Australian Chlamydia Control Effectiveness Pilot (ACCEPt): a cluster randomised controlled trial of chlamydia testing in general practice (ACTRN1260000297022).

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Australian Chlamydia Control Effectiveness Pilot (ACCEPt): trial protocol

Summary

Chlamydia trachomatis is the most commonly diagnosed bacterial sexually transmitted infection (STI) in many developed countries including the USA, the UK, and Australia. There is considerable debate about the effectiveness of organised population-based chlamydia screening programmes for reducing chlamydia transmission and its associated morbidity. This protocol outlines the design of the Australian Chlamydia Control Effectiveness Pilot (ACCEPt). The trial has a cluster randomised controlled design targeting all young people aged 16–29 years who have ever had sex for annual chlamydia testing in general practices and Aboriginal Medical Services (AMSs). The trial aims to determine whether an intervention to increase chlamydia testing reduces the transmission of chlamydia and the incidence of complications in the population attending primary care clinics.

Primary care clinics (general practices and AMSs) in geographical areas (e.g. towns or postcodes) located in 54 rural locations across four Australian states will be invited to participate. Areas (clusters) with 100% participation of clinics will be randomised into the control or intervention arm of the trial. A multifaceted intervention will be implemented to maximise chlamydia testing rates over a period of up to 4 years. The intervention includes: a computer alert prompting general practitioners (GPs) to test eligible patients; an incentive payment for tests conducted; a patient recall and reminder system; an education pack for GPs and practice nurses; patient information on chlamydia and partner notification; and regular feedback on testing performance. Research staff will work with clinic staff to identify the optimal 'chlamydia testing pathway' for each clinic. Clinics in the control group will be encouraged to continue their usual chlamydia testing practices. The primary outcome is the prevalence of chlamydia in primary care clinic attenders. Secondary outcomes are the incidence of PID and epididymitis and the uptake of chlamydia testing. Generalised estimated equation models will be used to compare outcomes between intervention and control clusters, taking account of cluster, clinic and participant variability.

Trial registration number: Australian Clinical Trial Register, ACTRN1260000297022

Background

Description of the condition

Chlamydia trachomatis (chlamydia) is the most commonly diagnosed bacterial sexually transmitted infection in many developed countries including the USA, the UK, and Australia [1-4]. Infection is most common in sexually active men and women under 30 years of age. The population prevalence of chlamydia among sexually active individuals aged 18 to 24 years has been estimated to be: 3.7% (95% CI: 1.2%, 8.4%) among women in Melbourne, Australia in 2003 [5]; and 3.0% (95% CI: 1.7%, 5.0%) in women and 2.7% (95% CI: 1.2%, 5.8%) in men in the UK in 2000 [6]. Incidence among 16 to 25 year old female users of general practice and sexual health clinics has been estimated to be 4.4 per 100 women-years (95% CI: 3.3, 5.9) in south-east Australia [7] and 4.9 (95% CI: 2.7, 8.8) per 100 person-years in 16 to 24 year old female users of general practice in two areas in England [8].

Chlamydia primarily infects the endocervix in women and urethra in men. Infection is asymptomatic in over 80% of cases in both women and men [9] and untreated infection lasts an average of 14 months [10]. There is little evidence of lasting immunity after antibiotic treatment for chlamydia and repeated detection of chlamydia within 12 months of treatment of a positive chlamydia test result is common. Repeat infection rates of 22.3% per year (95%CI: 13.2, 37.6%) among 16 to 25 year old women attending general practice and sexual health clinics in south-east Australia [7] and 29.9% per year (95% CI: 19.7, 45.4%) amongst 16 to 24 year old women attending general practice in two areas in England [8] have been reported.

Chlamydia can cause costly long-term health consequences if left untreated. In women, chlamydia can cause pelvic inflammatory disease (PID) if the infection ascends from the endocervix into the upper genital tract [11]. This in turn can lead to fallopian tube scarring, ectopic pregnancy, tubal factor infertility and chronic pelvic pain [12-15]. The cost to the Australian public healthcare system of chlamydia and its sequelae in women was estimated at AUD$27 million for a prevalence of 5.7% with no active screening in 2002 [16]. The incidence of diagnosed PID has been falling for many years in several countries. The fall predates the introduction of widespread testing for chlamydia and has been observed in countries with and without established chlamydia control measures [17].

There is ongoing debate about the natural history of chlamydia infection [18] . In one study in London, the risk of PID (diagnosed clinically) was 9.5% (4.7, 18.3%) amongst female students with untreated chlamydia infection over a 12 month period [19]. A mathematical modelling study, based on data from the same study, found that PID might occur throughout the course of a chlamydia

infection [20]. There is also some evidence from observational studies that the risk of PID increases with the number of repeat chlamydia infections [21, 22]. Such studies are at risk of diagnostic ascertainment bias, because knowledge of a woman's chlamydia infection status can influence the interpretation of clinical symptoms and signs of PID.

In addition to reproductive consequences for women, chlamydia transmitted during labour can cause neonatal conjunctivitis and pneumonitis [11, 23, 24] and there is now evidence from a prospective cohort study of an association between chlamydia infection in pregnancy and preterm birth [25]. Chlamydia also causes epididymo-orchitis in men [26] and can act as a co-factor in increasing the risk of HIV transmission in men and women [27].

Chlamydia is usually diagnosed by detection of chlamydia-specific nucleic acid sequences in self-collected urine (women and men) or vulvo-vaginal swabs (women). Antibiotic treatment is with a single dose of azithromycin or a course of doxycycline [28].

Chlamydia among young heterosexual adults in Australia

Chlamydia is the most commonly diagnosed bacterial sexually transmitted infection affecting young heterosexual adults in Australia. Diagnosis rates have increased steadily in Australia from 87.2 per 100,000 in 2000 to 363.6 per 100,000 in 2012, with over 82,000 cases diagnosed in 2012 [29]. Young Australians aged 16 to 29 years have the highest chlamydia diagnosis rates with estimates of chlamydia prevalence of 3 to 5% in this age group [30]. Unlike the United States and the United Kingdom [3, 31], gonorrhoea diagnosis rates remain relatively low among non-Aboriginal heterosexual populations in Australia with an overall diagnosis rate for this group of 22 per 100,000 in 2011 [1]. Chlamydia, gonorrhoea and syphilis diagnosis rates are alarmingly high among Aboriginal Australians living in remote parts of Australia.

Description of the intervention

Screening is a public health service that involves identifying infection or disease in people who do not know they are affected [32]. Screening programmes for infectious diseases must achieve sufficient participation rates at frequent enough intervals to interrupt transmission so that the population benefits of screening can be sustained.

Given that chlamydia is largely asymptomatic, screening of asymptomatic patients at risk of infection is needed to detect the majority of infections. [28, 33-36]. Annual chlamydia screening is recommended in several countries and usually targets young sexually active women or both women and men for opportunistic screening in routine health services [28, 36-40]. The goals of chlamydia

screening are to i) treat infections before they cause PID or other complications and ii) reduce the incidence and prevalence of infection, which also prevents complications indirectly by reducing exposure to infection.

A chlamydia screening intervention includes all of the following components: testing for chlamydia infection, treating those with positive test results and doing partner notification to ensure that sexual partners receive treatment. There are some important features of screening interventions to prevent chlamydia that differ from screening to prevent morbidity or mortality from chronic diseases like cancer. First, the result of the screening test is used as a diagnostic test, with antibiotic treatment given to all those with positive test results. Second, measurement of chlamydia prevalence as the outcome requires testing of a sample of the target population (and treatment and partner notification for those who test positive). Evaluations of the outcome therefore need to ensure that the effect of the intervention itself is not influenced. Third, the frequency of repeated infections after treatment means that screening has to be repeated. Brunham and colleagues [41, 42] have suggested that screening and treatment for chlamydia infections increases the rate of repeat infections because immunity after antibiotic treatment is less than after natural clearance. The hypothesis is based on evidence from studies in mice infected with *Chlamydia muridarum* [43]. In humans, Geisler et al. [44] have recently found that repeated infections were more common in women who received antibiotic treatment for a prior chlamydia infection than those who cleared the infection spontaneously.

Medicare Australia, the government run health insurance provider that provides public funded health care for Australians, has strict guidelines about the use of the term 'screening', which is restricted to established organised programs. As a result, the term chlamydia 'testing' is used in Australia to describe testing an asymptomatic person for chlamydia, but the term screening might be applied to the same practice in other countries.

Systematic review of the effectiveness of screening

A systematic review of studies published up to 2007 found no randomised or controlled clinical trials showing that screening reduces the incidence or prevalence of chlamydia in the target population [45]. There were two individually randomised controlled trials showing that the incidence of PID after a year of follow up was about 50% lower in women actively offered chlamydia screening (64% to 93% uptake of testing) than women who received usual care [46, 47]. However, both had methodological limitations that threaten the validity of their results. In response, the review concluded that well designed trials with biological endpoints and multiple rounds of screening are

needed [45]. Since then, further trials have been published and searches have been updated. By July 2012 there were still no RCTs of the effect of opportunistic chlamydia screening evaluated over multiple screening rounds with biological endpoints. Two individually randomised controlled trials have found smaller effects on the incidence of PID after a year of follow up. Oakeshott and colleagues [19] found a reduction of 35% (95% CI, –66 to +24%) amongst women in London (100% uptake) and Andersen et al. [48] found a reduction of 11% (95% CI, –44 to +42%) in Aarhus, Denmark (uptake 24%). In the Netherlands, the effect on chlamydia transmission of yearly systematic screening by postal invitation was compared with usual care in a cluster controlled trial [49, 50]. The percentage of people with a positive chlamydia test in the intervention blocks at the first invitation was the same as in the control block (4.3%) and 0.2% lower at the third invitation (odds ratio 0.96, 95% CI 0.83 to 1.10). Participation was lower than expected and fell over time (16% after the first invitation and 10% after the third).

There are methodological challenges in using other study designs to evaluate the effects of chlamydia screening. Routine case counts recorded by public health surveillance cannot show trends in population chlamydia prevalence because they are so heavily influenced by the numbers of tests being done [51, 52]. Repeated cross-sectional population prevalence surveys in the USA have shown conflicting results and cannot control for other secular changes [53]. Modelling studies can help examine the potential impact of chlamydia screening and are useful for comparing the relative effects of different strategies. Decisions about model structure and parameter assumptions differ between models and will affect the results [54, 55].

Cost effectiveness of screening

There have been two systematic reviews investigating the cost effectiveness of chlamydia screening [56, 57]. The review by Roberts and colleagues [57] was comprehensive and well conducted. It reviewed the literature from the earliest date to August 2004 and identified 29 studies of economic evaluations addressing different aspects of chlamydia screening. Most of these studies found opportunistic and proactive chlamydia screening to be cost-effective and partner notification to be an effective adjunct to a chlamydia screening program. However, as stated by Roberts et al [57], two main methodological issues threatened the validity of the findings of the studies included in this review. Firstly, most studies used a static modelling approach that is inappropriate for the study of infectious diseases [58]; and secondly, most studies did not acknowledge or investigate the uncertainty associated with chlamydia infection or the risk of sequelae associated with chlamydia [18]. This review concluded that “the inappropriate use of static models to study interventions to

prevent communicable disease means that uncertainty remains about whether chlamydia screening programs are cost-effective or not."

The recent review by Gift and colleagues [56] aimed to review the literature for evidence of the cost-effectiveness of screening for men. The reviewed studies examined both proactive and opportunistic screening and included screening of particular population groups and the general population. A total of 29 papers were included in the review, six of these used dynamic transmission models. Several studies included sufficient data to examine the cost-effectiveness of male screening compared with female screening. The studies that compared the two have generally found that screening men from the general population is not preferred to screening women from the general population.

An Australian study using a decision–analytic model to determine the incremental cost effectiveness ratio (ICER) of opportunistic annual screening of women under the age of 25 years by GPs estimated a cost per quality-adjusted life years (QALY) of $2968 [59]; however, the estimated range was wide, highlighting the need for better data on the natural history of chlamydia infection and effectiveness of screening to better parameterise cost-effectiveness models.

Systematic review of interventions to increase the uptake of chlamydia screening

A systematic review of interventions to increase chlamydia screening in primary care up to September 2010 included 16 published studies [60]. Interventions that promoted offering a chlamydia test to all eligible clients had the greatest impact on increasing screening in primary care. A cluster RCT of a complex intervention in paediatric clinics in the United States involved identifying a 'practice champion' in each clinic and providing educational packages and regular feedback on chlamydia testing rates [61]; testing increased by 60% in intervention clinics vs. 7% in control clinics ($p<0.01$). In Australia, a simpler intervention involved only a computer alert prompting GPs to discuss chlamydia screening with 16 to 24 year olds; the proportion of women tested increased more in intervention (from 8 to 12% after 12 months) than control clinics (from 9 to 11%, odds ratio 1.3, 95% CI: 1.1, 1.4) [62].

There has been one RCT investigating the impact of incentive payments ($5 to $8 (AUD) per test) to GPs for each chlamydia test ordered, but this failed to find an effect [63]. However, this trial was inadequately powered and payments were not made until the end of the 12 month trial when GPs had little recollection of their participation. Systematic reviews evaluating the impact of financial incentives targeting preventive care and/or chronic disease management activities, each with different inclusion/exclusion criteria [64-69], unanimously conclude that the effects on quality of

care and patient outcomes remain largely uncertain because of serious methodological weaknesses. Some individual studies have found small incremental benefits. RCT evidence has demonstrated modest improvements in vaccination rates over usual care with absolute increases of 7.8% in a US study of immunisation in the elderly (additional payment of $0.80 (USD) to $1.20 (USD) per shot to provider) [70] and 9.9% in a US study of immunisation in children ($5 per shot plus $15 per patient visit to provider) [71], although this latter study included enhanced provider feedback as part of the intervention. A controlled before and after study in the US among clinics receiving a payment of US$0.23 per patient per month for each performance target that was met or exceeded, found that there was a small but significant improvement for cervical screening (3.6% higher screening rate in intervention compared with control, p=0.02), but for mammography or glycosylated haemoglobin monitoring, there was no difference between the intervention and control groups [72].

Rationale for the trial

Before introducing a screening programme, evidence from high quality randomised controlled trials (RCTs) is needed to show that the benefits of screening, with sufficient participation rates, outweigh the harms at reasonable cost. There is ongoing debate about the effectiveness of chlamydia screening in controlling transmission and preventing complications, based on the results of controlled trials [73]. Evaluating chlamydia screening compared with no screening is not possible, given existing recommendations. Interventions to increase the uptake of regular chlamydia testing above levels achieved through routine health services should be evaluated.

There is reason to believe that an organised programme of screening for chlamydia could be effective. Mathematical modelling suggests that systems that ensure high levels of annual chlamydia testing, treatment and partner notification are needed to interrupt transmission and reduce chlamydia prevalence sustainably [74]. These levels of testing have been achieved through a multifaceted intervention in paediatric clinics reported by Shafer and colleagues [61].

General practice is well placed as a setting for chlamydia screening; in Australia, 90% of women and 70% of men aged 15–24 years present to a general practitioner (GP) each year [75]. Levels of general practice attendance are similar in the UK [76]. In addition, a large proportion of diagnosed chlamydia cases are notified from general practice [52]. Research with Australian GPs shows that they believe that general practice is an appropriate place for chlamydia screening to take place [77, 78]. They also cite factors that could facilitate increased chlamydia testing, including chlamydia education for providers and the community, incentive payments, increasing the role of practice nurses, recall/reminder registers and resources to help with partner notification. In Australia, 15.7% of

practice nurses have attained post-registration accreditation to perform Pap screening, and 20.7% report regular involvement in women's healthcare including pap smears, breast care, fertility, and menopause [79]. This suggests that there is capacity for practice nurses to increase their involvement in chlamydia testing and management, including maintaining clinic resources and recall lists and assisting with discussions with patients around partner notification and safer sex practices.

Annual chlamydia testing for sexually active men and women under 30 years is recommended in Australia [80], yet testing rates remain low with 8% of 15 to 29 year olds testing each year. Guidelines also recommend that a repeat test be performed 3 months after a positive chlamydia diagnosis, yet rates of repeat testing are low. An audit of repeat testing at 25 Australian general practice clinics in 2008–2009 found that only 26.4% of 16–29-year-olds diagnosed with chlamydia were re-tested within 1.5–4 months following a positive chlamydia test [81]. Rates of repeat testing at sexual health services in Australia between 2004 and 2007 were found to be even lower: 8.6% in men who have sex with men (MSM), 11.9% in heterosexual males and 17.8% in heterosexual females [60]. Low repeat testing rates have also been reported in the USA [82].

This trial is designed to address the gap in evidence about the effectiveness of an organised program of annual chlamydia testing in young general practice attendees. Its strengths are its cluster randomised design, biological endpoints and multiple rounds of testing.

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Main centres

The main research centres involved in the study are:

- Melbourne School of Population Health, University of Melbourne (managing institution)
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Aims and Objectives

The study is a trial of the effectiveness of an intensive multifaceted intervention to increase rates of annual chlamydia testing in primary care clinics (general practice clinics and AMSs). The hypothesis is that by increasing testing rates to 30% of men and women aged 16 to 29 years, prevalence in clinic

attenders will decrease from about 4% to 2% in this population by the end of the trial period by the end of the trial period.

Primary objective

- To determine whether an intervention to deliver organised regular chlamydia testing for women and men aged 16 to 29 years who have ever had sex attending primary care clinics (general practices and AMSs) leads to a reduction in estimated chlamydia prevalence in 16–29-year old primary care attendees when compared with usual care.

Secondary objectives

- To determine whether an intervention to deliver organised regular chlamydia testing in primary care clinics (general practices and AMSs) leads to a reduction in the incidence of PID in 16–29-year old primary care attendees.

- To determine whether an intervention to deliver organised regular chlamydia testing in primary care clinics (general practices and AMSs) leads to a reduction in the incidence of epididymitis in 16–29-year old primary care attendees.

- To determine whether an intervention to deliver organised regular chlamydia testing in primary care clinics (general practices and AMSs) can increase chlamydia testing rates.

- To determine the proportion of individuals tested who return for a repeat test 12 months after a previous negative test result.

- To determine the proportion of individuals tested who return for a repeat test three months after a positive chlamydia test result.

Design

The trial is called the Australian Chlamydia Control Effectiveness Pilot (ACCEPt). The design is a cluster RCT with the unit of randomisation being a geographical area. Each cluster is defined by Australian postcode boundaries, and all are in rural locations, usually defined by a single rural town. Since people in Australia are able to choose which clinic to attend and can change clinics at any time, basing the RCT in rural Australia reduces the opportunity for people to attend both participating and non-participating clinics, or control and intervention clinics, which would likely occur in large cities with multiple postcodes. Within each cluster all general practice clinics and AMSs are enrolled. If

neighbouring postcode areas are recruited and there is less than 30 minutes travel time by car between them, the postcodes are merged into one cluster.

The setting for the trial is primary care clinics (general practices and AMSs) in rural Australia. Most Australian general practices are small businesses that vary in the number of GPs, number of practice nurses (PNs) and other supporting staff, and facilities available. Some rural general practices are affiliated or co-located with their local hospital. Most AMSs in Australia are members of the National Aboriginal Community Controlled Health Organisation (NACCHO) and state-based representative organisations. Individual services are run by, and accountable to, the Indigenous communities in which they operate and provide culturally sensitive primary care services to those communities. About 5% of towns participating in the trial will include an AMS.

Randomisation at the level of clusters is required for two reasons. Firstly, for an infectious disease like chlamydia, randomising a group of people in the same geographic area will allow the intervention to be delivered to people within the same social and sexual networks, which reflects the situation that would occur if a chlamydia screening programme was rolled out nationally. Secondly, for a complex health service intervention requiring organisational change at the clinic level, the intervention should target all eligible patients attending that clinic, rather than randomising individual patients. A flowchart of the trial is shown in Figure 1.

Inclusion and exclusion criteria

There are inclusion and exclusion criteria at the level of the cluster, the primary care clinic, healthcare professionals and individual patients.

Clusters

Inclusion criteria

- Rural areas (postcodes) in the Australian States of New South Wales, Victoria, Queensland and South Australia.
- A minimum population size of five hundred 15 to 29 year olds, as determined by the 2006 census data from the Australian Bureau of Statistics.
- Up to six general practice clinics.

Exclusion criteria

- Postcodes with army bases, mining towns, holiday towns or towns with intensive chlamydia control activities.
- Postcodes with seven or more general practice clinics.
- Postcodes where one or more clinics refuse to participate in the trial.

General practice clinics and Aboriginal Medical Services (AMSs)

All general practice clinics and AMSs (irrespective of size) within a cluster will be invited to participate.

Inclusion criteria

- Over 75% of GPs working at the clinic must consent to participate in the trial.

Exclusion criteria

- None.

General practitioners and practice nurses

General practitioners (GPs) and practice nurses (PNs) in clinics within eligible clusters will be invited to participate. Consenting GPs and PNs will be recruited prior to the baseline prevalence survey, and newly employed GPs and PNs at participating clinics will be recruited during the trial.

Inclusion criteria

- GPs and PNs (fully qualified, locum, and in training) working at participating general practice clinics or AMSs.

Exclusion criteria

- None.

Individuals during the intervention period

GPs will assess the eligibility of patients for chlamydia testing during a clinical consultation.

Inclusion criteria

- Men and women aged 16 to 29 years of age who have ever had vaginal or anal sex will be targeted for annual chlamydia testing when they attend a participating clinic for any reason during the trial.

Exclusion criteria

- None

Individuals enrolled in the baseline and final prevalence survey

Research staff will assess eligibility.

Inclusion criteria

- Male and female patients aged 16–29 years attending a clinic for consultation with a GP.
- Ever had vaginal or anal sexual intercourse.

Exclusion criteria

- Language barrier, intoxication, incapacitation (e.g. severe illness), intellectual difficulty, or other circumstances that hinder a patient's ability to give informed consent.

Intervention

Multifaceted chlamydia screening intervention

The intervention is an organised programme for the delivery of annual chlamydia testing and treatment in general practices and AMSs in Australia. Clinics will receive a multifaceted intervention package that will encourage staff to offer chlamydia testing to all eligible patients in the target population. The intervention package has been designed to be delivered and evaluated as a whole, with the logistics of implementation tailored to the needs and resources of each clinic. The components of the intervention package include:

- Chlamydia and PID education package for GPs and other clinic staff. This provides a number of strategies for introducing chlamydia testing during a consultation; health education and promotion materials for health care providers and patients; guidelines to facilitate the consistent application of clinical criteria for the diagnosis of PID and epididymitis; and information on effective partner notification.

- A computer alert programmed into the practice patient management system or as part of a separate consulting sidebar tool (www.racgpoxygen.com.au/what-is-sidebar/), prompting GPs or other clinic staff to discuss chlamydia testing with eligible patients.

- A patient reminder system within the practice patient management system that will recall tested patients via letter, phone or SMS after 12 months if chlamydia negative and after three months if chlamydia positive.

- Feedback on testing rates provided every three months in the form of quantitative reports, showing the GP's quarterly chlamydia testing rates over time.

- GP incentive payments: $5 per eligible patient tested up to 20% of eligible patients tested; $7 per eligible patient tested for >20% to 40% of eligible patients tested; $8 per eligible patient tested for >40% of eligible patients tested. Payments will be made every three months to the GP ordering the test.

- Practice nurse (PN) incentive payments: clinics will receive an additional $10 payment per test conducted if a PN discussed chlamydia testing with a patient and initiates a test. The nurses will also receive an education pack on chlamydia testing. Payments will be made every three months to the participating clinic.

- Partner notification information and resources will be provided including referral to www.letthemknow.org.au, a partner notification resource for health care providers and patients.

The intervention will be in place for up to four rounds of annual chlamydia testing.

Chlamydia diagnosis and case management

- Self-collected specimens will be recommended where possible, including first catch urine specimens from men or women or self-collected vaginal swabs for women. If a female patient is having a Pap smear during her consultation, an endocervical swab can also be used. In Australia, the National Cervical Screening Program promotes routine screening with Pap smears every two years for women between the ages of 18 (or two years after first sexual intercourse, whichever is later) and 69 years [83].

- Diagnosis will be based on nucleic acid amplification tests (NAAT) conducted through the clinic's usual pathology provider using their own testing and results reporting protocols.

- First line treatment for uncomplicated chlamydia in Australia is 1 gram Azithromycin as consistent with the National Management Guidelines for Sexually Transmissible Infections [84].

- Anyone diagnosed positive for chlamydia is recommended to have a test for repeat infection 3 months after the initial diagnosis.

- Partner notification is recommended for all sexual partner in the past 6 months, in line with the Australasian Contact Tracing Manual guidelines [85].

Control group

Control GP clinics and AMSs will be asked to continue diagnosis and management of chlamydia according to their usual practice and consistent with the Royal Australian College of GPs (RACGP) guidelines for preventive activities ('Red Book') [35]. GPs in the control arm of the trial will receive a minimal education pack with information on the diagnosis of PID and epididymitis and partner notification. This is to ensure that, as much as is possible, diagnosing practices for PID and epididymitis are consistent across the two arms of the trial, and that patients are encouraged to notify sexual partners of a positive chlamydia diagnosis.

Randomisation sequence generation

The trial statistician generates the randomisation sequence using a computer-generated minimisation algorithm according to the following baseline variables:

- Location (State);

- Estimated baseline chlamydia prevalence;

- Estimated overall baseline testing rate;

- Estimated percentage of population aged 16 to 29 years.

Allocation concealment

Concealment of the computer-generated randomisation sequence until allocation will minimise selection bias. The trial statistician will be located at a site away from any of the participating geographical clusters. The statistician allocates each cluster according to the computer-generated minimisation algorithm when data on all baseline variables are available. The statistician informs

research staff of the cluster allocation, and research staff, in turn notify, all general practice clinics and AMSs in the cluster of the allocation.

Blinding

Blinding of clinics and GPs to their trial allocation is not possible given the nature of the intervention. Patients attending participating clinics will be made aware that the clinic is taking part in a trial of chlamydia testing via posters and information cards available in the waiting room but will not be told whether they are in an intervention or control cluster.

Pathology providers that conduct chlamydia tests will not be deliberately blinded but will not be told explicitly whether participating clinics are in intervention or control clusters.

Assessment of PID and epididymitis as clinical outcomes will be performed by an endpoint assessment committee that is blinded to whether the woman is in an intervention or control cluster. This will help reduce bias in the clinical diagnosis of PID.

The trial statistician will conduct a blinded analysis of the primary outcome.

Trial endpoints

Primary endpoint

Chlamydia prevalence in clinic attenders

The primary biological endpoint is estimated chlamydia prevalence in the population served by the clinics. Chlamydia prevalence will be estimated at baseline (pre-trial) and at the end of the intervention period. Prevalence is estimated as the proportion (with 95% CI) of 16 to 29 year old women and men attending a participating clinic who have ever had sex who test positive for chlamydia.

The prevalence surveys are conducted independently from the offer of opportunistic chlamydia testing by GPs. A research assistant employed by the research team will be based in each clinic to recruit patients for the prevalence survey. About 80 patients per cluster area will be recruited (see sample size calculation); the number of patients per clinic will be proportionately allocated across all clinics in the cluster according to the number of 16 to 29 year olds on the clinic files. Consecutive patients will be approached to minimise selection bias. The research assistant will approach patients in the clinic waiting room and determine eligibility (patient age, whether they have ever had vaginal or anal sex). If the individual meets the eligibility criteria, they will be invited to participate in the

study and signed informed consent will be obtained. Basic data (age, gender and ever had sex) will be collected from all patients to determine the response rate and assess non-response bias. It is not logistically feasible to estimate the population prevalence of chlamydia from cross-sectional surveys of representative samples of the whole target population in each cluster. It is likely that chlamydia positivity measured in clinic attenders is higher than true population prevalence but it is a valid proxy under the following conditions: the participation rate is high enough to minimise selection bias, the response rate at the end of the intervention period is similar to the baseline response rate and the characteristics of clinic attenders do not change systematically during the intervention period. Baseline prevalence in clinic attenders will be estimated prior to cluster randomisation, so should be balanced in intervention and control clusters.

Secondary endpoints

Pelvic inflammatory disease (PID)

The cumulative incidence of PID due to any cause in the intervention and control groups will be measured; the numerator is the number of cases of PID diagnosed during the intervention period among women aged 16–34 years attending participating clinics. The denominator will be the number of female patients aged 16–34 years with at least one consultation at the clinic during the intervention period. The upper age limit will allow diagnoses to be included from women aged 25 to 29 years at enrolment, who develop PID some years after chlamydia infection.

To help reduce measurement bias, GPs in both intervention and control clusters will be provided with the same PID diagnosis and management education pack which has been accredited by both the Royal Australian College of General Practitioners and the Australian College of Rural and Remote Medicine. GPs are advised to diagnose PID according to the clinical criteria of the Centers for Disease Control and Prevention, which recommend treatment when any one of the following signs are present: uterine tenderness, adnexal tenderness or cervical motion tenderness in sexually active young women at risk of STIs where no other cause is identified [28]. Clinical diagnostic criteria have been shown to have sensitivity and specificity of 87% and 50%, respectively in hospital settings [86]. It is acknowledged that ascertainment bias in the diagnosis of PID by GPs cannot be eliminated because their clinical judgment can be influenced by knowledge of a woman's chlamydia test status.

GPs will be advised to record PID diagnoses in their electronic medical records via drop-down lists and pre-coded lists where available, in preference to recording the diagnoses as uncoded free text. STI test results associated with the PID diagnosis will be extracted and linked with the PID diagnosis.

The number of hospital admissions or emergency department attendance associated with PID (on the basis of ICD 10 codes) will be obtained from each State health department. Hospitalisation data will include the age and residential postcode for each patient. Any GP referral for PID to a hospital will be collected.

Epididymitis

The cumulative incidence of epididymitis due to any cause in the intervention and control groups will be measured; the numerator is the number of diagnoses of epididymitis during the trial period among men aged 16 to 29 years. The denominator will be the number of male patients aged 16 to 29 years with at least one consultation at the clinic during the trial period. The diagnosis of epididymitis will be based on clinical symptoms, as described by Trojian and Lishnak [26]. In order to minimise measurement bias, GPs in the intervention and control groups will be provided with information on the diagnosis of epididymitis and will be requested to use consistent clinical reporting text in the medical records. STI test results associated with the epididymitis diagnosis will be extracted and linked with the epididymitis diagnosis.

Testing uptake rates

Testing uptake per year (with 95% CI) of eligible patients will be assessed in intervention and control groups as an overall measure, as well as stratified by sex, age group (16 to 19, 20 to 24, 25 to 29 years) and Aboriginal and/or Torres Strait Islander status. The numerator will be the number of individuals aged 16 to 29 years who were tested for chlamydia at least once in the past year; the denominator will be the number of unique individuals aged 16 to 29 years who had a consultation with a GP at the clinic in the past year. The denominator will include patients who have not had sexual intercourse, as this information is not recorded on patient records. The Australian Study of Health and Relationships [87] or similar up-to-date data will be used to adjust denominators for the proportion likely to be sexually active.

Annual re-testing rate

Overall annual re-testing of eligible patients will be determined in intervention and control clusters, and stratified by sex, age group (16 to 19, 20 to 24, 25 to 29 years) and Aboriginal and/or Torres Strait Islander status. The numerator will be the number of individuals aged 16 to 29 years who were tested for chlamydia 12 months (allowable range 10 to 15 months) after a previous chlamydia test; the denominator will be the number of unique individuals aged 16 to 29 years who had at least one

chlamydia test in the previous year. The Australian Study of Health and Relationships [87] or similar up-to-date data will be used to adjust denominators for the proportion likely to be sexually active.

Test for repeat infection

Tests for repeat infection in eligible patients following a positive chlamydia diagnosis will be measured overall in intervention and control clusters, and stratified by sex, age group (16 to 19, 20 to 24, 25 to 29 years) and Aboriginal and/or Torres Strait Islander status. The numerator will be the number of individuals aged 16 to 29 years re-tested for chlamydia three months (allowable range six weeks to six months) after a positive test; the denominator will be the number of unique individuals aged 16 to 29 years who tested positive for chlamydia in the previous year.

Repeat infection rates

Repeat infection rates in eligible patients in intervention clusters only will be assessed as the number of people with a positive repeat chlamydia test taken from 6 weeks to 6 months after an initial positive test, as a proportion of all chlamydia positives at the initial visit. It will not be possible to distinguish re-infection from an untreated partner from persistent infection following treatment failure or acquisition of infection from a new partner, because samples tested in routine diagnostic laboratories are not retained for genotyping.

Data collection

GP characteristics

GP characteristics will be collected via questionnaires and analysis of clinic consultation data prior to commencement of the trial and will include demographics (age, sex, years worked as a GP); education details (country of qualification, postgraduate qualifications); and knowledge, awareness, attitudes and practices with respect to chlamydia testing and management. GPs' partner notification practices and their familiarity with the clinical diagnostic features of PID will be assessed in the questionnaire.

Patient characteristics

Data from patients taking part in baseline and final prevalence surveys will be collected by self-completed questionnaire using handheld computers. Data items include demographics (age, sex, Aboriginal and/or Torres Strait Islander status, ethnic/cultural background, postcode of residence); sexual behaviour data (proportion currently in a sexual relationship, number of sexual partners by sex within last 3 and 12 months, number of new sexual partners in the last 12 months, duration of

most recent sexual partner, any concurrent or overlapping partnerships); presence of any symptoms associated with chlamydia; and history of past chlamydia testing. The postcode of residence of sexual partners will not be collected.

Minimal data including age, gender and whether ever had sex will be collected from all patients who refuse to participate in the prevalence survey. These data will be used to assess non-response bias.

Chlamydia testing, diagnosis and sequelae data

A data extraction tool (GRHANITE™, licensed by the University of Melbourne; www.grhanite.com) will be installed on clinic computers where possible. This data extraction tool will provide ongoing collection of consultation and chlamydia testing data, with patients de-identified but including a unique identification code. As a backup, consent will also be obtained to collect quarterly chlamydia testing numbers from each clinic's pathology provider, and from Medicare Australia, the Australian Government Insurance Scheme that funds chlamydia general practice consultations and chlamydia tests in Australia. The data obtained via the pathology provider or Medicare will not include a unique identification code. The data collected will include chlamydia testing rates for the 12 months prior to trial commencement; chlamydia positivity rates for the 12 months prior to trial commencement, and; number of PID and epididymitis diagnoses for the 12 month prior to trial commencement. During the trial, the data collected will include the number of consultations with 16–29 year olds; the number of chlamydia tests for 16–29 year olds; the number of repeat tests for 16 to 29 year olds; the number of 16–29 year olds testing positive for chlamydia and re-testing following testing positive; the number of PID cases diagnosed among women aged 16–34 years at participating GP clinics and local hospitals; and the number of epididymitis cases diagnosed among men aged 16–29 years at participating GP clinics and local hospitals. The number of cases of PID and epididymitis associated with chlamydia will be reported where a laboratory test has been done and the number of PID cases referred to a hospital will also be extracted. The automated data extraction tool provides data from clinics in intervention and control areas in a way that cannot be subverted. This will help to minimise bias in the measurement of chlamydia test uptake and re-testing rates.

Adverse-events reporting

Patients receiving the intervention could experience adverse events after receiving a diagnosis of chlamydia or from antibiotic treatment. Levels of anxiety and of partnership breakdown in women screened for chlamydia in the USA have been reported to be more common in those receiving a

positive than a negative test result [88]. Azithromycin can cause minor gastrointestinal upset, but rarely causes serious side effects [84, 89].

During the intervention period passive surveillance for adverse events will be undertaken. The overall numbers of events in intervention and control clinics will be reported. Diagnoses of anxiety and referrals for psychological or psychiatric treatment will be extracted from the clinics' electronic medical records where possible. However, it will not be possible to assess causality from these data. In the final prevalence survey, the questionnaire administered to patients attending both intervention and control clinics will ask them to report whether they experienced any anxiety or issues with their partner following any chlamydia test they had during the intervention period and whether their chlamydia test result was positive or negative. These data will also be reported.

Statistical analysis plan

Sample size and power calculations

Table 1 summarises the total numbers of randomised clusters required to detect differences in estimated chlamydia prevalence (the primary outcome measure) between intervention and control arms at the end of the trial. The calculations were based on the following assumptions:

1. The intra-class correlation coefficient (ICC) was estimated from individual practice data to be 0.009 [90]. Since combining practices into clusters in the trial design is likely to reduce the ICC, calculations were also performed using ICC = 0.007 and ICC = 0.005.

2. The design effect (the inflation of the sample size to allow for between area variability) was calculated as $1 + (n - 1)*ICC$, where n is the number of people tested at each area.

3. All calculations are for 80% power and use a two-sided significance level of 5% [61].

Table 1 shows that 54 clusters (27 in each group) are required to detect a difference in chlamydia prevalence between the intervention and control groups of 2% at the end of the trial with 80% power (4% in control and 2% in intervention group). Within each of the geographical areas, 80 men and women aged 16 to 29 years will be tested for chlamydia during each prevalence survey. Statistical power will be increased if a higher than expected chlamydia prevalence is obtained at baseline or if the ICC is lower than estimated. If the ICC is found to be 0.005, 54 clusters will give 89% to detect a difference of 2% at the end of the trial.

Baseline data

Cluster, clinic and participant baseline characteristics will be summarised by randomised group as appropriate. There will be no statistical hypothesis tests for this comparison.

Type of analysis

Primary analyses of the trial endpoint will be according to the intention to treat principle, with clusters analysed according to their randomised group, regardless of the level of uptake of the intervention. Secondary analyses of the measurement outcomes will explore the effect of adherence to the intervention, first by excluding clusters with poor adherence, and second by regression of measures of cluster adherence on outcomes.

Statistical tests

Formal statistical comparisons will be based on generalised mixed models that can account for cluster, clinic and participant variability. Generalised estimating equation (GEE) approaches, with robust standard errors, will be adopted using STATA statistical software (StataCorp, College Station, TX, USA). Initial analyses will be simple, unadjusted comparisons of randomised areas. If there appear to be any important imbalances between randomised groups in terms of baseline covariates, adjusted analyses will also be performed, and presented in addition to unadjusted comparisons. The impact of other potential confounding factors such as age and gender of the patients and GPs, and socio-economic profile of the area served by the clinic will also be investigated in this analysis. The difference between intervention and control clusters will be estimated, with 95% confidence intervals and p-values form the corresponding hypothesis tests. Statistical significance will be taken as a two-sided p-value less than 0.05, with no adjustment for multiple comparisons.

Outcome measures will be assessed as follows:

- Chlamydia prevalence in clinic attenders after the intervention period will be summarised by randomised group, and by sex and age group. Formal comparisons will be based on hierarchical logistic regression models.

- Incidence of PID per 100 female patients seen at a clinic will be summarised by randomised group and by age group. Analyses will be based on Poisson regression models.

- Incidence of epididymitis per 100 male patients seen at a clinic will be summarised by randomised group and by age group. Analyses will be based on Poisson regression models.

- Testing uptake rates, testing coverage, annual re-testing rates, testing for reinfection and rates of re-infection will be summarised by randomised group and compared using appropriate hierarchical models.

Planned subgroup analyses

The effect of the intervention within different subgroups of clusters will be explored, but interpreted cautiously given the relatively small number of clusters. Subgroups may include sex, age group, area type, Aboriginal and/or Torres Strait Islander status, estimated baseline chlamydia prevalence and baseline testing rate. Intervention and control clusters will be compared within each subgroup and evidence for heterogeneity of effects assessed using tests for interaction between randomised intervention and subgroup. The effect of GP and clinic characteristics on testing uptake, annual retesting rates, retesting after a positive diagnosis and chlamydia prevalence will be investigated. The impact of patients attending from an area outside of the cluster will be investigated by analysing patient postcode and its association with chlamydia prevalence.

Ethical issues

Ethics committee approval

The ACCEPt trial has been approved by the RACGP National Research and Evaluation Ethics Committee and the University of Melbourne Human Research Ethics Committee. Approval has also been obtained from the Aboriginal Health and Medical Research Council (AHMRC) Ethics Committee to conduct the ACCEPt trial in AMSs. Specific services may also request ethical approval be sought from local ethical committees.

Informed consent and information sheets

ACCEPt research staff will explain the data collection requirements of the trial to all clinic staff prior to them providing informed consent. Informed consent will cover all data collection activities of the trial, recognise the principles of confidentiality and data ownership and define processes for reporting of findings and release of trial results. A plain language participant information sheet will be provided, which summarises the trial, participation requirements, confidentiality and disclosure of information, and ethics approval and complaints contacts.

GPs can withdraw from the trial by notifying ACCEPt staff at any time and completing a withdrawal of informed consent form. Unless otherwise requested, data collected from the clinic up until the time of withdrawal will be included in the analysis of the trial. Practice nurse participation will also

require informed consent. A plain language information sheet will be provided and withdrawal at any time is possible with a withdrawal of informed consent form.

For the prevalence surveys, ACCEPt staff will explain prevalence survey participation to patients attending clinics for consultations with a GP. Informed consent will cover the provision of chlamydia test results to ACCEPt, and confidentiality of the test results and questionnaire responses. Plain language participant information sheets for females and males will be provided, summarising the trial, the requirements of participation in the prevalence survey, confidentiality and disclosure of information, and ethics approval and complaints contacts. Patients may withdrawal at any time with a withdrawal of informed consent form.

Interim analyses and stopping rules

There will be no interim analyses of the primary endpoint, and no formal stopping rules adopted.

Data monitoring committee

No independent data-monitoring committee has been appointed. An advisory committee has been appointed to give advice about the intervention and its implementation in general practice clinics and AMSs. The advisory committee is comprised of representatives from general practice, including GPs, practice nurses and practice managers; a pathology provider; the National Aboriginal Community Controlled Health Organisation (NACCHO); a youth advocacy group; and a rural sexual health researcher.

Indemnities

The trial is covered by the University of Melbourne's Professional Indemnity Insurance Policy (Vero Profin, Melbourne), General and Product Liability Policy (Unimutual Limited, Sydney). The University of Melbourne is also a WorkSafe Victoria approved self-insurer for workers' compensations.

Publication plan

The trial results will be submitted to peer-reviewed journals for publication and presented at national and international conferences. Results for chlamydia prevalence, PID and epididymitis incidence, and chlamydia testing rates will be published separately. Results obtained through the pre-trial prevalence survey will also be submitted for publication.

Reporting

Reporting of the trial will be in accordance with the Consolidated Standards for Reporting Trials extension to cluster randomised trials (CONSORT statement) [87]. These standards ensure the complete and transparent reporting of a core set of components of the design and conduct of a randomised controlled trial.

Trial registration

The trial has been registered with the Australian Clinical Trial Register. (http://www.anzctr.org.au)- number ACTRN12610000297022.

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Start date

- Date trial started: July 2010

Finishing date

- Expected end date: December 2015

Reporting date

- Expected reporting date: June 2016

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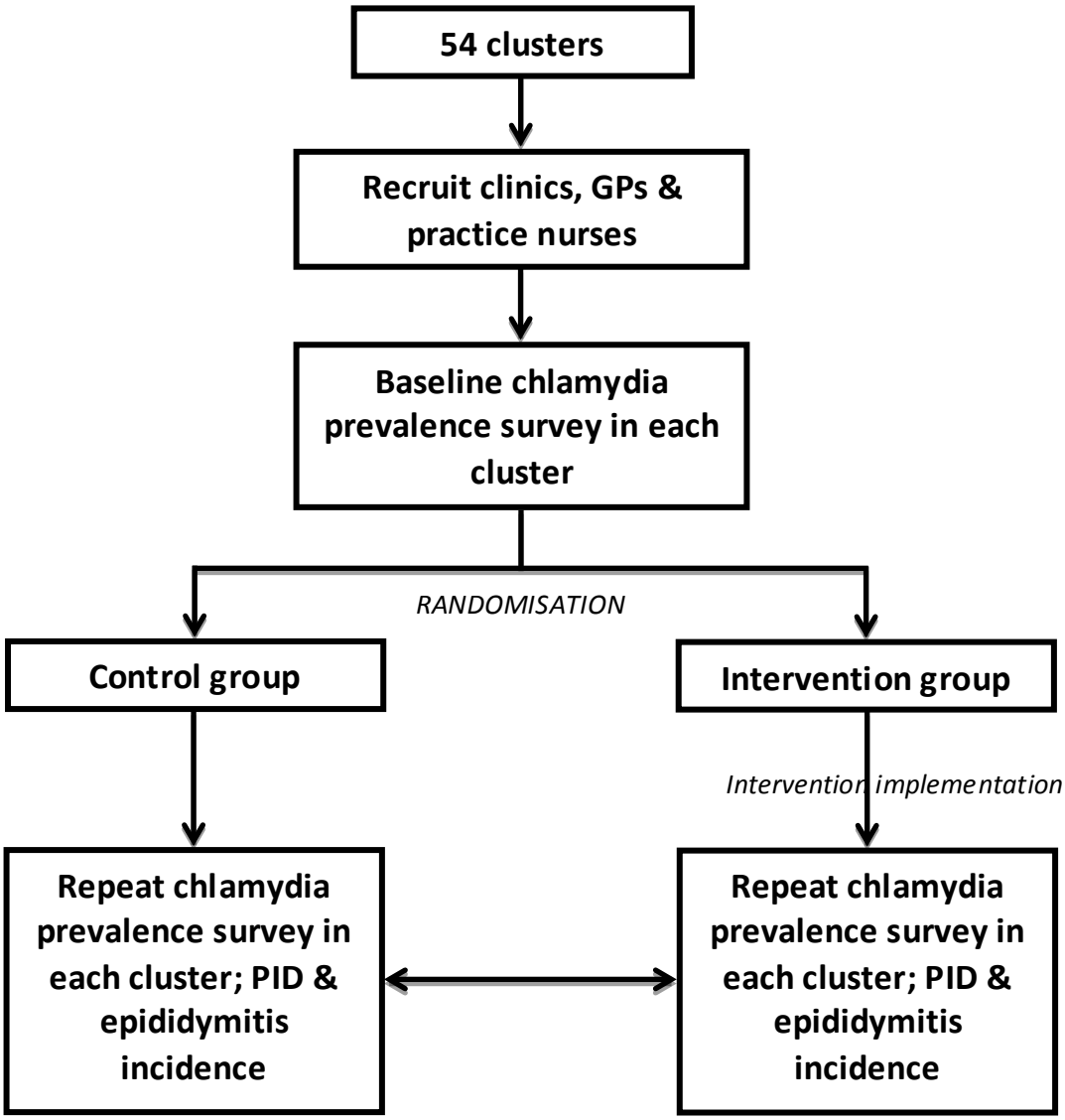

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935 **Figure 1. Trial flow chart**

936 **Table 1. Sample size calculations showing number of areas required to detect given differences between**
937 **testing and control arms in chlamydia prevalence at end of pilot. ICC, intra-class correlation coefficient.**

Control proportion	Intervention proportion	1:1 sample size[a]	ICC effect	Design	Inflated	Total sample areas[b]
0.04	**0.02**	**2478**	**0.009**	**1.71**	**4400**	**54**
			0.007	1.55	3900	48
			0.005	1.40	3500	44
0.045	**0.025**	**2644**	**0.007**	**1.55**	**4106**	**51**
			0.005	1.40	3688	46

938 a. Assuming 80% power

939 b. Based on about 80 participants per cluster.

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