to PHE

gg. These data (including negative tests) must be mandatorily reported to PHE. This should be mentioned here. This is separate from Health Protection Notifiable diseases/organisms. Data should be reported directly to PHE as per;

http://www.datadictionary.nhs.uk/data_dictionary/messages/clinical_data_sets/data_sets/chlamydia_testing_activity_data_set_fr.asp?shownav=1

Financial barriers	
No.	
Recommended action	a. **NONE** Pooled samples have been removed from the document.

	b. **ACCEPT** Text removed from the scope. c. **ACCEPT** Text updated and reference included. d. **NONE** The group felt that the document was clear and did not need to be restructured to separate out LGV testing. e. **NONE** The group felt that the current text was appropriate for the introduction section of the document. f. **PARTIAL ACCEPT** The group agreed that the text relating to screening was useful background information and should remain in the document. g. **ACCEPT** Text updated. h. **NONE** Difference in recommendation noted. i. **ACCEPT** Text updated. j. **PARTIAL ACCEPT** The text has been moved to a new paragraph. k. **ACCEPT** This part of the document has been amended to make it clearer. l. **NONE** Text updated in the laboratory diagnosis section. m. **ACCEPT** BASHH guidance and additional reference added. n. **ACCEPT** BASHH guidance and additional reference added. o. **NONE** Pooled sampling has been removed from the document. p. **NONE** Pooled sampling has been removed from the document. q. **PARTIAL ACCEPT** It was acknowledged that dual NATT for *C. trachomatis* and *N. gonorrhoea* is in wide use. It was agreed that this

	should be added to the work plan for the next review of this document. r. **ACCEPT** Table removed. s. **ACCEPT** Text added. t. **ACCEPT** Text removed. u. **NONE** Reference to POCT removed from the document. v. **ACCEPT** The reference and text has been updated. w. **NONE** The comment refers to guidelines which UK SMIs are not authors of. x. **PARTIAL ACCEPT** Text updated to include local laboratory with validated test. y. **ACCEPT** Text updated. z. **NONE** It is outside the scope of UK SMI to suggest treatment options. aa. **ACCEPT** Text updated. bb. **ACCEPT** Text updated. cc. **NONE** This document does not cover dual NAATs testing. dd. **ACCEPT** Text updated. ee. **ACCEPT** Text amended. ff. **NONE** The group decided that this footnote should be removed. gg. **NONE** This is already covered in the document.

Comments received outside of consultations

Comment number	1		
Date received	02/06/2016	**Lab name**	Royal College of Physicians
Section	All		
Comment			
The RCP is grateful for the opportunity to respond to the above consultation. We have liaised with our JSC for GU Medicine and would like to formally endorse the response submitted by the British Association for Sexual Health and HIV.			
Recommended action	**NONE** No response required.		