NETSCC, HTA

5 August 2010

TITLE

The relative clinical and cost-effectiveness of three contrasting approaches to partner notification for curable sexually transmitted infections (STIs): a cluster randomised trial in primary care.

OBJECTIVES

1. To standardise, appropriately for the primary care setting, three contemporary and evidence based models of partner notification for sexually transmitted infections (patient referral, contract referral and provider referral).
2. To compare the clinical effectiveness of these three models.
3. To compare the cost effectiveness of these three models.
4. To enhance the efficiency of the trial through mathematical modelling of the potential impact of each modality of partner notification on outcomes for different types of partner (main, casual and ex-partners) and for men who have sex with men.
5. To determine the acceptability to patients of each approach to partner notification, and to identify means for improving partner notification rates for "highly connected" partnerships.
6. To provide comprehensive, definitive evidence for policymakers and public health practitioners on the implementation of clinically effective and cost- effective partner notification for the patients diagnosed with sexually transmitted infections in the primary care setting.

NULL HYPOTHESIS:

Provider referral and contract referral offer no advantage over patient referral in partner notification for curable sexually transmitted infections in the primary care setting.

PRIMARY CLINICAL OUTCOMES OF RCT

1.Number of partners per index patient treated for chlamydia and/or gonorrhoea/nonspecific urethritis/pelvic inflammatory disease.
2.Proportion of index patients testing negative for the relevant STI at 3 months*

SECONDARY OUTCOMES OF RCT

1.Number of partners per index patient presenting for treatment.
2.Proportion of index patients having at least one partner treated
3.Number of main, casual and ex-partners per index patient tested for the relevant STI.
4.Number of main, casual and ex-partners testing positive for the relevant STI.
5.Number of index patients tested for HIV by 3 months*
6.Number of current partners tested for HIV by 3 months*.
7.Time to definitive treatment of index patient for the relevant STI.
8.Time to definitive treatment of current partner for the relevant STI.
9.Uptake by index patients of "contract" and "provider" referral for one or more partners, within the relevant randomised groups.
10.Patient-related factors impacting on partner notification or STI disclosure to main, casual and ex-partners.
The outcomes marked * will be measured at a three month review of the index patient, by telephone. Primary outcome 2 will be assessed through a posted urine sample, tested for chlamydia using NAAT tests and (in selected cases) gonorrhoea.

Others outcomes will be assessed through research health adviser interviews with the index patient at 6 weeks or through routine trial administrative data, with the exception of patient related factors, which will be addressed in the substudy described below.

Background

The public health importance of sexually transmitted infections in primary care. Sexually transmitted infections (STIs) are increasingly diagnosed and treated within the primary care setting[1;2], and around a third of patients presenting to genitourinary medicine (GUM) clinics first seek care from their GP surgery[3]. Maximising the quality of care for patients seen in general practice with STI has considerable potential for public health gain.
Current partner notification practice. Partner notification is the process of supporting patients in enabling treatment for their sexual partners following diagnosis of an STI. Treatment of partners is important for two reasons - to protect the original patient from reinfection and its health consequences, and to prevent the further spread of infection by infected partner(s). At population level, it reduces transmission of STIs by shortening the duration of infection, which is a key determinant of onward transmission rates[4].
Partner notification is generally undertaken by specialist "health advisers" based in genitourinary medicine clinics, though increasingly with the growth of the National Chlamydia Screening Programme in England this specialist work is undertaken in community settings by a "chlamydia co-ordinator"[5]. Most patients are supported by a

health adviser in "patient referral", in which the patient contacts sexual partner(s) to arrange treatment[6]. However, the extent to which this is supplemented by health providers contacting partners on the patient's behalf, and with their agreement ("contract" or "provider" referral) is variable[7].

Specific challenges in partner notification, and partner notification research, for the primary care setting, in relation to the commissioning brief. Partner notification has been shown to present particular challenges to primary care practitioners[8]. There is evidence that only 30% of UK general practitioners would treat a partner[9], and as few as 13% of index patients have a documented attendance at the GUM clinic[10]. GPs may overestimate how much partner notification they do[11], while patients treated by a GP are more likely to require retreatment than those treated in a GUM clinic at the outset[12]. Specific difficulties for the general practitioner or practice nurse include the following: (a)The sexual partner(s) of index patients are often not registered at the practice, and general practice has no mechanism for enabling STI treatment in this situation, or for following up compliance. (b) Even if the partner(s) are registered at the practice, the duty of confidentiality to individual patients presents difficulties in partner notification where the index patient declines to discuss his/her infection with the partner. (In GUM by contrast, anonymous referral is possible, though not commonly used in practice)[7]. (c)Staff in general practice may not be experienced in common problems of partner notification, which is time-consuming and requires training[13]. (d) Index patients appear to be less willing to give frank information on number of partners, particularly casual or concurrent partners, to familiar staff than to a specialist STI service[13;14].

Recognising these difficulties, recent NICE guidance recommends that all patients with an STI, regardless of the setting of diagnosis, should be offered support in partner notification, which may be within the primary care setting or through referral to a partner notification specialist[15]. It does not however specify standards for content or delivery of this support. A high quality randomised controlled trial has demonstrated that specifically trained practice nurses can achieve partner notification outcomes equivalent to those achieved by referral to attend a GUM clinic[16]. This trial provides important evidence that partner notification in the form of patient referral can be undertaken within a highly motivated and specifically trained primary care setting. However it does not provide an adequate model for a comparison between patient, provider and contract referral in a primary care setting, since it is implausible to suppose (based on the above) that provider or contract referral could become routine work among all general practice surgeries. The practices involved in this study were specifically trained, and were participating in a large trial of screening for chlamydia[17]. However the question posed by the HTA relates to the large proportion of patients who present to, or are diagnosed with an STI within, the majority of practices which have no specific interest in sexual health.

The HTA requires a comparison between three approaches to partner notification, none of which is routinely used in primary care, and none of which is provided in a standardised way across the network of genitourinary medicine (GUM) clinics in the UK. All these factors present challenges in defining the appropriate technology for the trial. NICE's recent recommendation also presents an ethical challenge to trial design. Although it is known that partner notification support is given only uncommonly in UK primary care[8], it will be ethically unacceptable to offer any patient in the trial, or indeed in trial practices, care below the minimum standard set by NICE.

The need to respond to modernisation of models of care. The increasing availability of mobile SMS messaging ("texting") and the internet have led to GUM clinics developing new approaches to communication with patients in recent years. It will therefore be essential to define and compare partner notification technologies that are relevant to contemporary practice for the purposes of this study. To base this study on existing methods of traditional partner notification could limit the future worth of this study. In particular, "Accelerated Partner Treatment" is being developed elsewhere by members of this team (see below). This is an approach in which medication is made available to partners, after a telephone clinical assessment with a sexual health care professional or through assessment with a community pharmacist in a retail pharmacy setting prior to testing, or with the option of contemporaneous testing, in order to complete treatment of the couple as quickly as possible. Though evaluation of this Accelerated Partner Treatment is not requested by the HTA, it will be essential to create a framework for comparison in the UK context. Finally, many authorities argue that the best measure of partner notification is a negative re-test of the index patient for the relevant infection at 3 months[6], due to the difficulty of measuring process outcomes, and the importance of avoiding reinfection or persistent infection for the index patient[18].

Interaction of the proposed study with the National Chlamydia Screening Programme (NCSP).

The NCSP is being rolled out across England, with coverage of the target 16-24 year old population recently varying between 0% to 14% in different PCTs[19]. Local NHS targets are currently 15%**.** Screening forms an increasing proportion of primary care STI diagnoses, and is likely to increase over the next three years. It is likely that NHS targets can only be achieved through growth of screening in primary care (REF NL), an important feature of the original pilots which has not yet been replicated in the NCSP[20]. Careful attention will need to be paid to the interaction between the NCSP and our proposed interventions.

The NCSP has encouraged the development of varying models of service provision. The organisation of partner notification varies markedly, with GUM clinics providing this service in some areas, community based chlamydia

co-ordinators in others, while some high volume areas do not specifically support partner notification in primary care. Dr Mary Macintosh, Director of the NCSP is involved in the study, and will assist by avoiding conflicting priorities, and enabling collaboration. The study has received the support of local chlamydia co-ordinators in the South East, with whom the Principal Investigator works as a consultant in health protection.

Summary of proposal. We propose a cluster randomised trial, with randomisation at the level of the GP practice. We will specify, standardise and compare 3 approaches to partner notification, all using modern communication methods and are based on recent evidence: **(1)PATIENT REFERRAL, (2)CONTRACT REFERRAL, (3)PROVIDER REFERRAL** (described below).

Choice of outcomes for the trial. The HTA proposes that the number of partners of index patients presenting for care, or actually treated, should be the primary outcome. The study is powered on this outcome, and we have included all measures proposed by the HTA. These established outcomes are important, though difficulties in their measurement are well known.

However there is also a growing view that the biological outcome of index case disease status soon after initial infection is an important and objective biological outcome that should supplement, if not replace, the "process" measure of partner treatment[6]. It has been repeatedly shown, in the UK and elsewhere, that patients diagnosed with chlamydial infection are at high risk of reinfection[21], with rates of up to 30% in a UK general practice population initially diagnosed through screening. Measurement of partner notification outcomes is known to be difficult, and the biological outcome of index disease status is likely to correlate with outcome of main partner, and less susceptible to misclassification.

This trial also provides an important opportunity to address the relative acceptability to patients of different modes of partner notification for different types of partnership, within the "provider" and "contract" arms. Unpublished qualitative work in the ongoing APT study (led by Estcourt and described below) suggests that patients may prefer "provider" or "contract" referral for ex- or casual partners, but wish to undertake "patient referral" for current partners. Individuals having multiple casual partnerships are less likely to use condoms than others[22], and are more important in onward transmission than current long term partners, who are a transmission "dead-end" even if they may re-infect the index patient. We therefore propose to explore this question through careful measurement of provider or contract referral uptake in relation to different types of partner. All patients will have the option to contact their partners directly.

Existing and pilot work informing the proposal:
The applicants have an established history of successful collaboration on closely related health services research in the field of sexual health. Four MRC funded projects in particular have provided essential groundwork for the proposed trial. The "APT" trial, described above in the outline proposal, (*Can Expedited Partner Therapy Improve Outcomes of Partner Notification? A Feasibility Study and Exploratory Trial.* MRC funded, £302,314, G050010, led by Estcourt) is an ongoing exploratory trial of "Accelerated Partner Notification", which has provided qualitative data on the acceptability of different approaches to partner notification. This work suggests that "contract" or "provider" referral, and other modalities in which the index patient need not contact a partner him/herself, are often preferred for ex- or casual partners. However, they are disliked for current partners. These findings have informed our approach to modelling, and the study of patient related factors, which will focus on the impact of "highly connected partnerships". This study has also provided us with experience of collecting standardized, trial quality partner notification data in a research setting, and developed a cadre of health advisers with research experience relevant to the study proposed here. The "APT" approach to partner care, while relevant to this study, is different from the approaches requested by the HTA, both in (i) being sited in the GUM clinic setting, and (ii) treating partners without a requirement for testing after GMC compliant telephone consultation or pharmacy consultation. It is an intervention which may eventually be translated into primary care, and as such we will collect outcome data consistent with its main measures.
Richens is PI for a recently completed, MRC funded randomised controlled trial of computer assisted sexual history taking, in a clinic setting. This will inform the standardised collection of patient data within practices using the web data collection tool, and from patients during follow-up

Cassell, Roberts and Rait have recently submitted a Final Report for the MRC funded study *Developing innovative strategies in the care pathway for STIs diagnosed in primary care*. (£294,931, G0300708) ("CAPSTI"). This study developed methods for STI surveillance in primary care, and an intervention to improve the management of patients with potential STI presenting to the primary care setting. The tools developed for this study (including a web patient management and audit aid for GPs) will be of considerable practical value in the development both of intervention and of data collection for the HTA proposed trial. This work has been further extended in *Public health outcomes, costs and cost-effectiveness of GUM and primary care based STI services: How to maximise STI control and cost-effectiveness for a population.* MRC, £374,000 in which Cassell and Rait are coapplicants. This study, which aims to develop a decision tool for sexual health service planning in UK

localities, will contribute to the development of feasible measurement and audit tools both for the RCT and any later intervention translated into routine practice.

Changes from outline proposal Further work on sample size considerations, involving analysis of laboratory data as part of the CAPSTI study (see above), and review of the recent NCSP chlamydia screening data has led us to believe that our original estimates, based on clinically diagnosed cases and current patterns of case finding, may have been optimistic. Details are given below. We will therefore supplement this opportunistic recruitment with active invitations to patients eligible for the NCSP to screen for chlamydia. This change has increased service support costs, but *not* research costs.

Overview of study design: We propose a cluster randomised trial of three contrasting partner notification technologies in the primary care setting, as requested by the HTA. This clinical trial will be accompanied by an economic study, addressing questions of cost and cost-effectiveness.

The details of the three approaches to be used (patient referral, contract referral and provider referral) draw extensively on the recent evidence based on effectiveness, and on current practice in primary care.

The question of problem of right skew in the number (and nature) of sexual partnerships will be addressed through a focussed mathematical modelling substudy, without undue inflation of trial size. Patient related determinants of partner notification will be explored, with a view to advising on targeting of different approaches.

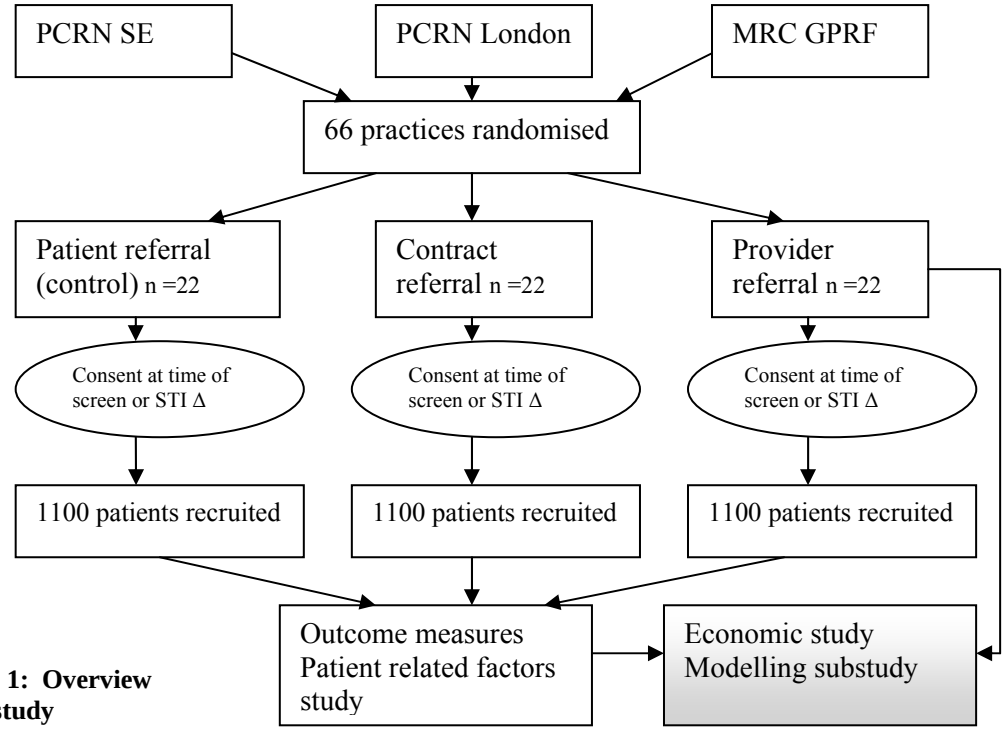


Fig 1: Overview of study

METHODS 1: RANDOMISED CONTROLLED TRIAL

Setting: A diverse sample of UK primary care practices, both in specific localities (Primary Care Research Network practices in East London and East Sussex), and nationally recruited (via the MRC General Practice Research Framework).

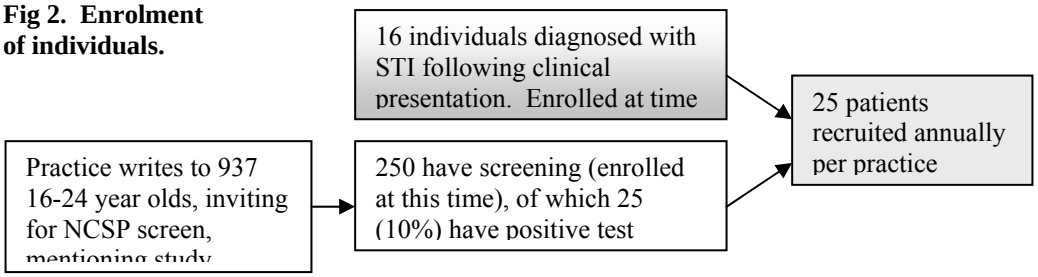
Target population: The target population will be all patients over the age of 16 who have been diagnosed (following clinical presentation or chlamydia screening) or are seeking care in primary care settings for a curable sexually transmitted infection.
Specifically, we seek to recruit:
(i) Male patients seen for: urethral discharge, or dysuria (with no evidence of urinary tract infection), or with a diagnosis of chlamydia, nonspecific urethritis or gonorrhoea.
(ii) Females diagnosed with chlamydia, gonorrhoea or pelvic inflammatory disease.

Technologies to be evaluated: We will compare three different interventions in partner treatment:
(1) ***PATIENT REFERRAL*** where patients are given information about their infection, and asked to tell their partner about the problem and the need to be treated.
(2) ***CONTRACT REFERRAL***, where, in addition to (i), patients will be asked to agree to a specialist health adviser (contact tracing expert) to inform partner(s) if this has not been done after a verbal agreed period of time (usually no more than 7 days).
(3) ***PROVIDER REFERRAL***, where, in addition to (i), patients will be asked to agree to a specialist health adviser contacting one or more of their partner(s) at the time of diagnosis.
Further details of each proposed intervention are given in Figure 3 on page 7.

Sample size:
Basis for sample size calculation. Data on partner notification outcomes are highly variable, and in our view the best comparator is current partner notification audit data from the NCSP, which reflects the population of index patients diagnosed outside the GUM clinic . These are highly variable, ranging from 5% to over 70%[23]. Our primary outcome 1 is the number of partners treated per index case, which will be a highly skewed variable most commonly taking value 0 or 1, but potentially two or more. We base our sample size calculation on the proportion of index cases with one or more partner treated as this is more mathematically feasible, as a proxy for primary outcome 1. As most index cases will either have zero or one partner treated the proxy outcome will for most participants be identical to the 'real' outcome. We have chosen an 11.5% increase from 20% to 31.5% in this proxy outcome as an important difference as the basis of power calculation for primary outcome 1, but any 11.5% improvement would be equally clinically important. Primary outcome 2 conservatively assumes that the reinfection rates shown in a recent NCSP study[21] are high, and instead assumes reinfection rates of 12% which is more challenging for our study, but consistent with the wider literature[24].

Our estimates for the number of achievable cases, given our recruitment strategy (see below) are based on data from pilots of the NCSP[20] unpublished NCSP data on the number of chlamydia cases diagnosed per practice in the UK currently, and published data on STIs in primary care preceding the NCSP[1;2;25]. Only one GP practice in the South East is currently making >20 annual diagnoses of chlamydia in the 16-25 age group covered by the NCSP (HPA unpublished), and positivity rates above this age are very low[25]. Though cases of gonorrhoea will be included in our study, below 4% of cases are diagnosed in primary care[1]. Men presenting with urethral discharge are a large group of eligible patients who are often currently not appropriately managed, and using a simple diagnostic algorithm will be eligible for the trial.

Fig 2. Enrolment of individuals.



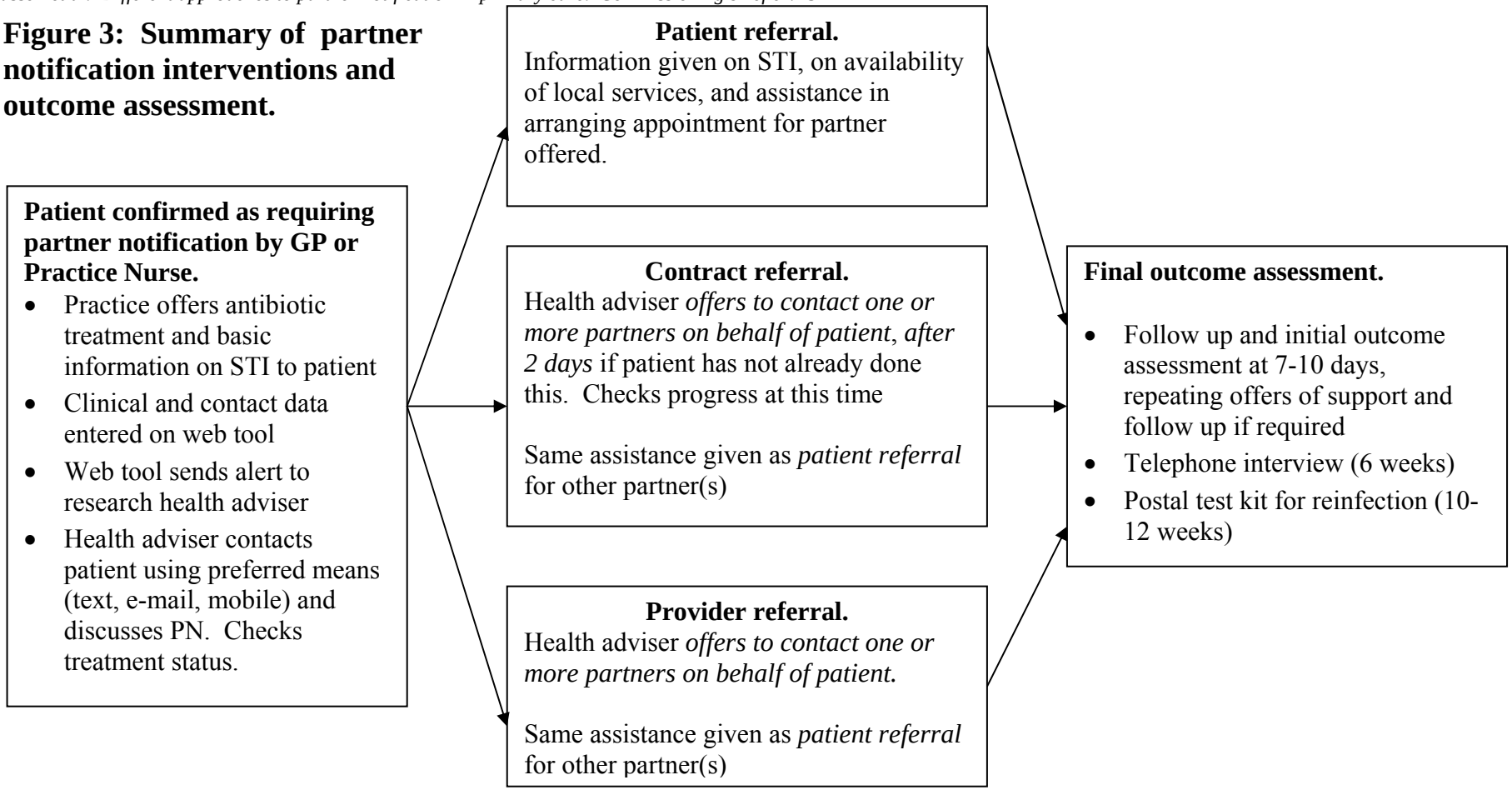
Sample size. We will recruit at least 9 male and 16 female patients per practice per year and at least 50 participants per practice over two years. With 22 practices per arm there will be a total of at least 3300 study participants. We assume a maximum plausible ICC of 0.05, leading to a design effect of 3.45 and effective total sample size of at least 957. Patient referral is treated as the control arm. For the proxy primary outcome 1 the

proportion is expected to be around 20% in the control arm and the sample size provides at least 80% power to detect as significant an increase to 31.5% in either intervention arm, based on a 2% significance level. The level is reduced from the standard 5% to account informally for the multiple (two) comparisons made with the control arm. For primary outcome 2, assuming a 12% reinfection rate in the control arm, this sample will provide at least 80% power to demonstrate noninferiority of either intervention relative to control (defined to be no more than a 5% higher rate than control) given that the intervention in fact delivers at least a reduction in the rate to 9.5%. This is based on considering a 1-sided test with 2% significance level, and assumes an 80% follow-up rate for this outcome.

The impact of improving outcomes for main, casual and ex-partners respectively will be explored through mathematical modelling in order to address the question of right skew in partner numbers without increase in trial size (see Methods 4, below).

We assume that all enrolled patients will be retained to the time of the primary outcome (number of partners treated as ascertained by the managing health adviser, but expect a 20% dropout both for the telephone interview and the follow-up repeat test. As mentioned above, and discussed below under "Ethical Considerations", in the context of NICE guidelines it must be assumed that there is a clear obligation of NHS providers to ensure partner notification for patients under their care for an STI. We will therefore assume that all patients enrolled (most at the time of testing, and initiated through our study) will remain in the trial for the purpose of primary outcome 1. Missing data at this stage will be treated as partner notification failure, and *not* as dropout. This consideration has informed our low estimates for partner notification (0.2 control, 0.3 intervention), and we consider that this reflects the "real life" purpose of this research. We will however consider alternative treatments of this missing data as part of a sensitivity analysis.

Figure 3: Summary of partner notification interventions and outcome assessment.



Inclusion and exclusion criteria for practices: We will seek to recruit practices from the MRC General Practice Research Framework (GPRF), the South East Primary Care Research Network (PCRN-SE) or the Primary Care Research Network Greater London (PCRN-GL). Selected practices will have registered populations of 5000 or more. A maximum of six practices considering themselves as "student health centres" will be recruited, and no more than four regarding themselves as running "locally enhanced services for sexual health".

Recruitment of practices: A wide range of practices will receive a letter from the GPRF or the relevant PCRN in which they will be asked to express an interest in this study. The invitation will emphasize that there is no requirement for the practice to have a special interest in sexual health.

Level of randomisation. Cluster randomisation at practice level has been chosen for two reasons. Firstly, there is a strong likelihood that clinical practice will be influenced by participation in the trial - were we to randomise at patient level, practitioners who considered that "provider referral" had advantages might more readily suggest that patients randomised to "patient referral" attended a specialist clinic. Secondly, randomisation of patients attending often unexpectedly in the middle of a busy surgery is more challenging than for chronic disorders, and practice randomisation reduces this difficulty.

Allocation of practices to intervention groups: Randomisation of practices will be undertaken by Dr Andrew Copas of the MRC Clinical Trials Unit. Practices will be stratified before allocation into "Student Health Centres", "Locally Enhanced Services" and "Other". Where a practice is both a "Student Health Centre" and a "Locally Enhanced Service", it will be randomised as a "Student Health Centre". Practices will also be randomised according to their research experience. Within each stratum blocked randomization will be performed, with variable block size to minimize the chance of correctly predicting the next allocation for those practices recruited sequentially. Adjustment for stratum in analysis will account for any minor imbalance arising in the randomization within strata.

Recruitment of individuals: Patient recruitment failure is the major risk in a trial of this kind. As described above, we have modified our original plans by introducing an element of chlamydia screening in accordance with eligibility for the National Chlamydia Screening Programme (NCSP) in England to the study in order to boost recruitment. Initial pilots for the NCSP indicated that high levels of screening were achievable in primary care, given appropriate incentives.[26] We anticipate that practices can typically identify 25 chlamydia positive patients patients per year through screening, of whom and 16 patients with STI through clinical presentation, of whom 25 will be recruited to the study. Recruitment is likely to be high, since surveys have shown that around 80% primary care practitioners welcome such support (Cassell, MD, Cambridge 2007), and most feel uncomfortable in managing partner notification without specialist help.

Enhanced chlamydia screening as aid to recruitment: A typical practice with 7500 registered patients will write to 937 patients aged 16-24 in year 1, and the same number in year 2 to invite them for screening. The letter will both invite them to the annual screening test recommended as part of the NCSP[19], and also alert them to the study. The practice will also invite 16-24 year olds attending the practice to have a screening test if they have not already done so that year, in accordance with that practice's routine NCSP practice (this will be highly variable within practices). Several studies have demonstrated that the effective screening rate achievable is approximately one-third[27]. Rollout of the NCSP will mean that some individuals will already have screened elsewhere. We therefore anticipate that an average practice will undertake 250 screening tests as a result of these activities, as a consequence of which 25 positives would be typically identified[28].

Recruitment at attendance: Clinical staff (usually practice nurses) will approach potential participants, either (a) at the time of first attending the practice either with symptoms of a suspected or presumptive STI (symptomatic patients), or (b) at the time of chlamydia testing (asymptomatic patients, most of whom will be tested as part of the NCSP). They will explain that the practice is taking part in a study, as part of which additional assistance may be given to patients needing partner notification for an STI. Consent will be sought either for participation now (individuals with a presumptive or definite STI), or in the event of a positive result (patients who have undergone screening or diagnostic tests for possible STI). Although this approach will entail initial recruitment of patients who in fact test negative, previous failed trials have demonstrated the difficulty in achieving recruitment at the same time as a positive diagnosis is communicated to the patient[29].

It will be explained that the practice has been randomly allocated to a group which will either help with providing care for STI patients up to the recommended national standard, or with additional options for support. Patients will be told the allocation of the practice. It will also be explained to that, should the patient be diagnosed with an STI, participation in the trial will mean, in all cases, that he or she will be contacted by an experienced health adviser. This health adviser will, depending on the trial allocation of the practice, assist them in their plans and actions to inform and obtain care for both current and ex-partners.

Patients agreeing to be recruited at this stage will provide personal details through which the study health adviser may communicate with them.

Transfer of clinical information on recruited patients to research health adviser. When a patient is recruited, minimal contact details to be used by the health adviser will be entered in a web tool, based on a tool currently

being used by the GPRF in a major study, and on the audit tool developed for the CAPSTI study (see above). At the time when a patient receives a definite STI diagnosis, practice staff will enter this information on the web tool, thus automatically sending the research health advisers at Barts the basic contact information needed to manage the patient, and information on randomisation status of the practice.

An informal evaluation of the pilot study will be conducted to better inform the main trial. Interviews will be conducted with the nurses, reception staff and health advisors. Participants will be asked to complete a short evaluation questionnaire. Interviews will not be recorded and are simply there to inform the operational aspect of the study.

Inclusion and exclusion criteria for individuals: Patients belonging to the target population above will be eligible for inclusion if they are over the age of 16 at the time of first attendance for this problem, or of screening for chlamydia. The following groups of patients will be excluded: learning difficulties; unable to read trial materials after discussion with clinical staff; no means of communication acceptable to the patient for him/herself (NB patients *will* be eligible if they refuse to communicate with partners, given the objectives of the study).

Outcome assessment and blinding. As summarised in Figure 2 (at end of document), there will be three major elements of outcome assessment:

1. Initial assessment of routine partner notification outcomes shortly after diagnosis.
2. 6 week telephone interview
3. Follow up testing at 10-12 weeks, using a posted self-taken chlamydia (+/- gonorrhoea sample), tested with a nucleic acid amplification test REF CLASS.

All these will be co-ordinated and undertaken by the research health adviser.
Blinding will be a major challenge, for two reasons. Firstly, in the sensitive area of sexual health, patients wish to speak to a limited number of individuals whom they trust, while secondly a requirement for outcome assessment by unknown individuals is likely to increase dropout rates. In order to address this, we will require the research health adviser to make the assessments using standard question formats developed from those currently used for the APT trial, and directly entered onto the web tool without the option for later editing by the health adviser. This will limit the impact of personal interpretation of outcomes. GPRF and PCRN staff will be aware of practice allocation for training purposes. Laboratory staff undertaking the repeat test at three months will not be aware of allocation.

Recruitment, compliance, bias, and follow-up issues.
Recruitment. In accordance with normal GPRF practice, practices will provide weekly updates on recruitment both of patients having screening, and for individuals already diagnosed as having STIs. The use of a web based data collection tool will enable real-time monitoring of recruitment, and support where required, building on GPRF experience with the ongoing "IID2" study which is also a joint GPRF/PCRN venture.
Collection of data on non-recruits. Basic demographic information on non-recruits will be collected, according to CONSORT guidelines, and also anonymised audit data on primary outcome 1 (treatment of one or more partners) collected from the practice (see below under Ethical Issues).
Post-recruitment bias. As randomization will be by practice, in advance of patient recruitment, there is a possibility of recruitment bias. This might arise because of differential attendance at the practices or differential participation when invited, due to advance knowledge by patients (or staff) of the randomization arm at the practice. We would anticipate that some protection against such bias will be provided by adjustment in the statistical analysis for patient characteristics such as gender and age, as these might account for some of the differential attendance or participation. Beyond that we aim to collect limited key data concerning the characteristics of those who are tested for chlamydia or diagnosed with an STI in primary care and refuse to participate and their reasons, inviting refusers to comment on whether knowledge of randomization arm played a role. Similarly for participants we will ask whether knowledge of randomization arm played a part in their decision to participate. This will allow us to provide some guidance as to the likely nature of any bias.
A specific issue in post-recruitment bias relates to incomplete data for patients who may receive partner notification support in ways not anticipated by the trial protocol. This issue is addressed in our sample size calculation, which states our approach to missing data. In addition, research health advisers will liaise with NHS colleagues in their own and other GUM clinics, to ascertain further details partner notification under their care, according to normal practice, and as done in an RCT of partner notification which was part of the CLASS study[16].

Plan of analysis. Primary and secondary outcomes and our null hypothesis are stated on page 1. Analysis will be by intention to treat, adjusting for patient sex, practice randomisation stratum and patient characteristics found associated with the outcome. Primary outcome 1 is the highly skewed number of partners treated, which we will view as ordinal data and so construct odds ratios under the assumption of proportional odds (i.e. through ordinal logistic regression). Primary outcome 2 is binary so that odds ratios can be directly calculated. The 'effect' of each intervention will be presented relative to the control arm as adjusted odds ratios with 95% confidence intervals, though due to multiple testing (2 intervention arms) we will be cautious in interpretation where these intervals

only just exclude 1. Allowance for the clustering of patients within practice will be achieved by the standard method of generalized estimating equations, with robust standard errors. Analysis will be performed using Stata 10. 'Subgroup analyses' will be performed by patient sex, in the sense that the interaction between sex and each outcome will be tested, to assess whether the effect of either intervention differs appreciably by sex.
Given the potential impact of the intervention on partner notification practice within the surgeries, we will also explore trends by time on study at practice level.

Sponsorship and research governance
The study will be sponsored by Brighton and Sussex Medical School, and by Barts and the London NHS Trust, which will be providing the research health adviser service. The trial will comply fully with the principles of Good Clinical Practice, in which all clinically trained lead investigators have been trained, and will be overseen by a Trial Steering Committee chaired by a senior academic who has no ongoing collaborations with any of the applicants.

Ethical considerations.
This study will require MREC approval, R+D approvals for all participating sites. Following the publication of NICE guidance as discussed above, it is now established that all NHS providers testing for chlamydia have an obligation to ensure patients receive adequate support with partner notification independently of whether they are part of a research study. However. given that such a service is not routinely provided in all primary care settings, we will incur an obligation to ensure a minimal provision of patient referral. In order to assure this, we will collect anonymised basic audit data from practices which will provide useful additional information, in addition to data collected from recruits. For the high proportion of chlamydia cases now likely to have been tested as part of the NCSP, there is a requirement for audit data on partner notification to be collected and sent to the NCSP central office – during the study, the study research health adviser will be responsible for partner notification services to all patients diagnosed in the practice, in order to avoid patients "falling through the net".

METHODS 2: STUDY OF PATIENT RELATED FACTORS DETERMINING PARTNER NOTIFICATION OUTCOMES.

Objectives: The main objective of this substudy is to provide detailed qualitative information on the reasons for disclosure of STI to sexual partners. More specifically, it will explore why some people are willing to disclose to health care workers, partners and ex-partners, and why some people are not. The proposed RCT will provide an important opportunity to look at these issues in more depth with a view to identifying means of improving PN rates for "highly connected" partnerships, and for ex- or casual partners.

The research to date seeking the patient's perspective about disclosure on partner notification programs is limited. Gorbach et al identified patient related factors such as expectations of monogamy amongst partners, partnership dynamics and perceptions of likely sources of infection[30]. Further research from outside the UK has suggested that the risk of gender-based violence may adversely affect the rates of PN[6]. However, there has been little exploration of whether the results from these studies are applicable in a UK primary care setting and whether tailoring PN approaches based on individuals' barriers to disclosure would enhance PN strategies. As described above, early data from the APT study suggest that tailoring offers of partner notification support to partnership type may have potential to improve partner notification rates for "highly connected" partnerships (especially ex- and casual partners).

Methods: Semi-structured interviews will be conducted by an assistant psychologist with experience of face-to-face interviewing about sensitive topics. A purposive sampling framework (sampling by age, gender, sexual orientation, type of infection and study location) of participants in each trial arm is proposed with the aim of recruiting approximately 40-45 respondents in total. This will ensure a diversity of opinions from a wide range of respondents.

Data collection will take place over 12 months and will be organised by the assistant psychologist. Interviews will be guided by the use of an interview schedule/ topic guide. The interview schedule/ topic guide will include items that have been identified within the literature but that have not previously been investigated in a UK primary care setting. Questions about expedited partner therapy and responder preferences for health care provider (e.g. general practitioner, health advisor, nurse) will additionally be asked.

Data will be analysed using a Framework Analysis Approach[31] on transcripts produced verbatim from digital recordings. This matrix based approach involves identifying recurring themes based on a combination of a-priori issues, emergent themes and recurring attitudes and experiences. Transcripts will be independently coded by two persons, the assistant psychologist and CL.

METHODS 3: ECONOMIC EVALUATION.

An economic evaluation will be carried out from the perspective of health service and extended to include the societal perspective as far as possible. Primary data on costs and resource use will be collected prospectively alongside the trial. These data will inform a decision analytic model, to evaluate the most cost effective strategy for accessing partners. Where information exists on alternative feasible strategies these will also be included in the analysis.

Objectives: The aim of the economic evaluation is to determine the relative cost-effectiveness of the alternative methods of partner notification, Contract Referral and Provider Referral, compared to the baseline strategy of Patient Referral. The principal outcome for the evaluation will be the restricted outcome of Cost per Partner Treated. A preliminary outcome of Cost per Partner Notified will also be assessed. These economic outcomes are identical to those being used in the APT study discussed above.

Methods: In the first instance, the evaluation will consider costs incurred by the health service in the delivery of the alternative treatment pathways. A priori, there is no reason to expect the alternative referral methods to cause variation in the private costs to individuals between the arms of the study, so primary data on the private out of pocket costs to individuals associated with the study will not be collected. However primary data on such costs have been collected by the economic applicant as part of another study[32] and these data can be used as a proxy for the private costs in order that an evaluation from a wider societal perspective can also be undertaken.

Cost data collection
Data collection will be undertaken prospectively at all practices participating in the trial. The process of collecting resource use data will be undertaken separately from data collection on unit costs.

The main resource use to be monitored include the following:

1) The time required by the specialist health advisor to make contact with the partner/s.
2) Costs involved with the procedure including level of health care professional involvement in the procedure, administration, telephone calls, letters etc.
3) Any additional procedures required where initial contact is unsuccessful or incomplete.

Unit costs will be obtained and attached to resource items in order that a cost can be calculated for each partner notified or treated. Unit costs will be obtained published sources and centres participating in the trial. Published sources will include Unit Costs of Health and Social Care (Netten & Curtis, 2007) and NHS Reference costs and the primary costs collected as part of the ClaSS study by the current applicant[32].

Economic analysis
Given the objective of the trial, only a within trial economic analysis will be carried out based on the restricted outcome of Cost per Partner Treated. The evaluation will use the decision tree model which has already been developed to evaluate alternative partner notification methods in the ongoing "APT" study described above by this group (Roberts, Cassell and Estcourt). The "APT" economic model has already been extended to include other available strategies available in the literature[18]. The outcomes used in our existing model are identical to those proposed for the current study. The use of this model will facilitate a complete comparison of the expedited partner notification strategies which are already under evaluation with those of the proposed study.

The analysis will adopt an incremental approach in that data collection will concentrate on resource use and outcome differences between trial arms. As the majority of cost data are skewed, and the mean cost of each procedure is of importance, a bootstrapping approach will be undertaken in order to calculate confidence intervals around the mean costs. The recommended approach to discounting will be followed if necessary.

We will present results of all economic analyses using cost-effectiveness acceptability curves to reflect sampling variation and uncertainties in the appropriate threshold cost-effectiveness value where appropriate.
Uncertainty in the confidence to be placed on the results of the economic analysis will be explored by estimating. These plot the probability that the intervention is cost effective against threshold values for cost effectiveness. The robustness of the results will be explored using sensitivity analysis. This will explore uncertainties in the trial based data itself, the methods employed to analyse the data and the generalisability of the results to other settings.

Choice of economic model. We will focus on the restricted outcome of Cost per Case Treated, rather than modelling wider impacts, for a number of reasons. Cost per Case Treated is often seen as incomplete because there are likely to be wider costs and effects that could occur beyond the outcome, that could, if analysed, change the decision. For sexually transmitted diseases these wider costs and effects include the possibility of further transmission to other individuals by partners who are not treated or re-infection of partners and index cases from those not participating in the trial. Such effects are typically evaluated using a transmission dynamic model[32].

However it has recently been shown that currently available 'state of the art' transmission dynamic models produce differing results[33]. It cannot be assumed at the present time that any single model is sensitive or reliable enough to show population effects as a result of differences in success of partner notification. Furthermore, the further development and comparison of such models is the objective of a recently funded study by the NCCHTA on which White, Roberts and Cassell are coapplicants (Ref. 07/42/02), and we wish to avoid duplicating this work.

METHODS 4: MATHEMATICAL MODELLING OF THE IMPACT OF DIFFERENTIAL PARTNER NOTIFICATION OUTCOMES BY PARTNERSHIP TYPE AND SEXUAL ACTIVITY GROUP ON TRANSMISSION.

Aim. Mathematical modelling will be used in this study specifically to address the problem of right-skew in partner numbers, as requested in the commissioning brief.

Background and pilot work.

Right-skew in distribution of the number of partners in a population of individuals with STI means that rare individuals with many sexual partners (the "core group")[34], who form a small part of the population and are hard to sample, play a key role in the transmission of many STIs. This is particularly the case for gonorrhoea, which requires an average of 12 partners per year to be maintained in developed world populations[35]. By contrast, chlamydia only requires 4 partners per year for maintenance[35], and so chlamydia index patients are more likely, on average, than gonorrhoea patients to belong to a "dead end network" (where there is only one person with whom that patient can directly or indirectly communicate infection). Gonorrhoea is far less common in UK primary care, with only about 3.5% of all cases diagnosed in this setting[1].

The impact of different modes of partner notification on gonorrhoea cannot be directly observed in this trial in sufficient numbers to distinguish the outcomes of gonorrhoea patients from those with chlamydia, a commoner infection. However, mathematical modelling of the impact of the various modes of partner notification, and their varying degrees of success, in relation to *partnership types* will enable us to infer their cost-effectiveness in relation to partnership types. Specifically, it will enable rational decision making about the cost-effectiveness of contract/provider/patient referral, in relation to "highly connected partnerships" – i.e. casual partners and, to a lesser extent, ex-partners. This will apply both to gonorrhoea and chlamydia, since the parameters for their transmission are well established[35].

We therefore propose to complement the economic study with a focussed element of modelling, which will address the relative cost-effectiveness of the different modalities of partner notification, at different level of outcomes (especially primary outcome 1) for *different partnership types.*

Specific objectives of modelling substudy.

(i) To perform sensitivity analyses to provide estimates of the relative importance of specific partner notification rates for:
- people with different numbers of sexual partners (i.e. to deal with the right skew in number of partners), and
- different partnership types: i.e. current vs former partners, and long-term vs casual partners.

(ii) To enhance the outputs of the economic work on the costs and effectiveness of the three different approaches to partner notification (patient referral, contract referral and provider referral as defined in the protocol).

Methods:

We will build on the modelling work of White, Cassell et al [36], which explored the impact of delayed care on the transmission dynamics of gonorrhoea in the UK. Outputs of the new modelling work will be numbers of transmission events averted over a one-year time horizon, given various outcomes of partner notification for different partnership types.

Our model stratifies the population into "sexual activity groups", which include casual and regular partnerships, which can differ in duration, sex-act-frequency, condom use, and care seeking behaviour. Incorporation of parameters from the trial relating to the success or failure of partner notification will allow examination of the relative importance of partner notification in regular vs casual partners in terms of infections averted. The model can be configured to represent any sexually-transmitted infection, but in this study will concentrate on gonorrhoea and chlamydia.

A time horizon of 1 year will be used for all analyses, and the mathematical modelling team will work closely with economists on the collection of data, and analysis and interpretation of the outputs.

In accordance with NICE recommendations, uncertainty will be reported. We will distinguish uncertainty from different sources and report its impact on estimated Cost per Partner Treated, and Cost per Case Averted to a time horizon of 1 year. We will report (i) uncertainty in parameter estimates from this study (e.g. in rates of uptake of PN services, proportion of partners treated) and literature (e.g. in cost data, and sexual behaviour parameters estimated from Natsal); (ii) uncertainty due to details of model structure (which are being examined in HTA Project Ref 07/42/02); and (iii) uncertainty arising from the intrinsically stochastic nature of infection transmission.

The proposed modelling work will complement the empirical data from this study and assist in the economic analysis. It will also complement the a recently-funded HTA modelling study (Ref. 07/42/02, in which White, Roberts and Cassell are involved) by providing important novel parameter estimates for PN rates, but without duplicating this separately funded work.

Project co-ordination

The study team has established collaborations, but is geographically dispersed, and careful attention has been paid to management structures for this trial. The study will have one trial manager, based in London at the GPRF and focussing on national recruitment, and liaison with PRCN-Greater London. A research co-ordinator will be based at PCRN-South East (Brighton and Sussex Medical School). The South East co-ordinator will, in addition to core co-ordination duties, focus on enabling the study of patient related factors affecting outcomes. The London manager will focus the web based data collection system, including the facilitation of data collection for the economics and modelling substudies.

Expertise

Applicants: The applicants are experienced in multidisciplinary health services research in the field of sexual health, and have existing collaborations which will ensure the joint working necessary to bring a complex study of this kind to fruition. Cassell (PI) is a clinical epidemiologist, specialisting in STIs in primary care, who is accredited both in genitourinary medicine and in public health and has an excellent track record in achieving high quality outputs and prestigious grants in collaborative sexual health research. She is currently the Health Protection Agency's regional lead for HIV and STIs in the South East, a role which involves active epidemiological of the NCSP, while remaining an active clinician. Estcourt is PI for the "APT" study of accelerated partner notification, on which Cassell, Rait and Roberts are coinvestigators and is a respected leader in the field of partner notification. Symonds, a principal health adviser who is involved in the APT study in a service capacity, will offer invaluable advice as an expert in the partner notification based in an innovative department. Rait and Cassell have recently completed a study involving the development of a web based management and audit tool for STIs in primary care, and their experience in this study will be highly relevant to designing a user friendly data collection tool that supports the clinical practice being studied in this RCT. White and Cassell have worked together successfully in STI modelling work, which collected and used novel data in a routine setting. Richens has recently completed work on computer assisted history taking in sexual health, and his experience in this field will inform design of the web tool. Roberts is a senior health economist specialising in sexual health, who has worked on partner notification in the context of the HTA funded CLASS study of chlamydia screening. Dr Mary Macintosh is the Director of the NCSP will assist by avoiding conflicting priorities with this developing screening programme, and enabling collaboration. The study will be supported throughout by Copas, an experienced statistician who is jointly based in the MRC Clinical Trials Unit, and UCL's Centre for Sexual Health and HIV Research. We will commission advice from Anatole Menon-Johansson on the technological and practical aspects of modern communication methods in the GUM clinic setting, as he has published in this area and his experience complements that of the applicants.

Primary care networks: The recruitment and management of this trial will benefit from synergy between the nationally dispersed recruitment of diverse practices via the *MRC General Practice Research Framework*, and the geographic focus possible through the *London and South East Primary Care Research Networks*.

This combined PCRN/GPRF model has been chosen for several reasons. Firstly, it will enable us to recruit both sexual health experienced and naive practices for the RCT. Research-experienced practices, in the GPRF are likely to take part in order to maintain their research infrastructure, despite no in-practice sexual health "champion". This is important in achieving a spread of practices relevant to "real life", because many practices with an interest in sexual health are currently negotiating "locally enhanced service", yet from a public health perspective the majority of patients who will continue to attend non-specialist practices which cannot provide partner notification support are the main focus of this study. Secondly, dispersion of practices it will limit the potential for intervention contamination between differently cluster randomised practices within localities. This would be a major risk, were we to recruit only through local PCRNs in a limited number of localities, since local initiatives for sexual health would bring participating clinical staff into regular contact, and "contaminate" the partner notification practice required for the trial. Finally, we will enhance opportunities to study local health

service effects and implications, and increase the efficiency of our studies of patient related factors by having a small number of our practices clustered together in PCRN based localities.
The established expertise of the MRC GPRF in successfully conducting large national studies, and in technical aspects of trial management (including web based data collection), will provide efficiency benefits for the study, along with capacity development benefits for the PCRNs.

Project timetable and milestones
In November 2010, analysis of pilot data and experience of trial processes will inform revision of trial documentation and procedures. The database will be closed by the end of December 2012, and analysis of RCT data will start immediately afterwards. However, economic and modelling work will be able to commence before data collection is complete.

Supervision arrangements
The co-investigators are all senior researchers or senior clinicians in the field of sexual health research. Estcourt and Symonds will supervise research health adviser activity in providing patient, provider and contract referral support for patients. Cassell, Rait and Smith will focus on supervision of the trial co-ordinators, and on co-ordination between the substudies and the main RCT, taking advice from other investigators as appropriate. Copas will supervise a junior statistician for trial analysis, White will supervise the modelling work, and Roberts will supervise Tsourapas in the modelling work.

Justification of support (including NHS support costs)
The support we seek for this trial aims to balance a need to contain costs, with the need to ensure through active case finding that the aims of the trial can be achieved. As discussed above, we have amended our original proposal to include active invitations to young people eligible for the NCSP to screen at the practice for chlamydia, with only a small increase in budget from the original proposal. This invitation to patients, and their recruitment at the time of attendance for screening forms a major element of our service support costs, and one which we consider to be justified in the light of failures to recruit in related studies at the time of an STI diagnosis. Costs have been estimated in accordance with MRC GPRF normal practice, but where appropriate these may be transferred to the two PCRNs involved.

The lead investigators will supervise junior staff, and this is reflected in the balance between the cost of investigator time and directly incurred staff costs. We will employ two full-time nurse-trained study co-ordinators, both with general recruitment responsibilities but also with the specific responsibilities for facilitating substudies which are described above. They will undertake close monitoring of recruitment rates, of which a major driver will be chlamydia testing rates which will be checked weekly. Both co-ordinators will require some administrative support, and this will be greater at the GPRF centre which will take lead responsibility for the development and provision of practice training materials. Administrative support will be 1.0 FTE at the GPRF, and 0.6FTE at PCRN-SE.

1.5 WTE research health adviser time is required for the duration of the trial, to assist partner notification for 3300 patients over 2 years and to collect clinical outcome data. Symonds will supervise these staff, and 0.1 WTE of his time is requested for this purpose, and for development work in the early stages of the study.

We request £51,000 at 2008 prices for a web-based data collection tool meeting NHS data protection standards, which will be commissioned based on GPRF experience with the IID2 study of infectious intestinal disease, also using the applicants' experience on other studies as described above) to ensure it collects data adequately in an acceptable and user friendly way, and supports clinical practice in accordance with the protocol. If successful, it could be used as an aid to clinical practice, and we will ensure that we take advice at an early stage on the appropriate intellectual property rights. Costs of £99,000 are requested for follow up chlamydia tests using posted samples, as currently used in many parts of the country for a proportion of chlamydia screening.

Computers will be required for research assistants, with study specific software for the statistician and psychologist.

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