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The eSexual Health Clinic system for management, prevention, and control of sexually transmitted infections: exploratory studies in people testing for Chlamydia trachomatis

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Summary

Background Self-directed and internet-based care are key elements of eHealth agendas. We developed a complex online clinical and public health intervention, the eSexual Health Clinic (eSHC), in which patients with genital chlamydia are diagnosed and medically managed via an automated online consultation, leading to antibiotic collection from a pharmacy. Partner notification, health promotion, and capture of surveillance data are integral aspects of the eSHC. We aimed to assess the safety and feasibility of the eSHC as an alternative to routine care in non-randomised, exploratory proof-of-concept studies.

Methods Participants were untreated patients with chlamydia from genitourinary medicine clinics, untreated patients with chlamydia from six areas in England in the National Chlamydia Screening Programme’s (NCSP) online postal testing service, or patients without chlamydia tested in the same six NCSP areas. All participants were aged 16 years or older. The primary outcome was the proportion of patients with chlamydia who consented to the online chlamydia pathway who then received appropriate clinical management either exclusively through online treatment or via a combination of online management and face-to-face care. We captured adverse treatment outcomes.

Findings Between July 21, 2014, and March 13, 2015, 2340 people used the eSHC. Of 197 eligible patients from genitourinary medicine clinics, 161 accessed results online. Of the 116 who consented to be included in the study, 112 (97%, 95% CI 91–99) received treatment, and 74 of those were treated exclusively online. Of the 146 eligible NCSP patients, 134 accessed their results online, and 105 consented to be included. 93 (89%, 95% CI 81–94) received treatment, and 60 were treated exclusively online. In both groups, median time to collection of treatment was within 1 day of receiving their diagnosis. 1776 (89%) of 1936 NCSP patients without chlamydia accessed results online. No adverse events were recorded.

Interpretation The eSHC is safe and feasible for management of patients with chlamydia, with preliminary evidence of similar treatment outcomes to those in traditional services. This innovative model could help to address growing clinical and public health needs. A definitive trial is needed to assess the efficacy, cost-effectiveness, and public health impact of this intervention.

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Introduction

Well evidenced, high-quality interventions need to be delivered in innovative and efficient ways to meet the growing health needs of the population. Digital technologies provide opportunities for alternative modes of health-care delivery and for public health interventions—so-called eHealth. UK health strategy strongly supports development of eHealth and self-managed care, with the aim of increasing both the quality and accessibility of health care while reducing total health expenditure.1 However, eHealth provision for medical management is mostly limited to monitoring or support for people with chronic disorders that have been diagnosed in traditional care settings.1 Yet the potential impact of eHealth extends beyond individual patients. In infectious diseases, for example, eHealth interventions could be used to facilitate risk-reduction strategies, provide clinical management of cases, and interrupt transmission in the population.

Chlamydia trachomatis is the most commonly reported bacterial sexually transmitted infection (STI) in the UK (220 000 reported cases per year in England). Chlamydia mainly affects people aged 16–24 years,2 an age group who use digital technology avidly.2 Untreated and repeat infections can result in serious and costly reproductive health sequelae.3 The National Chlamydia Screening

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Programme (NCSP) was established in England in 2003, and offers opportunistic screening to young sexually active people. Around half of all cases of chlamydia are managed within genitourinary medicine (GUM) or sexual health services, which offer open-access specialist care without the need for referral from a general practitioner. In England, data for new diagnoses are submitted to Public Health England by the service provider or laboratory for surveillance purposes.

Recommended first-line treatments include a single dose of oral azithromycin. Uncomplicated chlamydia could therefore be an appropriate candidate for an eHealth intervention. However, a systematic review of contemporary mobile applications for people seeking information about STIs did not identify any apps that provided clinical care online. Some National Chlamydia Screening Programme areas now offer an online results service, a feature that was not available at the time of our study and has not been formally assessed elsewhere.

Research in context

Evidence before this study

We did several searches of published work and grey literature to inform this study, including on individual components of the pathway (results service, clinical consultation, partner notification, treatment and prescribing). Within contemporary sexual health services in the UK, some digital technologies, such as text messaging of test results for sexually transmitted infections (STIs) and postal self-sampling, are well established. However, face-to-face or telephone contact with a clinician is still required for assessment and treatment of people with diagnosed infections. In a 2014 study based in California, investigators explored the acceptability and feasibility of an online system for integrated STI care in women. However, only eight participants were diagnosed with an STI and clinicians had to fax individualised prescriptions to a pharmacy. A systematic review of contemporary mobile applications for people seeking information about STIs did not identify any apps that provided clinical care online. Some National Chlamydia Screening Programme areas now offer an online results service, a feature that was not available at the time of our study and has not been formally assessed elsewhere.

Added value of this study

We have shown the safety and feasibility of a complex online clinical and public health intervention integrated within traditional sexual health services, the eSexual Health Clinic (eSHC) system for management, prevention, and control of sexually transmitted infections, and preliminary evidence of effectiveness and public health potential. Our results show that the eSHC can be integrated with existing genitourinary medicine clinical care pathways and internet-based self-sampling services, to provide management of both patients with uncomplicated chlamydia and those who test negative, wholly remotely from traditional services.

Implications of all the available evidence

The eSHC offers a novel approach to provision of care by allowing management of a subsection of people with uncomplicated chlamydial infection with an automated online clinical care pathway—a major departure from any method of care delivery in current practice. This rigorously developed, online, remote, automated approach to clinical care and public health provision could be applicable to many medical conditions.

Methods

Background work and the eSHC

We followed the UK Medical Research Council framework for the development of complex interventions, and did extensive multidisciplinary, mixed-methods preliminary work before our study. This work included in-depth scrutiny of the legal and regulatory requirements of online care, a review of sexual health apps, addressing issues in linking online pathways to surveillance, and qualitative interviews with young people exploring acceptability and user-centred design and interface testing. We developed the eClinical Care Pathway Framework, a novel structure for the creation of online complex clinical care pathways, which we applied to develop the innovative eSHC system.

The eSHC system (figure I) consists of a web application with different portals for patients, results administrators, health advisers, and researchers. Care is self-directed and achievable entirely remotely from traditional medical services. The patient interface includes a results service, access to health promotion, and the online chlamydia pathway. After patients provide online consent, those who test positive for chlamydia engage in an automated online consultation (a clinical decision-making tool), which adheres to national guidance for chlamydia management and includes assessment of symptoms, past medical
history, medication and allergy history, sexual history, and a risk assessment. It encompasses all clinical and public health surveillance data routinely collected in traditional services.

If medically appropriate, the patient nominates one of 30 participating community pharmacies from which to collect antibiotic treatment, which is authorised via automated email sent via secure NHS email. Sexual partners of people with chlamydia are recommended to receive treatment (partner notification). Index patients can request a unique access code for their sexual partners to access care via the online chlamydia pathway.

Patients whom the clinical algorithm predicts are inappropriate for online care (eg, those with symptoms, allergies, or drug interactions) are directed to call the clinical helpline. The helpline, which was accessible from 0900 h to 1700 h on weekdays, was staffed by research health advisers (ie, employees of sexual health clinics who are responsible for partner notification and sexual health promotion, among other roles), who were able to facilitate face-to-face care.

**Study participants and settings**

To assess the safety, feasibility, and public health potential of the eSHC, we did non-randomised proof-of-concept exploratory studies in three different groups of participants across Greater London: untreated patients with chlamydia from two GUM clinics serving deprived, ethnically diverse local populations and a commuter population; patients with chlamydia who were tested through the Checkurself NCSP online service—which enables people to request a self-sampling kit and post a urine (men) or vulvo-vaginal swab sample (women) to a laboratory for testing; results are received via text message, letter, or phone call, and infections are managed via traditional services—in six NCSP areas in South London, where the prevalence of chlamydia infection is high; and patients in the same six areas who used the NCSP’s Checkurself online service but tested negative for chlamydia. In GUM clinics, we hypothesised that the eSHC could be used to complement face-to-face specialist care by managing uncomplicated cases. For NCSP Checkurself users, we assessed the feasibility of the eSHC in a group of potential users who have already engaged with online care (if successful, scale-up within the NCSP would be possible). Inclusion of people who tested negative enabled assessment of uptake and timing of use of the eSHC to access results and health promotion. Ethical approval was granted by Brighton & Sussex (NHS) Research Ethics Committee.
Eligible patients were aged 16 years or older (or aged 16–24 years in the NCSP Checkyourself group) and able to read and understand English. Exclusion criteria were coexisting STIs, having already received presumptive treatment for chlamydia, and extragenital chlamydia. All eligible patients who provided consent were managed by the eSHC. The eSHC sent an automated text message to eligible patients, informing them that their test results were available and inviting them to follow a link to a password-protected web app, designed specifically for the study, to access their result (online results service), and then online treatment. Chlamydia-negative users received an automated text message containing a link to the online results service followed by health-promotion advice and a short acceptability survey. Research health advisers telephoned all patients 2 weeks after diagnosis for clinical follow-up, ascertainment of partner-notification outcomes, and collection of research data. People who declined to participate in the study were managed according to routine clinical practice.

Outcomes

The primary outcome was the proportion of patients with chlamydia who consented to the online chlamydia pathway (index patients) who then received appropriate clinical management either exclusively through online management or via a combination of online management and face-to-face care. We collected demographic data and outcomes only for patients who consented to the study. Quantitative secondary outcomes were the proportion of index patients who received antibiotic treatment solely online, time from diagnosis to appropriate treatment in index patients, and proportion of sex partners treated online. We also captured adverse treatment outcomes.

Treatment outcomes were captured by the eSHC system when the community pharmacist who provided the azithromycin to the patient confirmed electronically that treatment had been collected (all pharmacists at included pharmacies had access to the secure email).

Treatment outcomes for patients who left the online chlamydia pathway at any stage were ascertained at the 2-week follow-up telephone assessment and from clinical records from participating clinics and NCSP Checkyourself services. Patients uncontactable at telephone follow-up and for whom no clinical record of treatment was available were assumed to be untreated.

Statistical analyses

We calculated the required sample size on the basis of the primary outcome. We aimed to demonstrate non-inferiority of the eSHC—ie, that treatment outcomes for index patients are better or only slightly worse than current routine care—while assuming that the online pathway would lead to a small improvement in outcomes. We calculated sample sizes separately for the exploratory studies in GUM clinics and NCSP Checkyourself services, because the proportion of patients who receive appropriate treatment in routine care differs substantially between the two (~98% in GUM clinics vs ~88% in the NCSP). For GUM clinics, assuming that the true proportion of index patients receiving appropriate treatment would be slightly higher in the eSHC (ie, 99%) than that in current care, then 121 patients would provide 80% power to show that the proportion is greater than 94% (ie, to show non-inferiority assuming a non-inferiority margin of 4%). Assuming that the proportion of index patients treated in the eSHC via the NSCP would be slightly higher (ie, 90%) than that in current care, 108 patients would be needed to show that the proportion is greater than 80%—ie, to show non-inferiority, assuming a non-inferiority margin of 8%. In the sample size calculations, we assumed one-sided statistical tests and a 2·5% significance level. We specified a single sample size of 121 patients for all outcomes only for patients who consented to the study.
clinics than for the NCSP, because in GUM clinics the treatment rate is higher, and therefore any reduction in the rate translates to a higher proportionate increase in the numbers untreated.

The proportion of index patients achieving the primary outcome is reported for each setting with an exact binomial 95% CI. These two-sided 95% CIs provide the basis of assessing non-inferiority in each setting, corresponding to one-sided tests at a 2·5% significance level. We plotted cumulative percentage of time to treatment. All analyses were done in Stata (version 14.1).

Role of the funding source
The study sponsor had no role in study design; data collection, analysis, or interpretation; or the writing of the Article. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
Between July 21, 2014, and March 13, 2015, 2340 people used the eSHC (figure 2). 197 patients with chlamydia (70 men and 127 women) were recruited from GUM clinics and 146 (66 men and 80 women) from the NCSP Checkurself service. 161 (82%; 95% CI 76–87) GUM patients accessed the online results service within 7 days of receiving the text message, of whom 116 (72%) consented to be included in our study. 134 (92%; 95% CI 87–96) NCSP patients accessed the online results service within 7 days, of whom 105 (78%) consented to inclusion.

Table 1: Characteristics of patients with chlamydia who consented to online management

<table>
<thead>
<tr>
<th>GUM clinics</th>
<th>NCSP Checkurself</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n=116)</td>
<td>Men (n=42)</td>
</tr>
<tr>
<td>Median age, years (IQR)</td>
<td>25 (23–28)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>104</td>
</tr>
<tr>
<td>White British</td>
<td>37 (36%)</td>
</tr>
<tr>
<td>White other</td>
<td>29 (28%)</td>
</tr>
<tr>
<td>Black</td>
<td>17 (16%)</td>
</tr>
<tr>
<td>Asian, mixed race, or other</td>
<td>21 (20%)</td>
</tr>
<tr>
<td>Number of sexual partners in past 6 months</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>83</td>
</tr>
<tr>
<td>0–1</td>
<td>20 (24%)</td>
</tr>
<tr>
<td>2–5</td>
<td>54 (65%)</td>
</tr>
<tr>
<td>≥6</td>
<td>9 (11%)</td>
</tr>
<tr>
<td>Previous chlamydia</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>84</td>
</tr>
<tr>
<td>Yes</td>
<td>25 (30%)</td>
</tr>
<tr>
<td>No</td>
<td>59 (70%)</td>
</tr>
<tr>
<td>Sexual partner from outside UK or Ireland*</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>84</td>
</tr>
<tr>
<td>Yes</td>
<td>34 (40%)</td>
</tr>
<tr>
<td>No</td>
<td>50 (60%)</td>
</tr>
<tr>
<td>Same-sex partner in past 6 months†‡</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>82</td>
</tr>
<tr>
<td>Yes</td>
<td>1 (1.0%)</td>
</tr>
<tr>
<td>No</td>
<td>81 (99%)</td>
</tr>
<tr>
<td>Ever had sex with a man*†‡</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>83</td>
</tr>
<tr>
<td>Yes</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>No</td>
<td>81 (98%)</td>
</tr>
</tbody>
</table>

Data are n (%) unless otherwise specified. Information is missing in this table because data were missing or patients left the online pathway. No patients reported injecting-drug use. GUM=genitourinary medicine. NCSP=National Chlamydia Screening Programme. *These questions are routinely collected markers of risk for sexually transmitted infections. †Patients were initially asked if they had had sex with a partner or partners of the opposite sex, same sex, or both sexes in the preceding 6 months. ‡Only men who reported having sex only with women in the past 6 months were asked this question.
Further results in patients with chlamydia are limited to those who consented.

Participant characteristics are shown in table 1. 36 (86%) of 42 men and 46 (62%) of 74 women recruited from GUM clinics completed the online consultation and had treatment authorised. Of these patients, 32 men (89%) and 42 women (91%) collected their treatment from their chosen pharmacy. Of the 34 GUM clinic patients who left the online pathway, 26 (73%; three men and 23 women) reported symptoms and needed assessment as to whether examination, further investigations, and treatment for complicated chlamydia were indicated. 30 of these patients subsequently received treatment; four were lost to follow-up.

112 (97%; 95% CI 91–99) of the 116 GUM patients were treated either via the eSHC or through traditional services (table 2). 74 patients (64%) completed the online consultation and collected their treatment at their chosen pharmacy, of whom 56 (76%) did not contact the clinical helpline (table 2). 32 (43%) of the 74 patients who completed the online consultation accessed their treatment on the same day as receiving the text message (shortest time to collection of treatment was 32 minutes; figure 3). By the end of the following day, 56 patients (76%) had accessed their treatment (figure 3).

83 (72%) of 116 GUM patients completed the online consultation at least as far as the section requiring reporting of sexual partner numbers (one subsequently left the online pathway); they reported 253 sexual partners within the past 6 months. 15 sexual partners accessed the eSHC—12 collected their treatment from their chosen pharmacy, two received treatment elsewhere, and one was lost to follow-up.

34 (29%) of the 116 GUM patients accessed health-promotion resources (18 [16%] logged back in to do so), of whom 11 (32%) followed links to access further information.

37 (82%) of 45 men and 32 (53%) of 60 women from the NCSP completed the online consultation and had treatment authorised (figure 2). 33 (89%) of these men and 27 (84%) of these women collected treatment from their chosen pharmacy. Of the 36 patients who left the online pathway, 25 (69%; six men and 19 women) reported symptoms, 27 (75%) received treatment, and nine (25%) were lost to follow-up.

93 (89%; 95% CI 81–94) patients from the NCSP Checkurself service were treated, and 60 patients (57%) were treated solely online and collected their treatment (table 2). 50 (83%) of these online-only patients accessed treatment completely remotely without needing to use the clinical helpline. 27 (45%) online-only patients accessed their treatment on the day that they received their results, and 40 (67%) accessed treatment by the end of the following day (figure 3). 71 patients from the NCSP Checkurself service reported 199 sexual partners online. 13 sexual partners accessed the eSHC, of whom seven collected treatment from their chosen pharmacy, two received treatment elsewhere, and four had unknown treatment outcomes.

32 (30%) of the 105 patients from the NCSP Checkurself service accessed health-promotion resources (17 [16%] logged back in to do so), of whom nine (28%) followed links to access further information.
No patients in either group who reported contraindicated health conditions, interacting drug therapies, or relevant allergies were prescribed azithromycin via the online pathway. No serious adverse reactions to azithromycin were reported.

1997 users tested negative for genital chlamydia, 1776 (89%) of whom accessed their test results within 7 days via the online results service. 433 (24%) of those who accessed their results online also accessed health-promotion resources, of whom 142 (33%) followed links to access further information.

Discussion
We have developed, implemented, and assessed an online system for management, prevention, and control of sexually transmitted infections, and demonstrated its feasibility and safety in exploratory studies. Each study provides information that can be used to refine the intervention, and shows how the intervention can be used in different settings. The eSHC is unique in that it integrates online results access with an automated clinical consultation, authorisation of antibiotics, partner notification, routing of patients into traditional care (when appropriate), and potential linkage to surveillance (panel).

Relative to our prespecified margins, we showed non-inferiority of the proportion treated by the eSHC relative to current care for NCSP patients but not for GUM patients. Although our outcomes are encouraging, they should be viewed as preliminary evidence of effectiveness. The target sample size for the primary outcomes in both GUM clinics and the NCSP was narrowly missed, and the small numbers prohibited sub-analyses. Furthermore, because GUM clinics and the NCSP have different sociodemographic, behavioural, and clinical mixes, and different proportions of patients receiving treatment under routine care, we do not compare characteristics or outcomes of the two patient populations.

Around three-quarters of eligible people chose to access the online chlamydia pathway and roughly 60% of patients managed their care completely remotely. Others moved effectively between online, telephone, and clinic-based care. Almost a quarter of patients contacted the clinical helpline at some point, suggesting that provision of telephone support is important. Those who were directed off the online pathway for clinical reasons were for the most part successfully managed in traditional settings. More women than men reported symptoms suggestive of complicated infection, in line with clinical expectations, which explains the higher proportion of women routed into face-to-face clinical assessment. A few patients did not collect their treatment from the pharmacy, but most of them accessed treatment elsewhere.

The online consultation facilitated safe prescribing. Integral to the eSHC is a sophisticated triage system, which allows individuals who need to be seen face-to-face to be fast-tracked to a sexual health clinic or other services.

Panel: Public health potential of the eSexual Health Clinic system

Primary prevention
Health promotion is included at various stages of the online care pathway. This information is tailored towards both individuals with chlamydia and those who test negative, and provides opportunities to link to health-promotion and risk-reduction websites.

Secondary prevention
Sexually transmitted infections, including chlamydia, are frequently asymptomatic. The eSexual Health Clinic system has the potential to enable individuals (especially those with high-risk behaviours) to be tested regularly to ensure early identification and treatment. Partner notification is an essential component of infection control and is facilitated by the system, which gives individuals with chlamydia the opportunity to discreetly inform their partners so that they too can obtain treatment for desired, breaking the chain of transmission.

Tertiary prevention
Treating people with chlamydia reduces the incidence of complications, including pelvic inflammatory disease, infertility, and ectopic pregnancy, which has implications for patients and for health-care resources.

Surveillance
The eSexual Health Clinic system collects data required for surveillance and has systems to ensure that people diagnosed by self-testing in the future are included in national statistics.

People with chlamydia require prompt treatment (at the time of our studies, the NCSP aimed to treat 95% of patients within 6 weeks), both to reduce development of sequelae and to limit the infectious period, thereby reducing opportunities for onward transmission of infection. The swift treatment afforded online through the eSHC could confer important personal and public health gains, especially in people who report high-risk sexual behaviours, such as some of the participants in our study. Similarly, the eSHC could be advantageous for people requesting internet-based postal self-sampling, who are more likely to report high-risk behaviours than other community populations. An increasing proportion of chlamydia screening tests are being requested and commissioned via this route. Management of exposed sex partners of people with chlamydia is challenging. We showed proof of concept for partner management online, but few partners were managed this way.

To interrupt chlamydia transmission, increased testing is needed in all young people, with a focus on those who are at high risk but are not accessing testing and engaging with care in traditional settings. STIs, and the groups who are most likely to be diagnosed with STIs, are often stigmatised. Assuming a person can take the first step online, the eSHC also provides opportunities for people facing barriers to accessing existing services. However, to achieve a reduction in the population incidence of chlamydia, eHealth interventions would need to be one of many components of a comprehensive chlamydia-control strategy.
The ability to provide automated surveillance information from both community and secondary-care settings, and to transfer these data to national surveillance systems, is essential to monitor trends, identify areas where local delivery needs enhancement, and inform public health needs. In line with the NHS Five Year Forward View, the NCSP model is based on local delivery, and our research shows that the eSHC is feasible in this context, with a range of configurations for health-service and screening-programme delivery. However, our studies also show the complexity of collecting online data for both surveillance and clinical purposes while keeping patients engaged with the pathway. Advances in STI self-testing diagnostics, which enable people to be tested and diagnosed completely unlinked to medical care, pose additional challenges for public health surveillance and prevention.

Further work is needed before wider implementation of the eSHC. It is not interoperable with, or directly embedded within, health service information-technology systems—integration will be required for delivery at scale. All aspects of the intervention need refining, including optimisation of health-promotion uptake, partner-notification uptake, and provision for partner testing, in line with national recommendations. Assessment in randomised controlled trials that include health economic analysis to assess cost-effectiveness is essential. Our results provide the key information needed for the design and delivery of such trials. Acceptance among health-care professionals and commissioners will underpin adoption into mainstream care. However, despite strong political support, the digital infrastructure and regulation of online medical care within the NHS remains outdated. The potential for eHealth to improve health outcomes will probably be limited if these issues are not systematically addressed.

With modification, this pathway could be used in combination with a home self-test for other bacterial infections for which a standard first-line antibiotic is recommended, such as streptococcal pharyngitis. People could potentially self-test, self-diagnose, and self-manage remote from traditional health services. Rapid progress in home diagnostics for several conditions, combined with the ability to inter-weave targeted health promotion, provide opportunities for diverse eHealth interventions. However, the effectiveness of primary prevention activities, such as health promotion, delivered in this format would need to be assessed alongside face-to-face alternatives.

Our promising findings suggest that the eSHC is an innovative model that could address growing population health needs. The eSHC’s reach goes beyond sexual health in the UK: it could apply more broadly across infections and non-communicable diseases in both developed and developing countries.

**Contributors**

CSE led the exploratory studies of the eSHC with contributions from JG, LJS, VG, LT, KH, CA, CML, EMH-E, SE, PO, AS, REA, AC, STS, and PS. LJS and JG led the design and development of the online chlamydia pathway with contributions from CSE, VG, LT, KH, CA, CML, EMH-E, SE, PO, AS, REA, AC, STS, and PS. CSE wrote the first draft and JG did the analysis, with further contributions from all authors. LT was the lead research health adviser. LJS was exploratory studies manager. STS was principal investigator and CSE, KH, CML, PO, AS, and PS were applicants on the Electronic Self-Testing Instruments for Sexually Transmitted Infection Consortium grant. CSE, KH, CML, PO, AS, STS, and PS wrote the initial Clinical, Public Health and Economics work stream protocol, with contributions from CA. All authors read and approved the final Article.

**Declaration of interests**

We declare no competing interests.

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