Electronically delivered, multi-component intervention to reduce unnecessary antibiotic prescribing in primary care. Cluster randomised trial using electronic health records (eCRT2)

Summary of Research

Design: Cluster randomised trial using the electronic health records (EHRs) of the Clinical Practice Research Datalink (CPRD).

Setting: General practices in England, Scotland, Wales and Northern Ireland.

Target population: General population of all ages.

Inclusion Criteria: All persons currently registered with participating CPRD general practices. Exclusions: none.

Health technology being assessed: There will be two trial arms. The Control trial arm practices will continue with usual clinical care. Practices in the Intervention trial arm will receive complex multi-component interventions, delivered remotely, as follows: i) feedback of each practice's antibiotic prescribing results in relation to peers, through monthly updated antibiotic prescribing reports estimated from CPRD data; ii) delivery of educational and decision support tools to support policies of no-antibiotic prescribing or delayed prescribing; iii) 'three minute webinars' to explain and promote effective utilisation of the intervention materials. The intervention will continue for 12 months.

Measurement of costs and outcomes: Outcomes will be evaluated from CPRD EHRs. The primary outcome will be the number of antibiotic prescriptions for RTI per 1,000 patient years. Secondary outcomes will be: the RTI consultation rate; the proportion of consultations for respiratory tract infection (RTI) with an antibiotic prescribed; sub-groups of age; different categories of respiratory infections; and quartiles of intervention utilisation. Safety outcomes will be diagnoses of pneumonia and lower respiratory tract infection, peritonsillar abscess, mastoiditis, skin infections and bacterial infections. Total health care utilisation will be estimated from CPRD data, using methods reported previously, and compared between trial arms.

Sample size calculation: The 120 trial practices may include more than 1.2 million individual participants, allowing very precise estimation of cluster-level statistics. Family practice-specific proportions will be included in a cluster-level analysis, adjusting for pre-intervention values. In eCRT the mean antibiotic prescribing rate for RTI was 112 per 1,000 (SD 39.8). Using analysis of covariance, with measures over 12 months before- and after- the intervention giving a correlation coefficient of 0.82, if there are 60 practices in each of two trial arms then, with alpha=0.05, there will be more than 80% power to detect an absolute reduction in antibiotic prescription for RTI of 12 per 1,000 registered patient years.

Project recruitment rate: During the first 12 months, we will refine the study intervention drawing on behaviour-change theory, systematic review evidence, clinical guidelines, qualitative research with non-trial practices, as well as process evaluation data from the eCRT study. General practices will be recruited and allocated. In eCRT, 100 CPRD general practices were recruited over 6 months. During the second year of the project, the intervention will be active. Each month, updated practice-specific prescribing information will be delivered to intervention practices. This will enable them to gauge their prescribing activity in relation to recommended standards, as well as in relation to their peers in CPRD. Prescribing decisions will also be supported by educational and decision-support tools delivered remotely through practices systems. Webinars will be delivered.

Expertise in team: The team has multi-disciplinary expertise in epidemiology, medical statistics, health psychology and primary care research applied to antibiotic prescribing in primary care. The team has methodological experience in CPRD data analysis, cluster trial design and analysis using CPRD, as well as complex intervention development and implementation.

Background and Rationale

Wider context

This research is proposed in response to the NIHR call for proposals on antimicrobial drug resistance. Antibiotic drug resistance is a growing problem that transcends national boundaries. Governments of all countries need to adopt a stewardship role so as to ensure that effective antimicrobial drugs are available to future generations (Annual Report of the Chief Medical Officer, 2013). This should include responding to the requirement to improve governance and standards of clinical practice with respect to antimicrobial drug utilisation. The present research addresses a subject of great public health importance because over-utilisation of antibiotics contributes to emergence of antimicrobial drug resistance and consequently infections that may be very difficult to treat. The UK Antimicrobial Resistance Strategy (Department of Health, 2013) identified education and training to reduce inappropriate and unnecessary antibiotic use as key measures to fight antimicrobial drug resistance. This research specifically aims to address the problem of inappropriate and unnecessary prescribing of antibiotics to patients with respiratory tract infections (RTIs) in primary care.

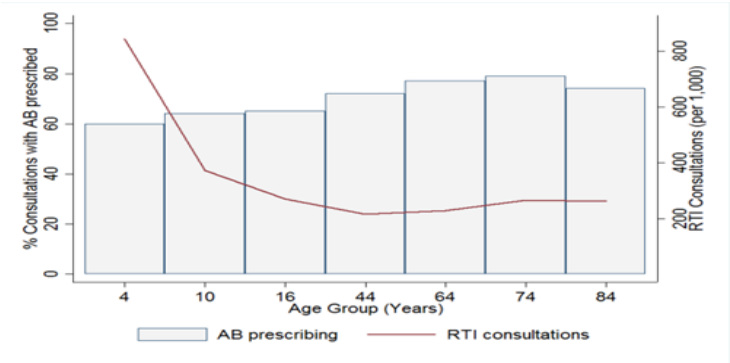


Figure 1: Age-specific consultation rates for respiratory tract infections and proportion of RTI consultations with antibiotics prescribed in CPRD, 2000. Source: Ashworth et al. (2006).

Respiratory tract infections in primary care

Respiratory tract infections (RTI) infections including colds, sore throats, cough, bronchitis, rhino-sinusitis and otitis media represent common reasons for consultation with a general practitioner (NICE 2008), with about 200 consultations for respiratory tract infections per 1,000 registered patients in primary care (Gulliford et al., 2009). Antibiotics are commonly prescribed to patients consulting with RTIs, accounting for about 60% of all antibiotics prescribed in primary care (NICE, 2008). There are substantial age-related differences in consultations for RTI, with children under five having extremely high consultation rates (Figure 1, Ashworth et al. 2006). Antibiotic prescribing for RTI generally increases with age (Figure 1) (Fossum et al. 2013).

Most respiratory infections are self-limiting without specific treatment (Little et al., 1997). Antibiotic treatment generally offers minimal benefit in terms of duration and severity of symptoms (Del Mar et al., 2006) but may be associated with side effects such as diarrhoea or rashes. Patients prescribed antibiotics are more likely to believe that this is an effective treatment and are more likely to consult in future (Little et al., 1997). The small minority of individuals who may benefit from antibiotics can be positively identified through indicators of severity of illness or comorbidity. Patterns of microbial colonisation begin to change soon after antibiotics are started (Dagan et al, 1998), leading to the emergence of drug-resistant organisms.

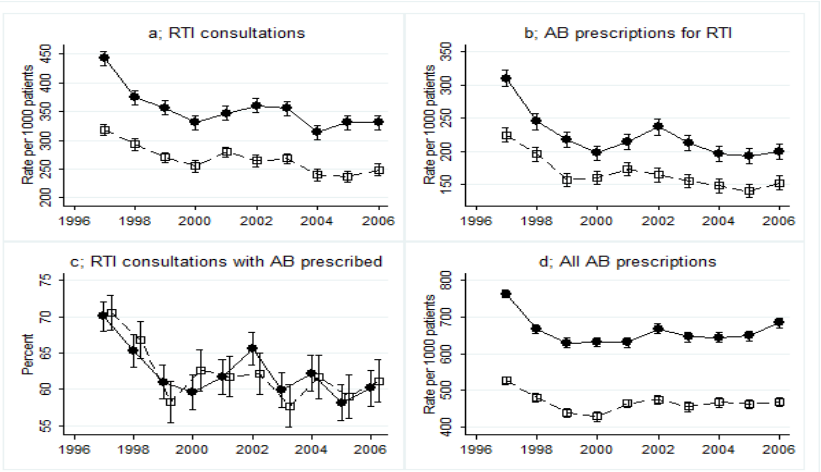


Figure 2: Data from CPRD for RTI consultations and antibiotic prescriptions from 1996 to 2006. Source: Gulliford et al. (2009).

Databases of primary care electronic health records, such as the Clinical Practice Research Datalink (CPRD), provide an important resource for understanding the epidemiology and public health impact of respiratory infections and antibiotic prescribing in primary care. Our research using CPRD showed that there has been a long-term decline in consultation for respiratory infections (Figure 2, Gulliford et al, 2009). During the 1990s, there was some reduction in the proportion of consultations at which antibiotics are prescribed, following the publication of the SMAC report, *Path of Least Resistance,* but there has been little change in antibiotic prescribing for RTIs since 2000 (Figure 2).

Table 1: Proportion (%) of consultations with antibiotic prescribed. Median (interquartile range) for 102 CPRD general practices in 2012-13.(eCRT study data 08_083).

Condition	% consultations with antibiotics prescribed
Colds	36 (3 to 81)
Cough and bronchitis	47 (10 to 73)
Otitis media	58 (0 to 96)
Rhino-sinusitis	90 (54 to 100)
Sore throat	57 (27 to 83)

Recent CPRD analyses for 2012, from the eCRT trial, showed that antibiotics are prescribed for about one third of consultations with common colds, more than half of consultations with sore throat or otitis media, and about 90% of consultations with sinusitis (Table 1). In the context of treatment recommendations that advise that most acute respiratory infections can be managed without antibiotics, these data clearly indicate an opportunity to make a major impact on unnecessary antibiotic prescribing.

There are striking variations between general practices in rates of consultation and antibiotic prescribing for RTI (Figure 3). The rate of antibiotic prescribing per 1,000 registered patients is always less than the consultation rate for RTI, consistent with an overall prescribing proportion of between 50% and 60%. In CPRD, less than 1% of general practices prescribe antibiotics at fewer than 20% of RTI consultations, while other general practices prescribe antibiotics at more than 80% of RTI consultations; 89% of general practices prescribe antibiotics at more than 40% of RTI consultations. Most general practices will be unaware of their pattern of antibiotic prescribing for particular indications, and its standing in relation to their peers, with only aggregated data being generally available for performance management.

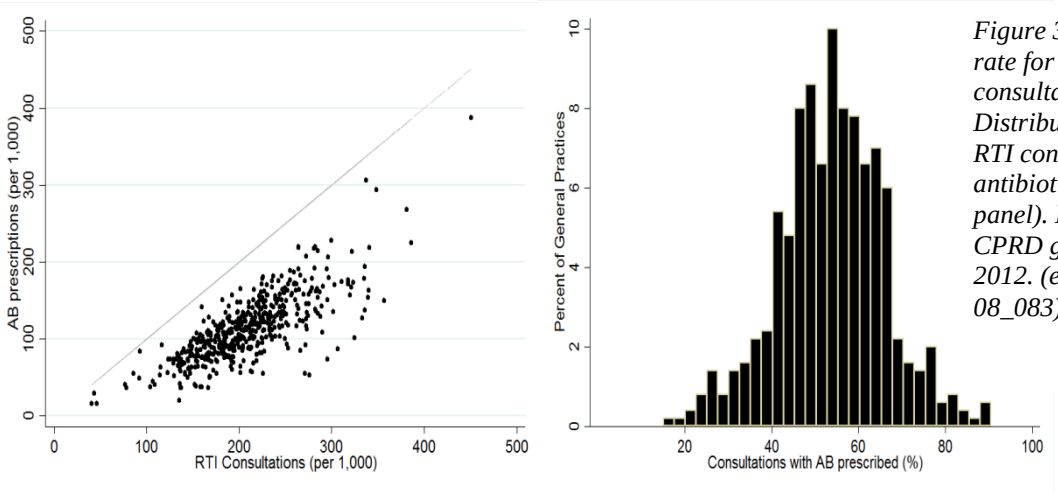


Figure 3: Antibiotic prescribing rate for RTI plotted against RTI consultation rate (left panel). Distribution for proportion of RTI consultations with antibiotic prescribed (right panel). Data are for 500 UK CPRD general practices in 2012. (eCRT Trial data 08_083).

Linder (2013) observed that nearly all general practices are currently prescribing antibiotics at rates that are 'way off the mark' in the context of good practice recommendations, which advise that most RTIs can be managed without the prescription of antibiotics (NICE, 2008). Based on this guidance, most practices might optimally be prescribing antibiotics at fewer than 20% of RTI consultations. These CPRD data suggest that considerable reductions in antibiotic utilisation for RTI are necessary in UK primary care. This raises a question concerning how reductions in antibiotic prescribing can be achieved?

Evidence from previous trials and systematic reviews

Strategies to reduce unnecessary antibiotic prescribing have been tested in a number of previous randomised controlled trials. Ranji et al., (2006 and 2008) performed a systematic review up to 2007. In 30 trials contributing to a quantitative analysis, Ranji et al. found a median reduction in the proportion of participants receiving antibiotics of 9.7% (interquartile range 6.6% to 13.7%). Most studies employed educational activities aimed at clinicians or patients, or audit of antibiotic prescribing with feedback of results, or a combination of these interventions. More recent trials have demonstrated similar reductions in antibiotic utilisation (Table 2), with reduction in antibiotic prescribing of up to 15% in the GRACE trial. These recent trials have used similar intervention strategies but have more frequently used electronic media to deliver advice on appropriate prescribing (Little et al. 2013; Hoye et al. 2013).

Table 2: Results of selected recent trials to reduce unnecessary antibiotic prescribing.

Trial	Setting	Intervention	Effect
Little (2013) (GRACE)	EU	Training in communication skills / CRP testing	9% - 15% reduction in AB prescriptions
Gerber (2013)	US	Education, audit and feedback	6.7% net reduction in antibiotic prescribing.
Gonzales (2013)	US	Education, audit and feedback, electronic decision support	~12 % net reduction in antibiotic prescribing
Gjelstrad (2013)	Norway	Education, audit and feedback	1.3% reduction in antibiotic prescribing
Butler (2012)	UK	Education, audit and feedback	4.2% net reduction

Systematic reviews of the wider implementation science literature are also informative in identifying features of audit and feedback or decision support that are associated with greater intervention effects. Ivers et al. (2012) found that feedback was more effective when performance is suboptimal, when feedback is given in written and verbal formats, and when explicit targets and actions are recommended. Roshanov et al. (2013) found that clinical decision support systems were more likely to be effective when these required active measures

before they could be over-ridden, or if patient information was provided in addition to clinician information.

eCRT study

The systematic review and recent trials are important in identifying strategies that may be effective at changing prescribers' behaviour. However, previous trials required resource intensive interventions and these intervention techniques have not yet been translated on a wide, and sustainable, scale into the NHS. For example, the trial by Gonzales et al (2013) required clinicians to participate in a half day training session; triage nurses provided patients with education leaflets to read before their consultation; a specially-designed structured template was programmed into the practice system to provide an algorithm-based probability of the patient having pneumonia; 'order sets' were created to group diagnosis and treatment options for different types of RTI. The challenge now is to take the components of intervention that have been shown to be effective and to find methods to deploy these efficiently into routine practice settings.

Our group recently completed a trial (eCRT) in which general practices that contribute electronic health records to a national primary care database, the Clinical Practice Research Datalink (CPRD) were randomised (Gulliford et al., 2011). The study included 104 general practices in England and Scotland. Decision support tools were delivered remotely to general practices. The effectiveness of the intervention was evaluated by analysing electronic health records that are routinely collected into the database. Data were analysed for more than 600,000 individual participants, with a financial cost of about 27 pence per participant (data reported at an NIHR Workshop on Routine Data, 5th September 2013). Even with a very simple intervention, the trial showed a near 2% reduction in antibiotic prescribing. This study showed that it was feasible to use the CPRD to evaluate interventions that may be readily scaled up to the population level. Feedback received in the eCRT process evaluation, together with evidence from other trials cited above, identifies ways to increase engagement in the intervention and increase effect sizes.

Evidence explaining why this research is needed now

The recent systematic review, together with the additional more recent trials, show that interventions to modify prescribing behaviour in primary care can be effective. However, there is a block in the translational pathway because it has not been possible to roll-out this evidence into routine practice; antibiotic prescribing for RTI remains high outside of trial settings. There is a lack of effective interventions that can easily be translated, in a sustained way, into routine practice settings. This proposal aims to use the strengths of electronic health records (EHRs) to inform, deliver and evaluate an intervention. This will be achieved with a high degree of efficiency by employing as the research environment a database of EHRs, CPRD.

This research is at a later stage of translation than previous trials. In order to overcome the block in the translational pathway, there is a now need to develop and evaluate more effective complex multi-component interventions that can be implemented, and delivered remotely. Development of the interventions will be informed by evidence from recent trials, as well the process evaluation of the eCRT study. The research will focus on interventions that can be readily scaled up, through remote delivery using electronic media, to large samples of unselected practices. The present proposal builds on previous experience of implementing the eCRT trial within CPRD. In eCRT, the intervention was an educational and decision support tool (McDermott et al. 2010) that aimed to support evidence-based antibiotic prescribing for

respiratory illness in primary care. The intervention was installed remotely at practices and utilisation of the intervention was monitored.

The approach of utilising the electronic health records of CPRD to provide the environment for delivering and testing the interventions has several advantages: i) Both the interventions, and a cluster randomised trial of the interventions, can be implemented at very low cost; ii) the sample available for study is nationally representative for the United Kingdom and large sample sizes are expected; iii) the sustainability of the effect of the intervention may be evaluated after the end of the trial, because data continue to be collected from trial practices; iv) utilisation of the intervention can be routinely monitored through electronic information routinely collected into EHRs; v) a cost-effectiveness analysis may be implemented using data on health care utilisation that are collected for all patients in CPRD (Gulliford et al., 2013); vi) translation of the trial results is readily feasible because the interventions are delivered using the practice systems that are employed in delivering routine care within the NHS.

Aims and objectives

Aim: To test the effectiveness, in a cluster randomised controlled trial, of electronically delivered, multi-component interventions to reduce unnecessary antibiotic prescribing when patients consult for respiratory tract infections (RTI) in primary care.

Specific Objectives are to:
1. develop, refine and implement complex multi-component but low-cost interventions to influence general practitioners' prescribing of antibiotics when patients consult with respiratory tract infections. The intervention will comprise:
i) feedback of monthly updated antibiotic prescribing information from CPRD as a major novel component,
ii) educational and decision support tools that include a summary of antibiotic prescribing recommendations, a summary of research evidence concerning no-antibiotic antibiotic prescribing strategies, information on the definite indications for antibiotic prescription, information and evidence on the risks from non-prescribing and patient information;
iii) and three minute web-based training (webinars) to promote effective utilisation of the intervention materials.
2. recruit 120 CPRD general practices and allocate them to Intervention and Control trial arms using minimisation, stratifying for region and baseline antibiotic prescribing quartile;
3. deliver the intervention electronically into intervention general practices;
4. update intervention information monthly during the 12 month intervention period;
5. estimate the difference between intervention and control practices in primary outcome (antibiotic prescription rate per 1,000 patients) and secondary outcomes (proportion of RTI consultations with antibiotic prescribed, RTI consultations, subgroups of age, infection type and intervention utilisation, safety outcomes and costs of health care utilisation), in an intention to treat analysis using the general practice-specific proportions as observations, adjusting for baseline prescribing and age and sex.
6. communicate the study findings to key audiences, and deliver impact within the National Health Service, by translating the research into routine clinical practice in all parts of the UK.

Research Plan

Design

This will be a two-arm cluster randomised trial with general practices as the unit of allocation. CPRD general practices will be allocated to intervention and control trial arms. A multi-component intervention will be delivered electronically to general practices in the intervention trial arms. The implementation of the trial interventions will continue for 12 months. Trial outcomes will be evaluated, with a repeated before- and after- cross-sectional sampling design, using the electronic health records of individual patients registered at trial general practices. Mixed methods will be used for intervention development and process evaluation of the intervention.

Theoretical framework

The research will draw on the framework that we used previously (McDermott et al., 2010). This identified theoretical components that relate directly to effective implementation in healthcare settings. We identified aspects of social cognitive theory (Bandura, 1977) and self-determination theory (Deci and Ryan, 1980) as possible influences on GP prescribing behaviour.

Social cognitive theory proposes that the environment plays a key role in influencing an individual's behaviour (Bandura, 1977). An individual's belief in their ability to exercise control over their environment is one of the most important mechanisms involved in successful behaviour change (Bandura, 2001). If an individual perceives their environment to be controllable and supportive, they will be more likely to succeed in performing the desired behaviour (Bandura, 1991). In the present research, this suggests that interventions which are embedded into the consultation environment and become active during the flow of care are more likely to succeed. Social cognitive theory also proposes that the strength of an individual's belief in his/her own ability to reach goals (that is, their self-efficacy) functions as a key determinant of motivation for a specific behaviour (Bandura, 1977). GPs' self-efficacy has also been implicated as a predictor of intended adherence to recommendations for prescribing (Eccles et al., 2007; Hrisos et al., 2008). Social cognitive theory also suggests that anticipated outcomes or 'outcome expectancies' of a behaviour influence the likelihood that it will be performed. Outcome expectancies relevant to prescribing decisions might include anticipated patient pressure (Little et al., 2004) or beliefs about risks and benefits associated with characteristics of a disease (Rashidian et al., 2008).

Qualitative interviews in our development study (McDermott et al., 2010) also identified views which were consistent with self-determination theory (Deci and Ryan, 1980). The theory proposes that behaviour change will occur and persist if it is autonomously motivated, in contrast to behaviour change which is brought about by perceived enforcement. GPs reported for example, that they would be unlikely to engage with an intervention which they were forced to view or which they felt was attempting to control their behaviour, but in contrast would be more inclined to engage with an intervention which they felt was there to support and aid them.

Our approach to developing the intervention aims to create a controllable and supportive environment, increases self-efficacy, promote expectations of positive outcomes, while reducing perceived negative risks, in order to support better GP adherence to prescribing recommendations (McDermott et al., 2010).

We will conduct systematic intervention planning to ensure that all relevant GP behaviours and influences on them are addressed by appropriate theory and evidence based behaviour change techniques within the intervention. The systematic intervention planning process will be guided by the behaviour change taxonomy identified by Michie et al (2013). This process will ensure that each component of the intervention contains appropriate behaviour change techniques to address barriers and promote the facilitators to reducing unnecessary antibiotic prescribing.

Health technologies being assessed

In the current standard care pathway, patients attending their general practice with acute respiratory tract infections are prescribed antibiotics at the discretion of their general practitioner. In the Control trial arm, therefore, there will be no difference from current standard clinical care

In the Intervention trial arm, patients attending their general practice with acute respiratory tract infections will continue to be prescribed antibiotics at the discretion of their general practitioner. However, the general practitioner's decision will be informed by the study interventions as outlined below. The interventions are designed to reduce general practitioners' unnecessary prescribing of antibiotics in consultations for respiratory tract infection.

Intervention trial arm:

The intervention will comprise three elements:

i) *feedback of each practice's antibiotic prescribing results in relation to recommended standards and peers in CPRD, through monthly updated antibiotic prescribing reports estimated from CPRD data.*

General practices already receive aggregated data reports on prescribing from the NHS Business Services Authority. Utilising data from CPRD will add considerable detail linking prescribing of antibiotics to clinical indications for the prescription, as well as enabling comparisons by case mix categories including age group, gender and comorbidity status.

Analyses of antibiotic prescribing for respiratory infection will draw on our previous analyses in CPRD (Gulliford et al., 2009). Data will be analysed for each practice in the intervention trial arm, using as comparators as all CPRD general practices (please see Figure 3 above). For each monthly CPRD release, we will be able to report on the total number of RTI consultations, as well as the total number of antibiotic prescriptions issued for RTI. We will also report on total antibiotic prescribing for all indications at the practice. Data will also be reported for five groups of respiratory conditions (colds, sore throats, cough and bronchitis, otitis media and rhino-sinusitis, following NICE, 2008) and for gender and broad age groups including children, adults and older adults. Reporting according to important co-morbidities including chronic respiratory disease, diabetes and cardiovascular disease will be included. By using the CPRD staff-id, we have the potential to disaggregate fully anonymised data to the level of the individual prescriber.

The rate of consultation for RTI exceeds 200 per 1,000 patients, so an average practice may have more than one thousand RTI consultations per year. This indicates that there will be sufficient data for informative feedback. In order to reduce the possibility of deductive disclosure, cell frequencies smaller than five will not be reported. Moving averages may be used where appropriate.

We will consult with experts and stakeholders, as well as implementing qualitative research with prescribers as outlined below, in order to frame the specific messages to be included in the prescribing report. This will include taking a view on whether practices should be encouraged to make an absolute reduction in antibiotic prescribing for RTI, or to achieve a relative reduction with reference to baseline prescribing, or to achieve reductions in relation to their peers in CPRD. These messages may offer differing motivations to different groups of prescribers, yet even those practices that are presently low prescribers of antibiotics may be able to considerably reduce their prescribing.

Practice prescribing reports will be professionally designed. They will draw attention to trends over time at the index practice and comparisons between the index practice and the wider population of CPRD practices. Prescribing reports will be delivered into practices via the DXS Point-of-Care (DXS-POC) system as well by email, through a secure link, as outlined below. The number of accesses of the practice's prescribing report will be monitored and practices will be contacted if the report is not accessed.

ii) *delivery of educational and decision support tools to support policies of no or delayed antibiotic prescribing*. The tools will provide information for education and decision support including a summary of antibiotic prescribing recommendations, a one-side patient information sheet, a summary of research evidence concerning no antibiotic or delayed antibiotic prescribing strategies, information on the definite indications for antibiotic prescription, as well as information and evidence on the risks from non-prescribing. Links to these tools will appear on an initial menu screen, allowing the GP to then select and view the screen of their choice. The support tools will include separate modules for sore throat, cough and bronchitis, otitis media, rhino-sinusitis, and common colds. The decision support tools will be delivered into individual consultations at trial practices by means of alerts in DXS-POC. In addition, prescribers at intervention trial arm practices will be enabled to access an internet-based version of the decision support tools at any time, with a link provided as part of the prescribing report. Finally, a professionally-designed hard copy of the decision support tools will be developed.

iii) *motivational three minute video linked webinar to promote utilisation of the intervention;* The behaviour change required to bring about a reduction in antibiotic prescribing is simple but the processes required to achieve this may be complex. The webinar will enable brief communications with GPs at intervention trial arm practices. The webinar will be delivered by a practising GP from the study team. The design of the webinar will draw on reported experience from the GRACE and STAR trials. This will:

- state the importance of behaviour change, drawing on recent news items. For example, the Chief Medical Officer referred to antibiotic resistance as a 'catastrophic threat' that is 'as big a risk as terrorism';
- remind GPs of current prescribing recommendations for RTIs based on NICE guidance (2008);
- illustrate patterns of antibiotic prescribing for RTI in CPRD general practices, this part of the webinar will be specifically tailored to practices in different prescribing quartiles;
- emphasise communication strategies that can be used to present alternatives to an antibiotic prescription, including patient information included in the decision support tools;
- demonstrate to GPs the decision support tools including evidence to inform a no or delayed prescribing strategy and the positive indications for prescribing antibiotics.

Intervention development, design and delivery

We will draw on our previous experience to develop the interventions (McDermott et al., 2010). At the start of the project we will develop, prototype versions of the intervention tools including the prescribing report, the decision support tools and the webinar. The development of the prescribing report will draw on our previous CPRD data analyses for eCRT. These will be brought up to date through new analyses using CPRD data for registered patients of all ages, with data up to 2014. CPRD analyses will estimate three main measures: the consultation rate for RTI; the rate of antibiotic prescribing for RTI; and the proportion of RTI consultations with antibiotics prescribed. Estimates will be derived by age group, gender and sub-groups of RTI as outlined above. CPRD derived estimates will be embedded in a professionally-designed prototype version of the prescribing report.

The decision support tools will derive from the experience of developing and evaluating a set of decision support tools for eCRT. A series of pages will be designed to promote adherence to antibiotic prescribing recommendations in accordance with the NICE (2008) guidelines (promoting no antibiotic prescribing, or delayed antibiotic prescribing, instead of the immediate prescription of antibiotics where appropriate for RTI). These will draw on aspects of Social Cognitive Theory (Bandura, 1997) including, environment, outcome expectancies, and self-efficacy, as outlined above. Messages will be designed to provide a controllable and supportive environment, promote positive outcome expectancies and increase self-efficacy. The pages will be triggered to appear on the GP's computer screen during a consultation for RTI. The pages will offer a range of functions and options for GPs to select. The GP can therefore control whether any information appears, and the specific information which will be presented. All functions will be supportive in terms of the messages and information to help the GP follow the guideline behaviour. Outcome expectancies will be addressed in the RTI prompts by presenting evidence that severity and duration of illness, as well as the risk of further complications, would not generally be increased by withholding an antibiotic prescription. Outcomes relating to concerns about patient expectations for antibiotics will be addressed by presenting evidence suggesting that patients not prescribed antibiotics may be less likely to re-consult and believe antibiotics to be effective in future.

Preliminary research with non-study practices will inform the development of the intervention including the content, format and design of the prescribing reports, decision support tools and the webinar. Semi-structured interviews will be held with prescribers at non-study general practices, using prototype versions of the interventions, to identify factors likely to influence successful implementation of the interventions and discover likely responses to the proposed messages, in order to further inform the final versions of the intervention tools. Participating GP's will be asked questions regarding their views, expectations, acceptability and feasibility of the intervention tools. Semi-structured interviews will be conducted after showing GPs prototype versions of the interventions. 'Think-aloud' interviews will be conducted to study reactions to the interventions. GPs will be asked to explore and try out the features of the prompts freely as they would if the messages had appeared during a consultation and say aloud what they were thinking and feeling about each feature. GPs will also be prompted to reveal which features were most/least useful or acceptable and why. The final versions of the intervention tools will be developed through the services of a professional design consultant.

The delivery of the interventions into practices will be through DXS Point-of-Care, supported by additional email, internet and hard-copy communications. 'Pop-ups' will be programmed to present clinicians with a concise message with several possible actions. The concise

message is intended as a 'lead-in' to more detailed material. The trigger for the 'pop-up' is the entry of one or more specific conditions in the patient record; in this study these will be Read codes for acute respiratory infections. In addition, we will trigger information delivery at given dates and times to ensure the intervention is delivered irrespective of diagnosis code. The user must interact with the 'pop-up' dialog in order to proceed. In addition, pop-ups will be configured to activate at the first entry of any code (as opposed to a specific one) and can also be timed to come into effect at a future date. DXS Point-of-Care will gather information that will be used to monitor intervention utilisation including the specific user who saw the message as well as how they interacted with it. We have budgeted to receive quarterly monitoring reports on intervention utilisation.

Patient and Public Involvement

We have engaged with a primary care patient participation group (in Lewisham, South London). The trial procedure and proposed intervention were presented to the group and feedback and views were obtained on all aspects of the intervention including the way in which messages would appear on GP screens, and information which would be presented to patients (such as patient information sheets). A member of this patient participation group will continue in an advisory role throughout the trial, by attending steering committee meetings every 6 months and providing feedback on all aspects of the study. We are also able to access public and patient involvement (PPI) advice through the NIHR Biomedical Research Centre at Guy's and St Thomas' Hospital. The BRC PPI programme manager will engage in the project in order to facilitate public and patient input.

Approval by ethics committees

The protocol for the research will be submitted to the MHRA Independent Scientific Advisory Committee, which is responsible for reviewing all proposed research in CPRD.

The protocols for intervention development (qualitative research) and the trial will be submitted to a local NHS research ethics committee early in the first year of the project. We anticipate that the trial will be given research ethics approval on the basis of a draft version of the intervention. The final form of the intervention will be approved through a subsequent amendment if necessary.

Informed consent to participation in the study will be requested from a senior partner at eligible CPRD general practices. The rationale for consent at the cluster level is that the intervention will be implemented for the whole cluster, through implementation of the intervention into the general practice software system, with the practice staff being the intended recipients of the intervention (Hutton, 2001). Individual patient health record data will be analysed to evaluate trial outcomes but the ethical issues associated with this data collection and analysis are covered by the overarching governance framework of CPRD. Weijer et al. (2012) propose that in trials of the present type, individual patients should not be regarded research participants because all treatment decisions remain the responsibility of the health professionals and are not determined by the trial allocation.

CPRD general practices participate in the database on the basis of anonymity. For this reason, all communications with practices will be through CPRD and the trial research team will not have any direct contact with the trial practices. However, the consent form for the study will include explicit consent for the practice to be identified to the intervention provider in order to allow activation of the intervention, as outlined above, in the event that the practice was allocated to the intervention trial arm. The consent form will also include an item to request

permission for the practice to be contacted by the research team for a qualitative interview for the process evaluation of the intervention.

As the location of CPRD practices is not generally made available to researchers, we aim to obtain approvals from all NHS primary care organisations in England, Scotland, Wales and Northern Ireland. In England and Scotland, approvals will be obtained through the NIHR Coordinated System for gaining NHS Permission (CSP) and NHS Research Scotland Permissions Coordinating Centre (NRSPCC) respectively, which facilitate the approval process at each local primary care organisation or health board (Scotland). In Wales and Northern Ireland approvals will be obtained from each health board. This process was implemented successfully for the eCRT trial, for which 149 English primary care trusts gave approval, while 10 declined, and all 10 Scottish health boards approached gave approval. (Scottish Health Boards that do not use the VISION practice system used by CPRD general practices were not approached). In a second CPRD cluster trial, all seven Welsh health boards gave approvals (Gulliford et al., submitted). We expect research governance approvals to be completed during the first year of the project.

Target population

The target population for this trial is the general population registered with general practices in the United Kingdom, including England, Scotland, Wales and Northern Ireland. The immediate participants in the research are health professionals who may issue prescriptions for antibiotics at United Kingdom general practices. Outcomes will be evaluated using the anonymised electronic health records for individual patients registered with UK general practices who may consult with respiratory tract infections and receive antibiotic prescriptions.

Inclusion/Exclusion Criteria

General practices will be included in the trial if they presently contribute up-to-standard data to CPRD, consent to participation in the trial, and are located in areas that have given research governance approval for the study. Data for non-trial CPRD practices will be eligible for observational data analysis to gauge the representativeness of practices and patients participating in the trial. Data for individual participants will be included if they are currently registered with CPRD general practices. There will be no other exclusion criteria.

Setting and Context

The Clinical Practice Research Datalink (CPRD) will provide the sampling frame and data source for this research. CPRD includes general practices in all parts of the UK. The CPRD registered population has a similar demographic distribution to the UK general population. The previous eCRT cluster trials included general practices in England, Scotland and Wales, the latter being included in a trial of stroke secondary prevention, this proposed study aims to include Northern Ireland practices in addition.

Sampling of research sites and individual participants

We will aim to obtain NHS research governance approvals from all primary care organisations in England, Wales, Scotland and Northern Ireland, as outlined in the section on research ethics. In order to preserve practices' anonymity, recruitment will be through the offices of CPRD. We will then send an invitation pack, including a letter, consent form and information sheet, to all CPRD general practices that are located in areas where research governance approvals have been obtained. CPRD general practices that give informed consent to the study will be included in the trial. Trial practices must have their UTS ('up-to-standard') start date before, and CPRD end-date after, the intended trial start date. Non-trial

CPRD practices will be included in observational analyses that will allow us to gauge the representativeness of findings obtained from trial practices.

Individual patient data will be included for participants that are currently registered with participating CPRD practices. All eligible person time will be analysed, in the event that registration starts or ends during the period of the trial analysis. This is a repeated cross-sectional sampling design, which will generally be associated with less bias than a cohort sampling design.

Allocation

Anonymised identifiers will be passed from CPRD to King's College London for allocation. Initially, region and antibiotic prescribing quartile will be linked to the identifiers as stratifiers. Practices will then be allocated by minimisation (Altman and Bland, 2005) using the MINIM progam (Evans et al., 2004). Anonymised practice identifiers will then be returned to CPRD with trial arm allocation attached. This information will then be used to enable intervention activation at practices in the intervention trial arms. This procedure is considered to ensure adequate concealment throughout the allocation process.

Sample size calculations

Family practice-specific proportions will be included in a cluster-level analysis.

Key measures include the consultation rate for RTI, the antibiotic prescribing rate for RTI (both per 1,000 registered patient years) and the proportion of consultations with antibiotics prescribed (%). As the primary aim of the intervention is to reduce antibiotic prescribing, antibiotic prescriptions for RTI per 1,000 registered patients will be the primary outcome for the trial.

Design parameters for the eCRT trial, which included participants aged 18 to 59 years, are shown in Table 3.

Table 3: Design parameters estimated from eCRT study.

	Mean (SD)	Coefficient of variation	Correlation before-after
Antibiotic prescribing rate (per 1,000)	111.9 (39.8)	0.36	0.82
RTI consultation rate (per 1,000)	214.7 (56.5)	0.26	0.83
% consultations with antibiotic prescribed	52.0 (10.5)	0.20	0.91

Using analysis of covariance, with measures over 12 months before- and after- the intervention giving a correlation coefficient of 0.82, if there are 40 practices in each of two trial arms then, with alpha=0.05, there will be 80% power to detect an absolute reduction in antibiotic prescription for RTI of 15 per 1,000 registered patient years (or 1.5 per 100). There will be more than 90% power to detect an absolute reduction of 3.5% in the proportion of RTI consultations at which antibiotics are prescribed. The previous eCRT study included participants aged 18 to 59 years, this proposed study will include participants of all ages. The standard deviation of practice specific rates might be higher when participants of all ages are included, though this is not yet quantified.. Stata version 13 was used for calculations.

Table 4: Proposed trial outcome measures (see Gulliford et al., 2009).

Measure	Definition	Details
Primary		
Antibiotic prescribing rate	Number of antibiotic prescriptions for RTI per 1,000 registered patient years	Antibiotics included in BNF section 5.1 excluding 5.1.9 (TB) and 5.1.10 (leprosy).
Secondary		
RTI consultation rate	Number of consultations for RTI per 1,000 registered patient years	252 Read codes for RTI. Repeat consultations within 10 days excluded.
Proportion of RTI consultations with antibiotic prescribed	Number of consultations for RTI with antibiotic prescribed / Total RTI consultations (%)	
Total antibiotic prescribing rate	All antibiotic prescriptions per 1,000 registered patient years	
Total antibiotic prescriptions dispensed	All antibiotic prescriptions dispensed per 1,000 registered patient years	From NHS Business Services Authority data
Sub-groups of RTI	Broad categories including colds, sore throat, cough and bronchitis, otitis media and rhino-sinusitis (NICE, 2008)	Sub-groups of Read codes
Health care costs	Estimated costs of all health care utilisation per 1,000 registered patient years	Health care utilisation from CPRD clinical, referral and consultation records (Bhattarai 2013; Charlton 2013). Costs from reference sources (PSSRU, 2013).
Safety outcomes		
Pneumonia and lower respiratory tract infections, peritonsillar abscess, mastoiditis, skin infections and bacterial infections	Number of events (by category) per 1,000 registered patient years	To be developed, including Read H2 (excluding influenza), H062, H06z, H15, F53, M0 and A3

Outcome data collection

Use of CPRD data to evaluate trial outcomes represents an important strength of this proposal as this will make it unnecessary to implement bespoke data abstraction from patient's paper notes or electronic records. Data available for each subject will comprise their entire anonymised electronic medical record, including medical (READ) codes associated with consultations and referrals; details of all drugs prescribed; records of weight, height, smoking and alcohol use, and tests including haematology, biochemistry etc (Williams et al., 2012). CPRD clinical records have been shown to have high predictive value for a range of specific medical diagnoses (Herrett et al., 2010). CPRD data also reliably include records of all prescriptions issued by general practices, coded using multilex drug codes. We have shown previously that health-care utilization may be estimated from CPRD records (Bhattarai et al., 2013). This includes utilization of primary care, including family practice consultations, telephone consultations, home visits and emergency and out-of-hours consultations;

secondary care, including hospital admissions, out-patient visits, day case visits and emergency visits; and all drug prescriptions issued. Utilization rates were based on person-time at risk. CPRD data are also linked to Hospital Episode Statistics (HES) data for consenting practices in England. Linked HES data will be used to evaluate hospital admissions with respiratory illness for participating practices in England. We plan to obtain data on antibiotic prescriptions dispensed for trial practices from the NHS Business Services Authority (NHS BSA). We have discussed this proposal with the NHS BSA who have affirmed that information on monthly aggregated total antibiotic prescriptions dispensed for trial practices will be accessible for analysis.

The proposed outcome measures for the trial are outlined in Table 4. Antibiotic prescriptions will be counted using multilex codes that map to section 5.1 of the British National Formulary (BNF), excluding tuberculosis and leprosy. RTI consultations will be evaluated from 252 Read codes for acute RTI. Antibiotic prescriptions for RTI will be those recorded on the same day as RTI consultations. Repeat consultations in the same episode will be excluded using a 10 day time window. The primary outcome measure will be the rate of antibiotic prescribing for respiratory tract infection per 1,000 participant-years over the 12 month intervention period. Secondary outcome measures will be the proportion of acute RTI consultations with antibiotics prescribed; the consultation rate for respiratory tract infection per 1,000 participant years, and estimates for each of cough and bronchitis, colds, otitis media, rhino-sinusitis and sore throat (NICE, 2008). We will also evaluate total antibiotic prescribing for all indications. This will be complemented by data on all antibiotic prescriptions dispensed from the NHS Business Services authority. The difference between these two estimates will provide a measure of the use of delayed prescriptions and the proportion of issued prescriptions that are not dispensed. We will evaluate health care utilisation and costs using methods reported previously (Bhattarai et al. 2013; Charlton et al. 2013), obtaining utilisation estimates from CPRD and costs of care from reference sources (PSSRU, 2013). We will also evaluate diagnostic shifts and safety outcomes through diagnoses of pneumonia, chest infection and lower respiratory infection, peritonsillar abscess, mastoiditis, skin infections and bacterial infections. We will also evaluate the total number of times the intervention tools (including the practice prescribing reports, the decision support tools and webinars) are accessed over the intervention period.

Plan of analysis

Before the start of the trial, observational analyses will be conducted of trial outcomes across all CPRD practices, including updated trends over time, in order to refine the trial design and to inform the development of the intervention (Gulliford et al., 2009).

In trial analyses, the period of time from 12 months before, to 12 months after the intervention start date will be analysed. The intervention start date will be the date on which the practices were randomised to the intervention or control arm of the trial. Analyses will be implemented according to the 'intention to treat' principle, including in the analysis all eligible person-time for all allocated practices, including data for any practices that later withdrew from CPRD or participants who subsequently ended their registration during the study period. Pre-intervention data on antibiotic prescribing for the 12 months preceding the intervention will be analysed as baseline. Person time eligible for analysis will be confined to the period from the patient's CPRD start date, if this is less than 12 months before the intervention start, to the end of study, or the subject's transfer out date or death date if these are earlier.

The original trial protocol envisaged that a general practice-level analysis would be performed, with data aggregated to practice level. However, two considerations now favour an individual level for analysis of primary, secondary and safety outcomes:

i) There has been significant attrition of CPRD trial practices, with six practices withdrawing from the intervention trial arm and five from the control trial arm. While data from practices that withdraw from the study can be included in the analysis, bias may be introduced if comparable periods of time are not included for each practice, when the condition of interest has a seasonal distribution.
ii) A preliminary publication from our group, (7) as well as analyses for the trial DMC, have drawn greater attention to safety outcomes of the study. Analysis of safety outcomes requires consideration of individual-level covariates (e.g. age and comorbidity), and these are also relevant for decisions to prescribe antibiotics.

Consequently, we now propose an individual level analysis as the primary analysis with a cluster-level analysis being considered secondary and for confirmation. The primary analysis will be of antibiotic prescribing rates for RTI. Data for antibiotic prescriptions and person years at each practice will be aggregated by age-group, gender, comorbidity status and study month. A random effects Poisson model will be fitted using the 'hglm' package in the R program. The dependent variable will be a count of antibiotic prescriptions. Explanatory variables will be: trial arm, gender, age-group, comorbidity status, region and baseline prescribing rate. Study month will also be included. Period will be based on wave of randomisation will be included, as practices in the 6 waves were randomised in different seasons. Period 1: Wave 1, randomised November 2016. Period 2: Waves 2 and 3, randomised January and February 2016. Period 3: Waves 4 to 6, randomised June to August 2016. Indicator variables for Period2 and Period3 will also be included, as well as the interaction of these terms with the baseline prescribing rate. A random effect will be included for general practice. The offset will be log of person years. The intervention effect will be tested by considering the statistical significance of the effect of trial arm.

Cluster-level analyses will be implemented using data aggregated to general practice level, using the family practice-specific rates or proportions as observations. This is the level for intended inferences. Effects of clinical and public health importance will be evident at this level. In general, a perfectly weighted cluster level analysis will give similar precision as an individual level analysis (Donner and Klar, 2000). Analyses for primary and secondary outcomes will estimate the difference (95% confidence interval) in the outcome between intervention and control trial arms. Primary and secondary analyses will be adjusted for the pre-intervention value of the outcome, in an analysis of covariance framework, as well as proportion by age group and proportion of women at the practice. Minimum variance weights will be used to allow for varying numbers of participants and consultations per practice (Kerry and Bland, 2001).

Intervention utilisation (number of times prescribing reports or decision support tools are accessed) will be divided into quartiles and a trend tests implemented by introducing these into analyses as continuous variables.

Data for health care utilisation and costs will be analysed at the individual level using a two-part model as reported previously (Bhattarai et al., 2013). Given the extent of data available

for analysis, we can readily evaluate shifts in practices' use of diagnostic categories, using pre-trial data to evaluate time trends.

We recognise that the trial intervention requires that information concerning the outcome measure (antibiotic prescribing) is analysed and fed back to practices. This might have the effect of unblinding the study team. However, data from electronic health records are collected into CPRD through an automated process and those implementing CPRD analyses can be blinded to practice's trial arm status.

Data for trial practices will also be compared with non-trial practices in order to gauge the representativeness of the trial practice sample.

We assume that for UTS practices consultation and prescribing data are complete. We do not anticipate any analyses to allow for missing data.

Process evaluation

A process evaluation of the trial will be implemented using a mixed methods design with an interview study and a questionnaire. Participants in the process evaluation will primarily include general practitioners, but staff involved with intervention implementation will also be included, aiming pragmatically for the maximal achievable sample. The interview and questionnaire development will be guided by criteria suggested by Linnan and Steckler (2002) for the process evaluation of public health interventions and research. Questionnaires will include both intervention evaluation and theory-based measures. The questionnaire will also include open-ended response options that can be included in a thematic analysis, as the questionnaire may elicit more responses than the interview. Semi-structured telephone interviews will be conducted with participants to explore participants' experiences of using the intervention materials and experiences of the study implementation. Inductive thematic analysis will be conducted on all transcripts.

Contextual information

We recognise that the trial will not be carried out in a uniform and unchanging environment. During the next three years there may be multiple initiatives to reduce antibiotic prescribing from the NIHR programmes, local and national NHS organisations, public health agencies in England and the devolved administrations, as well as local and national governments. This study has the strength that it will recruit CPRD general practices from throughout the UK, minimising the potential influence of any particular local initiative. Allocation of practices will be stratified by region, this will tend to distribute locally confounding influences between the two trial arms. However, as part of the process evaluation we will collect contextual information on initiatives to influence antibiotic prescribing both locally and nationally. This will include periodic surveys of documentary sources, primarily those accessible on the internet. It will also include specific questionnaire items concerning participating practices exposure to other influences, such as interaction with local NHS prescribing advisers.

Dissemination and projected outputs

The research will deliver impact by developing complex multi-component electronic interventions that can be translated into routine clinical settings at low-cost in order to influence prescribing of antibiotics in primary care.

The results from this study will be disseminated through conferences, seminars and peer-review publications. We anticipate that the intervention, if shown to be effective, may be readily translated into practice. We are collaborating with DXS Point of Care Ltd in the delivery

of the intervention. DXS Ltd already contracts with clinical commissioning groups to deliver information and guidance into general practices. This provides a model through which the intervention can readily be implemented. We will hold a workshop to communicate the findings of the research to key stakeholders and decision-makers in order to promote implementation.

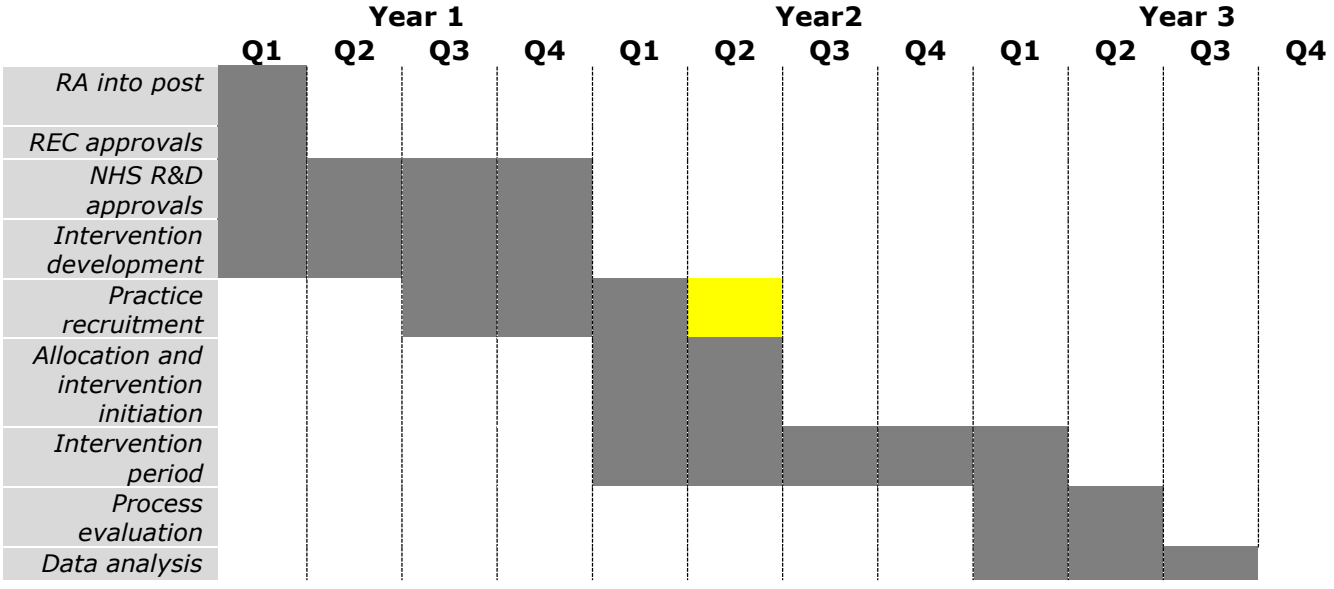
CPRD presently includes research quality data from general practices that use the Vision practice system. CPRD is presently expanding to include practices that use the Emis and TPP practice systems. DXS is presently active in EMIS as well as Vision, while integration with TPP is in progress. This potentially offers wide access to the intervention across UK primary care. The interventions may also have application in other high-income countries.

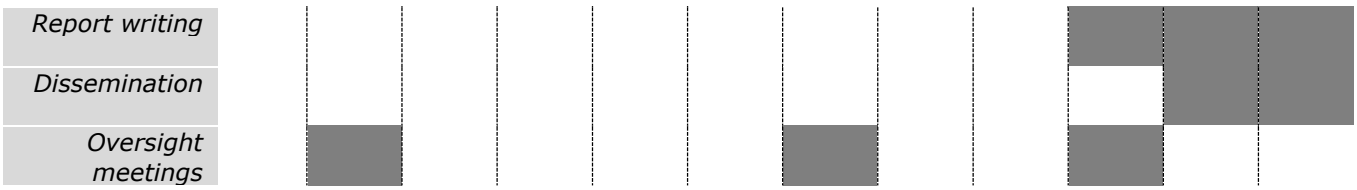
We have discussed the proposal with the behavioural insights team at Public Health England (PHE) who have indicated their interest in the project as potentially providing evidence on scalable behaviour change strategies that may be used to support the government's strategy on antimicrobial resistance (please see attached letters). We anticipate that links with PHE will facilitate the delivery of impact from this research.

The research will have an international impact by developing a research methodology, for evaluating electronically-delivered interventions, that can be applied across a wide range of topics of clinical and public health importance.

The proposed plan of investigation is shown in the Gantt chart.
By the end of the first year of the project: The research assistant will have come into post. Research ethics approvals, and NHS R&D approvals for potential trial sites, will have been obtained. Qualitative research to support intervention development and intervention design will have been completed. General practice recruitment will be in progress.
By the end of the second year of the project: Practice recruitment will be complete; practices will be allocated to trial arms; the intervention will have been initiated at intervention trial arm practices. CPRD data analysis to support intervention delivery will be ongoing. A process evaluation will be in progress.
By the end of the third year of the project: The intervention phase of the trial and the process evaluation will have been completed. The trial dataset will have been extracted from CPRD. The trial analysis will have been completed. The final report will have been completed and dissemination activities will have been delivered.

Plan of investigation and timetable





Project management
The Principal Applicant will provide overall leadership and supervision. Key members of the study team will meet on a regular basis to ensure progress towards key milestones is achieved. A Trial Management Group, comprising the team of applicants and other relevant individuals will meet approximately quarterly to monitor progress and address any difficulties that might arise. There will be a Trial Steering Committee (TSC) with an Independent Chair and independent members, as well as a Data Monitoring and Ethics Committee (DMEC). Subject to approval, the Public Health England behavioural insights team will be invited to contribute an independent member to the Trial Steering Committee.

Expertise and justification of support required
The trial will offer excellent value for money. First, the trial will benefit from the study team's previous experience of delivering the eCRT Trials (Wellcome Trust and Research Council's Joint Initiative in Electronic Patient Records). Experience with eCRT assures us that key elements of the trial including research governance, practice recruitment and allocation, intervention delivery and data analysis, are all feasible. Secondly, the trial will benefit from the efficiencies of implementation within CPRD, an existing repository of electronic health records. This will give the trial access to data for very large samples of individuals, with a minimal marginal cost from increasing the sample size. Thirdly, the study team already have a considerable amount of experience of research into antibiotic utilisation using electronic health records.

Martin Gulliford has wide experience of CPRD research and has successfully led the completion of two cluster randomised trials within CPRD. He has also engaged in methodological research in cluster trials and has experience of cluster trial implementation. *Mark Ashworth* is a GP partner at the Hurley Clinic in South London, as well as being Senior Lecturer in General Practice at King's College London. Mark participated in the intervention design and implementation for the eCRT trials and will contribute clinical advice on the intervention development and delivery for this trial. *Judith Charlton* has wide experience of statistical programming for CPRD data analysis. She will provide all data analyses for intervention delivery and trial analysis. *Alex Dregan* has experience in CPRD research and contributed to the successful implementation of previous cluster trials in CPRD. Alex will contribute to trial implementation, practice allocation, intervention monitoring and trial analysis and reporting. *Gerard McCann* is Clinical Trials Manager at CPRD. He delivered CPRD practice recruitment for the eCRT trials. He will be responsible for practice recruitment and liaison with trial practices. *Lisa McDermott* trained in health psychology and has expertise in behavioural science as applied to primary care trials. Lisa developed the interventions, and completed the process evaluation, for eCRT. She will have similar roles with respect to eCRT2. *Toby Prevost* is Professor of Medical Statistics at King's College London, he has expertise in primary care trials and will advise on the design, conduct and analysis of the study. *Lucy Yardley* is Professor of Health Psychology at the University of Southampton. She has expertise in the development and evaluation of behavioural interventions for primary care trials, especially those using electronic media. She will provide advice on the development and delivery of the trial intervention. *Paul Little* has wide experience of primary care trials and antibiotic utilisation. He will provide advice on the design, conduct and

reporting of the trial. *Michael Moore* is the RCGP Clinical Champion for antimicrobial stewardship. He will provide clinical advice on the implementation of the trial including intervention development and delivery.

Response to board feedback points

The choice of two active interventions selected should be justified and in particular whether the use of financial incentive will override all other intervention components. Thank you. We have now presented additional material on the rationale for the intervention. We acknowledge the Board's reservations about the financial incentive and have removed this part of the proposed study.

The applicants should consider measuring clinical outcomes and adverse outcomes. Thank you. Clinical outcomes and adverse events will now be evaluated using CPRD data, please see Table 4, page 15.

The intervention is complex and needs to be more fully described. The development, implementation and evaluation of the intervention are now described in full, please see pages 9 to 11.

Patient and Public involvement and comment needs to be actively sought and included in the next stage. Thank you. Please see section on patient and public involvement, page 12.

The board thought the outcome measure should be the total number of prescriptions issued. The board questioned whether a 3% drop in prescribing would be meaningful if the denominator for this measure (number of consultations) changed as a result of intervention. Thank you. We have adopted the Board's suggestion to employ the rate of antibiotic prescriptions for RTI per 1,000 registered patient years as the primary outcome for this research, with the proportion of consultations with antibiotics prescribed as the secondary outcome. The study outcomes are discussed further on pages 14 to 15.

The applicants need to consider how much the primary outcome may be influenced by changes in coding. Thank you, we agree this is an important point. We will evaluate diagnostic shifts and changes in the utilisation of Read codes over time, we will also evaluate total antibiotic prescribing for all indications. Please see Table 4, page 15.

The board thought the target of 150 practices seemed ambitious and the board wondered whether the applicants had considered stratification of practices. Thank you. We have now reduced the number of practices required to 120. In the two eCRT trials, 104 and 106 general practices respectively were recruited within 6 months of the first invitation letter. Subsequently, the Pleasant study has included more than 120 CPRD general practices. We therefore believe that it will be feasible to recruit sufficient CPRD general practices for this study. Allocation of practices will be stratified by region and antibiotic prescribing quartile (page 14).

The exclusion of children should be justified. Thank you. We agree that children represent an important group to include in the study, we have now adopted the Board's suggestion to include persons of all ages, reporting age-specific results where appropriate.

The applicants should show how the information supplied relates to and takes account of any local initiatives. We agree that there may be current (or previous) local initiatives to influence antibiotic prescribing. These may confound the effect of the intervention. However, the general

effect of randomisation will be to ensure that such effects are equally distributed between trial arms and the sample size is sufficient to enable this. Allocation will be stratified by region and this will facilitate this. However, we plan to collect, as part of the process evaluation of the trial, contextual information concerning local and national initiatives on antibiotic prescribing that might influence underlying trends in antibiotic prescribing during the study period (page 17).

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