Effectiveness and safety of electronically-delivered prescribing feedback and decision support on antibiotic utilisation for respiratory illness in primary care. REDUCE cluster-randomised trial

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Effectiveness and safety of electronically-delivered prescribing feedback and decision support on antibiotic utilisation for respiratory illness in primary care.

REDUCE cluster-randomised trial

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ABSTRACT

Objectives: To evaluate the effectiveness and safety at population-scale of electronically-delivered prescribing feedback and decision support interventions at reducing antibiotic (AB) prescribing for self-limiting respiratory infections (RTI).

Design: Open-label, two-arm, cluster randomised controlled trial

Setting: UK general practices in the Clinical Practice Research Datalink

Participants: 79 general practices (582,675 patient-years) randomised (1:1) to antimicrobial stewardship (AMS) intervention or usual care.

Interventions: The AMS intervention comprised a brief training webinar, automated monthly feedback reports of AB prescribing, and electronic decision support tools to inform appropriate AB prescribing over 12 months. Intervention components were delivered electronically, supported by a local practice 'champion'.

Main outcome measures: The primary outcome was the rate of AB prescriptions for RTI from electronic health records. Serious bacterial complications were evaluated for safety. Analysis was by Poisson regression with general practice as a random effect, adjusting for covariates. Pre-specified sub-group analyses by age-group are reported.

Results: There were 41 AMS trial arm practices (323,155 patient-years) and 38 usual care trial arm practices (259,520 patient-years). AB prescribing rate ratios (RR) were: unadjusted, 0.89 (0.86 to 1.16); and adjusted, 0.88 (95% CI, 0.78 to 0.99, P=0.04); with AB prescribing rates of 98.7 per 1,000 patient-years for AMS (31,907 AB prescriptions) and 107.6 per 1,000 for usual care (27,923 AB prescriptions). AB prescribing was reduced most in adults aged 15-84 years (adjusted RR 0.84, 95%CI 0.75 to 0.95), with one antibiotic prescription per year avoided for every 62 (40 to 200) patients. There was no evidence of effect for children less than 15 years (adjusted RR 0.96, 0.82 to 1.12) or adults aged 85 years and older (adjusted RR 0.97, 0.79 to 1.18). There was no evidence that serious bacterial complications increased (adjusted RR 0.92, 0.74 to 1.13).

Conclusions: Electronically-delivered interventions, integrated into practice workflow result in moderate reductions AB prescribing for RTI in adults, which are likely to be of importance for public health. Antibiotic prescribing to children or older people requires further evaluation.

Trial registration: ISRCTN95232781

Key words: antibiotics; primary care; respiratory tract infections; pneumonia; peritonsillar abscess; mastoiditis; implementation science, audit, decision support

PRINT ABSTRACT

Study question: Can electronic-delivery of prescribing feedback and decision support interventions reduce antibiotic (AB) prescribing for self-limiting respiratory infections (RTI) in primary care?

Methods: We conducted a two-arm, cluster randomised controlled trial in UK general practices contributing to the Clinical Practice Research Datalink; 79 general practices were randomised (1:1) to antimicrobial stewardship (AMS) intervention or usual care. The AMS intervention included a brief training webinar, automated monthly feedback reports of AB prescribing, and electronic decision support tools to inform appropriate AB prescribing over 12 months. Intervention components were delivered electronically, supported by a local practice 'champion'. The primary outcome was the rate of AB prescriptions for RTI from electronic health records. Serious bacterial complications were evaluated as safety outcomes. Analysis was by Poisson regression with general practice as a random effect, adjusting for covariates. Pre-specified sub-group analyses by age-group are reported.

Study answer and limitations: During 12 months follow-up, antibiotic prescribing was reduced by 12% (95% confidence interval 1% to 22%). The AB prescribing rate was 98.7 per 1,000 patient-years for AMS (31,907 AB prescriptions in 323,155 patient-years) and 107.6 per 1,000 for usual care (27,923 AB prescriptions in 259,520 patient-years). AB prescribing was reduced in adults aged 15-84 years, with one antibiotic prescription per year avoided for every 62 (40 to 200) patients. There was no evidence of reduced AB prescribing for children less than 15 years (RR 0.96, 0.82 to 1.12) or adults aged 85 years and older (RR 0.97, 0.79 to 1.18). There was no evidence that any of 12 different serious bacterial complications might be increased (RR 0.92, 0.74 to 1.13). The imprecision of the effect estimate suggests that a smaller effect might be possible, but even a smaller effect could be of public health importance. While larger than previous studies, this trial did not have sufficient statistical power to provide conclusive evidence of safety with respect to rare outcomes.

What this study adds: Multi-faceted interventions, drawing on electronic health records data, may be scaled-up at low cost to promote effective antimicrobial stewardship in primary care. The needs of very young or old patients require special consideration.

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Trial registration: ISRCTN95232781

What is already known on this topic

Widespread unnecessary prescribing of antibiotics is contributing to the emergence of antimicrobial drug resistance.

A systematic review of antimicrobial stewardship interventions found low- to moderate-strength evidence that single interventions including patient and public education, point-of-care testing, audit and feedback and electronic decision support might be associated with reduced antibiotic utilisation, but previous interventions have been resource-intensive and have not been implemented at scale.

The relevance of previous trials to clinical practice is also unclear because of limited reporting of adverse clinical outcomes and lack of detail concerning possible effect modifiers, including patient characteristics.

What this study adds

This large study included more than 0.5 million patients from 79 general practices from throughout the UK, using used 'real-world' data from electronic health records (EHRs) to evaluate effectiveness and safety outcomes. The multi-component intervention comprised a training webinar, monthly feedback of antibiotic prescribing data from EHRs, and electronic decision support tools.

The results showed that use of this multi-faceted intervention was associated with reduced antibiotic prescribing. Patient age was identified as an effect modifier; the intervention reduced antibiotic prescribing for adults but not children or people aged 85 years or older. There was no evidence that the incidence of serious bacterial complications was increased.

Multi-faceted interventions, drawing on electronic health records data, may be scaled-up to promote effective antimicrobial stewardship in primary care. The needs of very young or old patients require further consideration.

INTRODUCTION

Over-utilisation of antibiotics in medical practice is contributing to the emergence of antimicrobial drug resistance (AMR). The US Centers for Disease Control estimated that each year in the U.S. at least 2 million people acquire antibiotic resistant infections and at least 23,000 people die as a direct result.[1] General practice and ambulatory care account for nearly three-quarters of all antibiotic (AB) prescribing, with respiratory tract infections (RTIs) representing the largest single group of indications for antibiotic treatment, including cough, acute bronchitis, common colds, otitis media, sinusitis and sore throat.[2] Antibiotic treatment generally has little if any effect on the severity or duration of RTI symptoms, is commonly associated with side-effects,[3,4] and encourages patients to re-consult in future episodes.[5] Current treatment recommendations suggest that a no antibiotic prescribing strategy should be agreed on with most patients presenting with self-limiting RTIs.[6] While there is limited evidence available to date, a lower AB prescribing strategy does not appear to compromise patient safety in terms of bacterial infections.[7,8]

A systematic review, updated to 2018, found that educational activities aimed at clinicians or patients, electronic decision support systems, and audit of antibiotic prescribing with feedback of results might be used to reduce unnecessary antibiotic prescribing.[9,10] However, the review concluded that it was unclear how useful these interventions might be in usual clinical practice because of a lack of information about possible adverse events, including possible increases in bacterial infections.[10] Previous studies also lacked information about effect modification by patient characteristics, such as age, gender and comorbidity, that might influence intervention effectiveness.[10] The review suggested that a strategy of combining interventions might hold promise and recommended that trials of multi-faceted interventions, including two or more interventions found to be effective individually, should be undertaken.[10] While some recent trials have used electronic media to deliver

interventions,[11,12] previous interventions have often been resource-intensive[13] and have not yet shown potential to be translated on a wide and sustainable scale into routine healthcare. The present research focused on low-cost interventions that can be readily integrated into routine practice workflow and scaled-up through remote delivery using electronic media to a large sample of unselected practices. The research developed a multi-component intervention that included a brief training webinar for prescribers, followed by monthly feedback reports of AB prescribing at RTI consultations and decision support tools to inform appropriate AB prescribing. The primary objective was to evaluate whether this multi-component intervention was effective and safe, when delivered electronically into general practices over 12 months, at reducing prescribing of antibiotics when patients consult with RTIs.

METHODS

Study design and participants

The study was an open-label, two-arm, parallel-group randomised trial with general practices as the unit of allocation. The target population for this trial was the general population registered with general practices in the United Kingdom, including England, Scotland, Wales, and Northern Ireland. The trial was conducted using the anonymised electronic health records of general practices contributing to the UK Clinical Practice Research Datalink (CPRD). The CPRD is one of the world's largest databases of primary care electronic health records, it includes monthly-updated data from general practices throughout the UK. CPRD data have been extensively evaluated and employed for epidemiological[14] and interventional research.[15] General practices contributing to CPRD were invited to participate in the study from September 2015. General practices were included in the trial if they were actively contributing data to CPRD and consented to participation in the trial. Data for all registered patients from trial practices in CPRD were included; there were no exclusion criteria.

The protocol was approved by the NHS London-Dulwich research ethics committee (14/LO/1730) and by the CPRD Independent Scientific Advisory Committee (ISAC 14_130). Trial oversight was provided by Independent Trial Steering (TSC) and Data Monitoring Committees (DMC). Each participating general practice gave written informed consent for participation. General practices were randomised between 11th November 2015 and 9th August 2016 and final follow-up was on 9th August 2017. The trial was stopped when the last general practices completed 12 months of follow-up. The study protocol has been reported previously,[16] the updated protocol including amendments to the sample size calculation and statistical analysis plan has been published online.

Randomisation and masking

Cluster randomisation was employed because intervention was delivered at general practice-level. CPRD staff (JS and KS) were responsible for recruiting practices to the trial and communicating allocations but had no access to the allocation procedure. Allocation to antimicrobial stewardship and usual care trial arms was performed at King's College London (MG, TP) by minimisation using the MINIM program,[17] stratifying for region and pre-trial fourths of antibiotic prescribing (as proportion of RTI consultations with AB prescribed). 'Region' comprised Scotland, Wales and Northern Ireland and, in England, North (including North East, North West and Yorkshire and Humber), Midlands (including East and West Midlands), South and East (including East of England, South Central and South East Coast), South West and London. As only two practices were recruited in the Midlands, this region was combined with North for analysis. As general practices consented to participation over an extended recruitment period, they were allocated in six waves, which were combined for analysis into three periods including: Period 1, practices randomised in November 2015; Period 2, January and February 2016; and Period 3, June to August 2016 respectively. One practice allocated to the intervention trial arm withdrew from CPRD before the intervention

started and was excluded from further analysis because no data were available. There was no blinding of health professionals to trial arm allocation.

Interventions

An intervention development study was conducted and is described in detail elsewhere.[16,18] Development of the antimicrobial stewardship (AMS) intervention drew on social cognitive theory[19] and self-determination theory,[20] experience from development of a previous intervention,[15,21,22] and qualitative interviews with 31 prescribers to refine prototype versions of interventions. The intervention comprised three elements that were delivered remotely into practices using electronic media as outlined in Table 1. A six-minute pre-recorded webinar introduced and provided brief training in use of the trial interventions. Antibiotic prescribing reports were prepared through analysis of CPRD electronic health records, which are updated monthly (Supplementary Figure 1). These were sent to each general practice by email, to present monthly-updated feedback of data for counts of respiratory consultations and antibiotic prescriptions for that practice, in comparison with the preceding 12 months. Data were not analysed at the individual prescriber level because this information is not consistently available within CPRD. Decision support tools were deployed remotely into existing practice software to provide patient information sheets and advice on the positive indications for antibiotic prescription during consultations for RTI (Supplementary Figure 2). Patient information sheets were provided for common colds and upper respiratory infections, sore throat, otitis media, sinusitis, and cough and bronchitis (Supplementary Figure 3). Separate sheets for children were provided for otitis media and cough and bronchitis. Recommendations for positive indications for antibiotic prescription followed NICE guidance (Supplementary Figure 4).[6] Intervention materials were accessible to all prescribers in AMS trial arm practices. General practices were asked to identify a general practitioner as 'champion' for the study, generally the research coordinator at the practice, who ensured that all prescribers at the practice were aware of the trial, learned how to use the decision support

tools, and received copies of the antibiotic prescribing feedback reports each month. Practices were encouraged to discuss the webinar and antibiotic prescribing feedback reports at practice meetings. A more extensive description of the intervention is published elsewhere.[18] There were no modifications during the course of the study. General practices randomised to usual care received no study interventions.

Outcomes

Outcomes for both antimicrobial stewardship and usual care trials arms were evaluated using anonymised individual-patient electronic health records from CPRD. Consultations for self-limiting RTIs were identified from medical codes for cough and bronchitis, otitis media, rhinosinusitis, sore throat and common colds. Medical codes were drawn from the Read code classification, which was in use in the UK at this time, including symptoms and medical diagnoses. Lower respiratory tract infections including 'chest infections', exacerbations of chronic bronchitis and pneumonia were not included because they are subject to different treatment recommendations. Antibiotic prescriptions were identified from product codes for antibiotics included in the *British National Formulary* section 5.1. We determined whether antibiotics were prescribed on the same date as the RTI consultation. In order to focus on prescribing decisions at initial presentations for RTI, repeat consultations for RTI during the same episode were excluded using a 14-day time window. As sensitivity analyses, we evaluated whether estimates differed for a 10-day time window or no time window. The primary outcome measure was the rate of AB prescribing for RTI per 1,000 patient-years over the 12-month intervention period. Secondary outcome measures were the proportion of RTI consultations with antibiotics prescribed; the consultation rate for RTI per 1,000 patient-years; AB prescribing for sub-groups of RTI; and total antibiotic prescribing for all indications. Safety outcomes were identified by the DMC as new occurrences of a wide range of serious bacterial complications including pneumonia, peritonsillar abscess, mastoiditis, intracranial abscess, empyema, scarlet

fever, pyelonephritis, septic arthritis, osteomyelitis, meningitis, toxic shock syndrome and septicaemia, and Lemierre's syndrome. Interim analyses of safety outcomes were presented to the DMC in October 2016 and April 2017. The comorbidity status of patients consulting with RTI was classified as present or absent based on 'seasonal flu at-risk' status including diagnoses of significant heart, lung, renal, liver or neuromuscular disease, as well as cystic fibrosis, diabetes, and immunosuppression or immunosuppressive treatment.[23]

Statistical Analysis

The primary outcome for the trial was the rate of antibiotic prescriptions for RTI per 1,000 registered patients. The sample size calculation was based on analysis of outcomes aggregated to cluster-level; it was informed by data from our previous eCRT trial[15] in CPRD. The distribution of general practice-specific AB prescribing rates had a mean 111.9 (SD 39.8) AB prescriptions per 1,000 registered patients, with a correlation coefficient of 0.82 between AB prescribing in the baseline and intervention periods. We initially aimed to recruit 120 CPRD general practices. Based on analysis of covariance, this would have enabled the study to detect an absolute reduction in antibiotic prescribing for RTI of 12 per 1,000 registered patients. During the recruitment phase of the trial, this target was not achieved because of declining numbers of general practices using 'Vision' software contributing to CPRD. An updated sample size calculation on 11th July 2016 found that that a revised total of 80 practices would give 80% power (with alpha 0.05) to detect an absolute reduction in AB prescribing rate of 15 per 1,000 registered patient-years.

Individual-level patient data for primary, secondary and safety outcomes were analysed according to the intention-to-treat principle. The original protocol[16] proposed a general practice-level analysis but this was amended in the statistical analysis plan, approved by the CPRD-ISAC, because attrition of practices during the trial and increased focus on safety

outcomes[7] required consideration of individual patient-level covariates and temporal effects in an individual-level analysis.

The trial dataset comprised full electronic health records data for all patients who consulted with RTI on one or more occasions during the trial baseline and intervention periods, together with denominator data for all patients registered at trial practices. For each registered patient, we evaluated the person-time at risk during the 12-month intervention period of the trial. A random effects Poisson model was fitted using the 'hglm' package in the R program,[24] with a random intercept for general practice and the log of person years as offset. The dependent variable was a count of antibiotic prescriptions. Covariates were trial arm, gender, age-group, comorbidity status, region, study quarter and baseline AB prescribing rate. The period of randomisation was included, as well as the interaction of period with the baseline AB prescribing rate. The baseline AB prescribing rate was included as an age-standardised rate for each practice, using the European standard population for reference. For practices that withdrew during the intervention period, baseline time was included pro-rata. Forest plots were constructed. A sensitivity analysis was conducted for the primary outcome by fitting an over-dispersed Poisson model using the 'dhglm' package in the R program.[24]

Data were visualised by calculating antibiotic prescribing rates for RTI by single year of age and fitting smoothed curves using third-degree polynomials. These empirical data were compared with estimates from a fully-adjusted random effects Poisson model incorporating a third-order polynomial term for age and the interaction with trial arm, with age 15 years was used as reference.

Safety outcomes were ascertained from CPRD clinical and referral files. The latter includes coded data for hospital referrals and discharge letters. Safety outcomes were analysed adjusting for age-group, gender and comorbidity. A random effect for general practice was included for the most common outcome of pneumonia, and for the composite, but this was omitted for the remaining outcomes.

Interaction terms were tested and pre-specified sub-group analyses were conducted. The statistical analysis plan included pre-specified sub-group analyses by age-group, gender, comorbidity, region, type of infection and baseline antibiotic prescribing fourth. Age-group was categorised: from 0 to 14 years, then ten-year bands, until 85 and over. The sub-group effect was assessed statistically on this basis and the effect was summarised more simply in those 0 to 14 years classed as children, those 15-84, and those 85 and over.

Data on utilisation of decision support tools was collected directly into the proprietary software used to deliver the tools. We estimated for each general practice the proportion (%) of RTI consultations at which decision support tools (DST) were viewed and evaluated a linear trend for the primary outcome across fourths of DST utilisation adjusting for the same covariates.

Patient and Public Involvement

The trial procedure and proposed intervention were presented to a primary care patient participation 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.

RESULTS

We recruited 80 general practices to the trial, of which one withdrew from CPRD before the start of intervention and the remaining 79 were included in the intention-to-treat analysis (Figure 1). The trial included general practices from throughout the UK (Table 2) and the registered population included patients of all ages. RTI consultation and AB prescribing rates were very similar overall between trial arms but showed wide variation among practices (Table 2). General practices at antimicrobial stewardship trial arm practices had slightly higher numbers of registered patients, but the range of practice sizes was similar across trial arms.

Primary outcome

Figure 2 presents the results for analysis of the primary outcome. The adjusted rate ratio for AB prescribing for RTI was 0.88 (95%CI, 0.78 to 0.99). There were 31,907 AB prescriptions for RTI during 323,155 patient-years at 41 antimicrobial stewardship trial arm practices and 27,923 AB prescriptions during 259,520 person-years at 38 usual care trial arm practices. There were 98.7 AB prescriptions per 1,000 patient-years in the antimicrobial stewardship trial arm and 107.6 per 1,000 patient-years in the usual care trial arm. Adjustment for covariates was pre-planned, prior to analysis, in order to improve the precision of estimated intervention effects. For comparison, the unadjusted rate ratio would have been 0.89 (0.68 to 1.16). An analysis of data aggregated to general practice level, gave a mean difference in age-standardised antibiotic prescribing rate of -0.5 (95% confidence interval -8.2 to 7.2) antibiotic prescriptions per 1,000 patient years. These imprecise estimates resulted from wide variations in AB prescribing between general practices; the data appeared to be over-dispersed with several extreme values. The coefficient of variation of general practice specific antibiotic prescribing rates was 0.51. Adjusting for covariates reduced the standard error of the coefficient and this was largely accounted for by adjustment for practices' baseline antibiotic prescribing for RTI. In a sensitivity analysis, an over-dispersed Poisson

model gave an adjusted rate ratio of 0.86 (95%CI, 0.75 to 0.97), which confirmed conclusions. Sensitivity analyses, which compared the base case 14-day time-window for excluding secondary consultations with either a 10-day time-window or no time-window, showed that the effect estimate was not sensitive to whether a time-window was used, nor its length (Supplementary Table 1).

Secondary outcomes

There was insufficient evidence for difference between trial arms for consultation rate for self-limiting respiratory infections (RR, 0.94, 0.86 to 1.03), the proportion of consultations with antibiotics prescribed (where RTI consultations rather than person-time represented the denominator) (RR, 0.96, 0.89 to 1.03), and antibiotic prescribing for all indications (RR, 0.93, 0.83 to 1.04) (Supplementary Table 2).[16] During the intervention period there were 185,924 antibiotic prescriptions in the intervention trial arm and 150,539 in the control trial arm (Supplementary Table 2).

Safety outcomes

Figure 3 presents numbers of serious bacterial complications by trial arm together with a Forest plot of rate ratios. There was no evidence to suggest that bacterial infections were more frequent in the antimicrobial stewardship trial arm (RR, 0.92, 0.74 to 1.13). There were slightly more scarlet fever events in the usual care trial arm, and slightly more empyema events in the antimicrobial stewardship trial arm, but these were likely to be chance findings. There was one case of Lemierre's syndrome in the usual care trial arm. There was no evidence that the adjusted rate ratio varied by age-group (chi-square=1.228, df=8, P=0.99); the adjusted rate ratio for children was 0.82 (0.44 to 1.51) and for adults aged 85 and older, 0.99 (0.59 to 1.70).

Sub-group analyses

Sub-group analyses by individual patient characteristics are shown in Figure 3. AB prescribing was strongly associated with age. A Wald test of the trial arm by age-group interaction gave chi-square=65.5, df=8, P<0.001. Results of a pre-specified sub-group analysis by age are shown in Figure 3. There was no evidence of an effect of intervention in children aged under 15 years (RR 0.96, 95%CI 0.82 to 1.12) or in people aged 85 years or older (RR 0.97, 0.79 to 1.18). In the control trial arm, children accounted for 23% of AB prescriptions, while people aged 85 years and older accounted for 2%. At intermediate ages, AB prescribing was lower in the antimicrobial stewardship trial arm. We summarised effect modification by age by comparing effect measures in children, adults aged 15 to 84 years and people aged 85 years and older (Supplementary Table 3). The intervention was associated with lower AB prescribing for RTI in adults aged 15-84 years (RR 0.84, 0.75 to 0.95). Based on the AB prescribing rate for adults aged 15-84 years in the usual care trial arm of 100.2 per 1,000, the absolute risk reduction was 16.0 (5.0 to 25.1) AB prescriptions per 1,000 patient-years. This is equivalent to the saving of one antibiotic prescription per year for every 62 (95%CI, 40 to 200) registered patients aged 15 to 84 years.

Figure 4 (left panel) presents empirical data for antibiotic prescribing rates for RTI by single year of age. Fitted polynomial curves suggest that from the late teens to the early eighties antibiotic prescribing for RTI was lower in the intervention trial arm but there was no evidence of reduced antibiotic prescribing in children or very old people. Estimates from the fully-adjusted regression model (Figure 4, right panel) show the same pattern of effect with evidence of reduced AB prescribing in the intervention trial arm from the late teens to early eighties. Data were relatively sparse at very advanced ages with fewer than 500 patient-years' follow-up at any single year of age over 90 years.

There was no evidence that the effect of intervention might differ by gender (chi-square=1.264, df=1, P=0.26) or comorbidity (chi-square=2.424, df=1, P=0.12). Analysis by sub-group of practice-level covariates (region and baseline antibiotic prescribing fourth) showed no consistent pattern of association (Supplementary Table 4). There was no evidence of association of intervention with AB prescribing for any sub-group of RTI separately (Supplementary Table 5).

Process Evaluation

We evaluated the primary outcome measure in relation to the level of utilisation of decision support tools (DST) at antimicrobial stewardship trial arm practices. In the lowest fourth of utilisation, DST were viewed at fewer than 1% of RTI consultations but up to 28% in the highest utilisation fourth (Table 3). There was evidence of a linear trend in the primary outcome across fourths of DST utilisation, with relative risk reduction of 3.4% per fourth (95% confidence interval 0.1 to 6.5%). This association appeared to be stronger for adults, with no evidence of association for children or people aged 85 or older (Table 2). In the intervention period, the number of patient information leaflets printed per practice ranged from zero to 555 with median 54 (interquartile range 7 to 97) leaflets printed per practice.

DISCUSSION

Principal findings of the study

In a nationwide sample of general practices, a low-cost remotely-delivered intervention using electronic health records data to provide antibiotic prescribing feedback reporting, together with computer-delivered decision support tools was effective at reducing antibiotic prescribing for self-limiting RTIs to adults. The reduction in AB utilisation was greater at practices that used the trial intervention decision support tools more frequently. There was no

evidence that the intervention was effective at reducing antibiotic prescribing to children or people aged 85 years or older. The trial decision support tools specifically addressed common diagnostic concerns in children, including otitis media and cough and bronchitis but prescribing to the youngest and oldest age groups may be more difficult to modify because safety concerns may be more salient at these ages.[25] Conversely, unnecessary prescribing may be more frequent, and possibly more readily modified, at intermediate ages.[26] The intervention was delivered at low cost. The budget for the trial was £533,580, which implies that the research and intervention were delivered for less than £1 per patient-year. The marginal cost of extending the intervention to more practices might be lower. Additional analysis found no evidence that overall costs of health care utilisation were different in the intervention and control trial arms.[18]

The trial was designed with the AB prescribing rate as primary outcome because AB prescribing can influence subsequent consultation patterns for respiratory illness. Patients are more likely to consult for RTI if they have been prescribed antibiotics recently.[5] The effect of AMS interventions on AB prescribing may be partly mediated by changes in RTI consultation patterns. Consequently, measures such as the proportion of RTI consultations with AB prescribed may under-estimate intervention effects. This study did not find sufficient evidence that the proportion of RTI consultations with antibiotics prescribed, or the rate of RTI consultations, were reduced by the AMS intervention but both measures tended to be slightly lower in the AMS trial arm.

The study did not find evidence that the intervention might influence the total utilisation of antibiotics at these practices. Antibiotic prescriptions that are clearly associated with a documented RTI represented a substantial proportion of prescriptions, but nevertheless a minority consistent with another recent study,[28] since an appreciable proportion of antibiotic

prescriptions are associated with non-specific medical codes or with no code recorded. Future studies should therefore address a wider range of prescribing indications, as well as issues of coding quality. We also note that only about one quarter of eligible general practices agreed to participate in the trial, and if this level of uptake were to be replicated in any future intervention roll-out, then any possible population benefits would be proportionately smaller.[28] The trial continued over 12-months and the trial did not provide evidence concerning any possible longer-term outcomes. The trial intervention did not address selection of different antimicrobial drugs, though nationally there has been a substantial reduction in prescribing of broad-spectrum antibiotics in recent years.[29]

Analysis of electronic health records data for serious bacterial complications as safety outcomes revealed no difference between trial arms. This study was considerably larger than most previous studies but was nevertheless not designed to provide conclusive evidence concerning the safety of reducing antibiotic prescribing. Even a much larger study might have limited power to evaluate less frequent safety outcomes or vulnerable sub-groups with precision.[7] The confidence intervals for several individual diagnoses including meningitis, empyema, and sepsis were wide because these outcomes are infrequent but nevertheless may have a high impact on affected individuals. Outcomes were ascertained from Read codes recorded in primary care electronic records. Additional information might have been obtained through linked hospital records (Hospital Episodes Statistics) but these data were not available for all trial practices. Safety outcomes were evaluated during the 12-month intervention period but some safety events might take longer than this to become apparent.

Strengths and limitations of study

The trial was conducted in the context of national efforts to reduce unnecessary antibiotic prescribing in primary care that might have impacted on both trial arms with possible under-estimation of intervention effects. Trial general practices represented all parts of the UK but

CPRD general practices in Scotland, Wales and Northern Ireland were more likely to agree to participate in the trial than practices in England. It is possible that general practices that agreed to take part might be more motivated to reduce AB prescribing. It is known that participation in research studies may cause individuals to alter their behaviour.[30] Prescribing feedback delivered to the intervention trial arm might have contributed to heightened awareness of research participation and this might have influenced antibiotic prescribing patterns. It is possible that smaller changes might be observed if prescribing feedback is employed outside of the context of a research study. The number of practices included was smaller than originally intended and several practices were unable to continue with the trial because they transferred to a different practice information system. In our previous study, allocation was stratified by practice list size and region[15] but in this trial allocation was stratified by antibiotic prescribing fourth and region. Consequently, there was good balance between trial arms for baseline antibiotic prescribing for RTI but trial arms were less well balanced with respect to practice list sizes. However, the range of practice list sizes was similar in both trial arms. There was wide variation in antibiotic prescribing for RTI between different general practices in both trial arms. This is consistent with data that we and others have reported previously for this outcome.[2,31] Consequently, the primary measure of effect was estimated imprecisely and neither a smaller effect nor a larger effect can be excluded. Based on sub-group analysis, we caution that the intervention appeared to be effective in adults but may not have effect on prescribing to children or adults aged 85 and older. We acknowledge that evaluation of multiple sub-group analyses might lead to false positive interpretations. However, our interpretation was guided by interaction tests, which provided strong evidence that the intervention effect varied by age-group but not by gender or comorbidity. We do not present P values within sub-groups. We found from analysis of data captured by the intervention delivery software that utilisation of decision support tools was associated with effect size, which adds evidence of a causal association. Decision support tools were used at a minority of consultations but it is possible that learning from the tools might be applied in consultations in which they were not viewed. Decision support tools were

necessarily triggered when prescribers entered medical codes into the practice system but some GPs may record data after the end of the consultation, or may rely on free-text entries, reducing the immediacy of this component of the intervention but this post-consultation exposure might contribute to the impact of the intervention over time. All prescribers also received antibiotic prescribing reports but we were not able to determine whether all prescribers read these each month. We acknowledge that there is likely to have been variation among prescribers within practices but we did not have consistent data for the prescriber level and no information concerning prescriber characteristics. We analysed data for antibiotic prescriptions issued by trial general practices. Patients may have received antibiotic prescriptions at consultations with walk-in centres and out-of-hours or emergency services and these alternative patterns of antibiotic utilisation might differ between trial arms. Additional data sources will be needed to evaluate this possibility. Altered diagnostic code selection might have occurred in order to justify antibiotic prescriptions,[32] we included both symptoms and diagnosis codes in order to limit this. Safety outcomes were ascertained from medical codes in primary care records and we were not aware of whether any confirmatory tests might have been performed. There was necessarily no blinding of general practice staff to the intervention.

Comparison with other studies

Previous studies of audit and feedback interventions across a range of indications show that these often have only small effects,[33] though some studies report larger effects.[34] Roshanov et al.[33] found that feedback interventions that provide advice to patients as well as physicians are associated with greater chance of success. This was exemplified in the REDUCE trial decision support tools, which offered patient information leaflets that could be viewed online or printed, as well as offering advice to physicians on the recognised indications for giving an antibiotic prescription. Gjelstad et al.[35] reported a comparable effect from face-to-face delivery of feedback and guideline recommendations in a study from Norway. A recent trial

reported on the outcome of quarterly feedback on antibiotic prescribing over two years among 2,900 Swiss physicians.[36] Over the first and second years of the trial, there was no difference in antibiotic prescribing to all patients but there was evidence of reduced antibiotic prescribing to adults aged 19 to 65 years that was not consistently observed over time. The feedback employed by Hemkens and colleagues[36] was less immediate, being provided quarterly rather than monthly. Additionally, Switzerland already has low antibiotic prescribing rates.[37] Hallsworth et al.[38] reported reduction in antibiotic utilisation following social norm feedback in a study focused on high prescribing general practices. A study of dental practices in Scotland found that feedback of past antibiotic prescription data was associated with a 5.7% relative reduction in AB prescribing over 12 months.[39] Audit and feedback has also been employed successfully to reduce other forms of high-risk prescribing in primary care.[40] However, purposely designed interventions might be more effective for prescribing to children.[41]

Conclusions and policy implications

In this cluster randomised trial, an antimicrobial stewardship intervention that was delivered remotely into practices and integrated into routine care delivery was associated with a 12% reduction in antibiotic prescriptions for RTI overall, with no evidence of increased serious bacterial complications. While the absolute impact is moderate, it is nevertheless likely to be important for public health in the drive to reduce antibiotic prescribing and the risks of antimicrobial resistance. We caution that the intervention might not be effective at reducing AB utilisation for children or people aged 85 or older. Intervention using data from electronic health records may be used to promote antimicrobial stewardship in primary care and might be readily scaled-up. The needs of very young or old patients require specific consideration. The results of the trial also suggest that further research into the safety of reduced prescribing is necessary.

[5,138 words]

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Data sources: The study is based in part on data from the Clinical Practice Research Datalink obtained under license from the UK Medicines and Healthcare products Regulatory Agency. However, the interpretation and conclusions contained in this report are those of the authors alone.

Data sharing: Requests for access to data from the study should be addressed to the corresponding author at martin.gulliford@kcl.ac.uk. The study protocol has been published. All proposals requesting data access will need to specify how it is planned to use the data, and all proposals will need approval of the trial co-investigator team, and CPRD before data release.

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Conflict of Interest: All authors have completed the Unified Competing Interest form (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

Trial Registration: Trial registration details: ISRCTN95232781. Date registered 18.11.2014.

Trial Steering Committee: Jackie Cassell (Chair), Susan Hopkins (Public Health England), Tim Chadborn (Public Health England), Nanik Pursani (Lay member)

Data Monitoring Committee: Christine A'Court (Chair), Helen Strongman (CPRD/MHRA), Derek Cook (St George's, University of London), Jason Oke (University of Oxford).

Contributorship: MG, trial design, conduct, analysis; TP, trial design, statistical analysis plan and statistical advice; JC intervention delivery, trial analysis; DJ, LM, LY design of the interventions and evaluation; JS, KS, MW, recruitment and coordination of trial; RF, AH, PL, MM, MA, design of the study, intervention development and interpretation of results. All authors contributed to and approved the final manuscript. MG is guarantor.

Transparency: The lead author (MG) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

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Table 1: Summary of final intervention content and delivery. AB, antibiotic; RTI, respiratory tract infection.

Intervention component	Content	Delivery
Webinar	Professionally produced video narrated by a practising GP in a general practice setting, summarising: • Importance of AMR • Introduction to decision support tools • Introduction to antibiotic prescribing reports including reduced AB prescribing and patient safety and reduced AB prescribing and patient satisfaction	• Webinar delivered through electronic link embedded in trial start letter • Webinar also delivered into practice system using proprietary software with active alerting • GPs encouraged to present and discuss webinar in practice meetings
Antibiotic prescribing reports	Monthly updated reports on antibiotic prescribing for RTI, including: • Professionally designed template • Data for number of RTI consultations and AB prescriptions for RTI aggregated by month • Automated calculation of estimates written into a template using a program written in R • Presented as table and bar-chart in pdf document • Comparison with previous year at the same practice • Accompanied by commentary and links to decision support tools	• Delivered by email to the GP identified as 'champion' for the trial at the practice • Requested to circulate prescribing reports to all prescribers at the practice • GPs encouraged to discuss prescribing reports in practice meetings • Provided evidence of audit for professional appraisals
Decision support tools	Professionally-designed decision support tools, including: • Printable patient information leaflets for cough and bronchitis, otitis media, sinusitis, sore-throat, and common cold and upper respiratory tract infection • Versions for children in otitis media and cough and bronchitis • Advice to patients and carers on expected duration of illness, expected course and lack of effect of antibiotics, recommendations for self-care, advice on appropriate help-seeking. • Summary for prescribers of the indications in which an antibiotic prescription is usually necessary based on national recommendations	• Decision support tools delivered into general practice systems through proprietary software • Activated during consultations when medical codes for RTI were entered into patient electronic records

Table 2: Characteristics of trial general practices and patient populations at baseline. Figures are frequencies (percent of column total).

		Antimicrobial Stewardship Trial Arm	Usual Care Trial Arm
General practices		**41**	**38**
Region	London	4 (9.8)	3 (7.9)
	Midlands and North England	4 (9.8)	4 (10.5)
	Northern Ireland	4 (9.8)	5 (13.2)
	Scotland	10 (24.4)	9 (23.7)
	South and East England	8 (19.5)	6 (15.8)
	South West England	3 (7.3)	4 (10.5)
	Wales	8 (19.5)	7 (18.4)
Period of randomisation	Nov 2015	7 (17.1)	11 (28.9)
	Jan-Feb 2016	18 (43.9)	13 (34.2)
	June-Aug 2016	16 (39.0)	14 (36.8)
Practice list size, median [range]		8,936 (1,086 to 18,425)	6,777 (2,530 to 18,557)
Total registered patients		348,158	278,467
Age Group (Years)	Under 15	55,577 (16.0)	47,509 (17.1)
	15-24	40,544 (11.6)	30,610 (11.0)
	25-34	45,545 (13.1)	37,444 (13.4)
	35-44	46,288 (13.3)	38,766 (13.9)
	45-54	52,447 (15.1)	41,507 (14.9)
	55-64	42,275 (12.1)	33,769 (12.1)
	65-74	35,746 (10.3)	26,760 (9.6)
	75-84	20,919 (6.0)	15,264 (5.5)
	Over 85	8,817 (2.5)	6,838 (2.5)
Gender	Male	173,383 (49.8)	138,588 (49.8)
	Female	174,775 (50.2)	139,879 (50.2)
Co-morbidity	No	288,594 (82.9)	238,106 (85.5)
	Yes	59,564 (17.1)	40,361 (14.5)
AB prescribing rate, median [range], per 1,000[a]		108 (4 to 244)	114 (20 to 266)
RTI consultation rate, median [range], per 1,000[a]		261 (11 to 454)	261 (76 to 526)
Proportion of RTI consultations with AB prescribed, median [range], %[a]		43 (12 to 64)	43 (24 to 78)

[a]figures were age-standardised using the European standard population for reference

Table 3: Association of AB prescribing rate for RTI with utilisation of decision support tools (DST).

Fourth of DST utilisation	RTI consultations with DST viewed (%)	All	Children 0:14 years	Adults 15:84 years	Adults 85+ years
		AB/ Person-years	AB/ Person-years	AB/ Person-years	AB/ Person-years
Control Trial Arm	-	27,923 / 259,519.7	6,432 / 46,019.6	20,811 / 207,611.4	680 / 5,888.7
Lowest fourth	0 to 0.6	7,190 / 85,805.1	1,932 / 15,699.9	5,089 / 68,220.1	169 / 1,885.1
Second fourth	0.6 to 2.9	7,765 / 74,868.3	1,706 / 12,009.4	5,837 / 60,825.5	222 / 2,033.4
Third fourth	2.9 to 6.1	10,647 / 91,986.9	2,339 / 15,233.4	7,957 / 74,735.5	351 / 2,018.0
Highest fourth	6.1 to 27.6	6,305 / 70,495.1	1,520 / 10,883.6	4,668 / 58,060.1	117 / 1551.3
Relative risk reduction (95% CI) per fourth increase in decision support tools. [a,b]		3.4% (0.1 to 6.5%)	1.60% (-2.7 to 5.7%)	4.3 (1.1% to 7.5%)	1.0 (-4.6% to 6.3%)
P value		0.04			

AB, antibiotic prescribing for RTI; DST, decision support tools; RTI, self-limiting respiratory tract infections

[a]adjusted for random effect of general practice and fixed effects of gender, age-group, comorbidity, region, quarter in study, practice-specific baseline rate and interaction with period

[b] RR represents the reduction in AB utilisation per fourth increase in decision support tools.

Legend for Figure 1: Flow chart showing trial general practices and registered populations.

Legend for Figure 2: Effect of intervention on primary outcome of antibiotic prescribing rate for self-limiting respiratory tract infection.

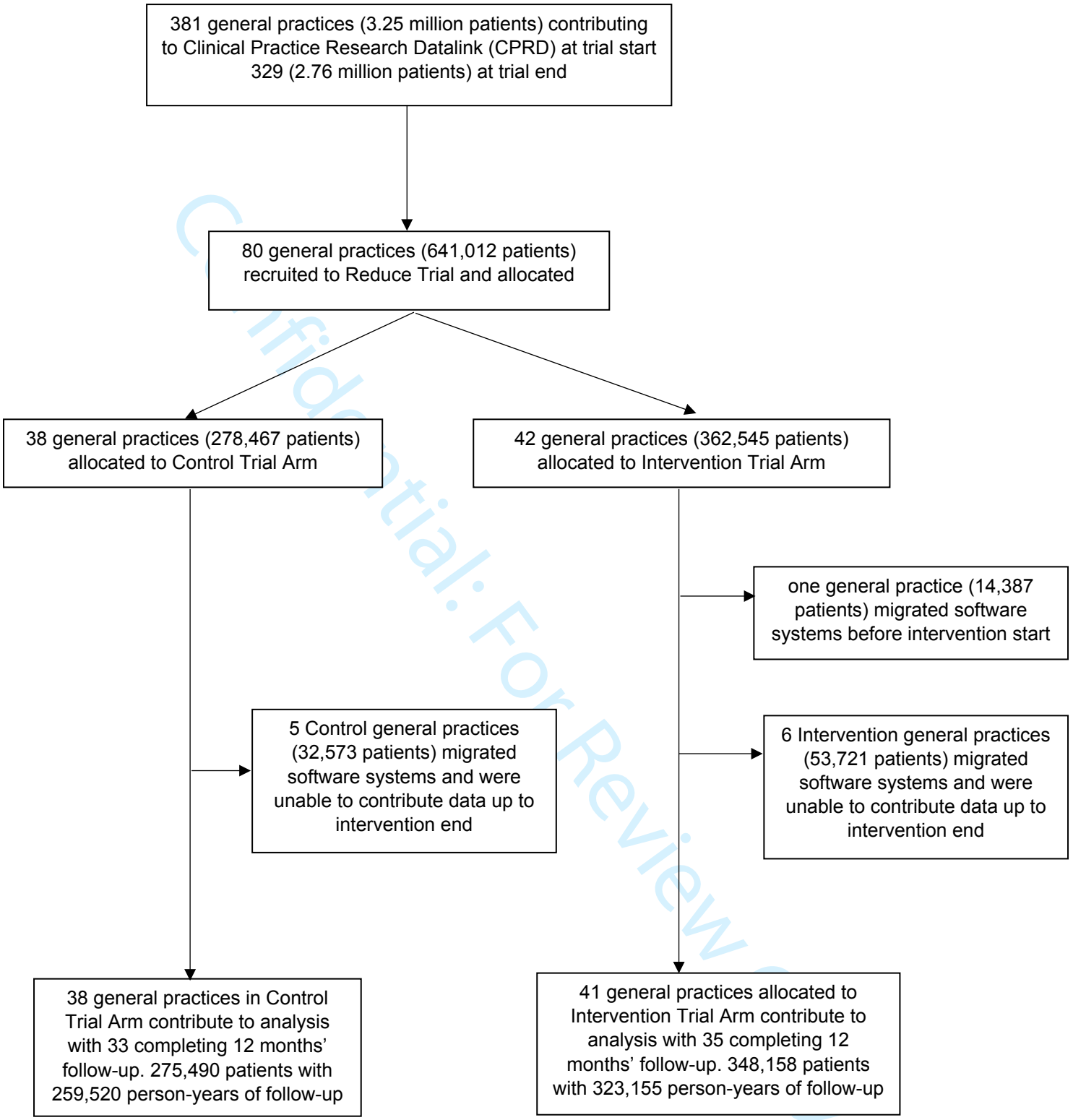
Footnote to Figure 2: Estimates were adjusted for random effect of general practice and covariates including gender, age-group, comorbidity, region, quarter in study, practice-specific baseline rate and interaction with period of randomisation. AB, antibiotic prescribing for RTI; AMS, antimicrobial stewardship intervention; RR, rate ratio.

Legend for Figure 3: Forest plot showing rate ratios (95% confidence interval) of safety outcomes in the antimicrobial stewardship trial arm compared to usual care trial arm as reference. Figures are frequencies except where indicated.

Footnote to Figure 3: Estimates were from a Poisson model adjusted for age-group, gender and comorbidity. Analyses for pneumonia and combined outcome were adjusted for random effect of general practice. One case of Lemierre's syndrome in the usual care trial arm is not shown. AMS, antimicrobial stewardship intervention; RR, rate ratio.

Legend for Figure 4: Comparison of antibiotic prscribing by single year of age for intervention and control trial arms. Left panel: antibiotic prescribing rates per 1,000 patient-years by single year of age, with fitted third order polynomial curve. Right panel: log relative risk estimates from random effects Poisson model using age 15 years for reference.

Footnote to Figure 4: Log relative risk estimates (right panel) were adjusted for random effect of general practice and covariates including gender, age-group, comorbidity, region, quarter in study, practice-specific baseline rate and interaction with period of randomisation. AB, antibiotic prescribing for RTI.



Footnote: numbers of patients are those registered with practices and contributing data in the baseline period

Covariate	AB prescribing rate per 1,000 AMS	Usual Care	RR (95%CI)
Total			
	98.7	107.6	0.88 (0.78 to 0.99)
Age−group (years)			
<15	139.3	139.8	0.96 (0.82 to 1.12)
15−24	83.6	94.3	0.92 (0.81 to 1.04)
25−34	78.2	86.4	0.90 (0.79 to 1.02)
35−44	78.6	83.4	0.90 (0.79 to 1.03)
45−54	79.9	86.0	0.84 (0.73 to 0.96)
55−64	99.6	112.8	0.79 (0.69 to 0.91)
65−74	113.8	132.8	0.80 (0.70 to 0.91)
75−84	121.7	146.1	0.79 (0.69 to 0.91)
85+	114.7	115.5	0.97 (0.79 to 1.18)
Gender			
Male	80.0	87.7	0.90 (0.80 to 1.01)
Female	117.3	127.3	0.87 (0.77 to 0.98)
Comorbidity			
Absent	60.9	72.5	0.86 (0.74 to 1.00)
Present	287.0	314.7	0.88 (0.79 to 0.99)

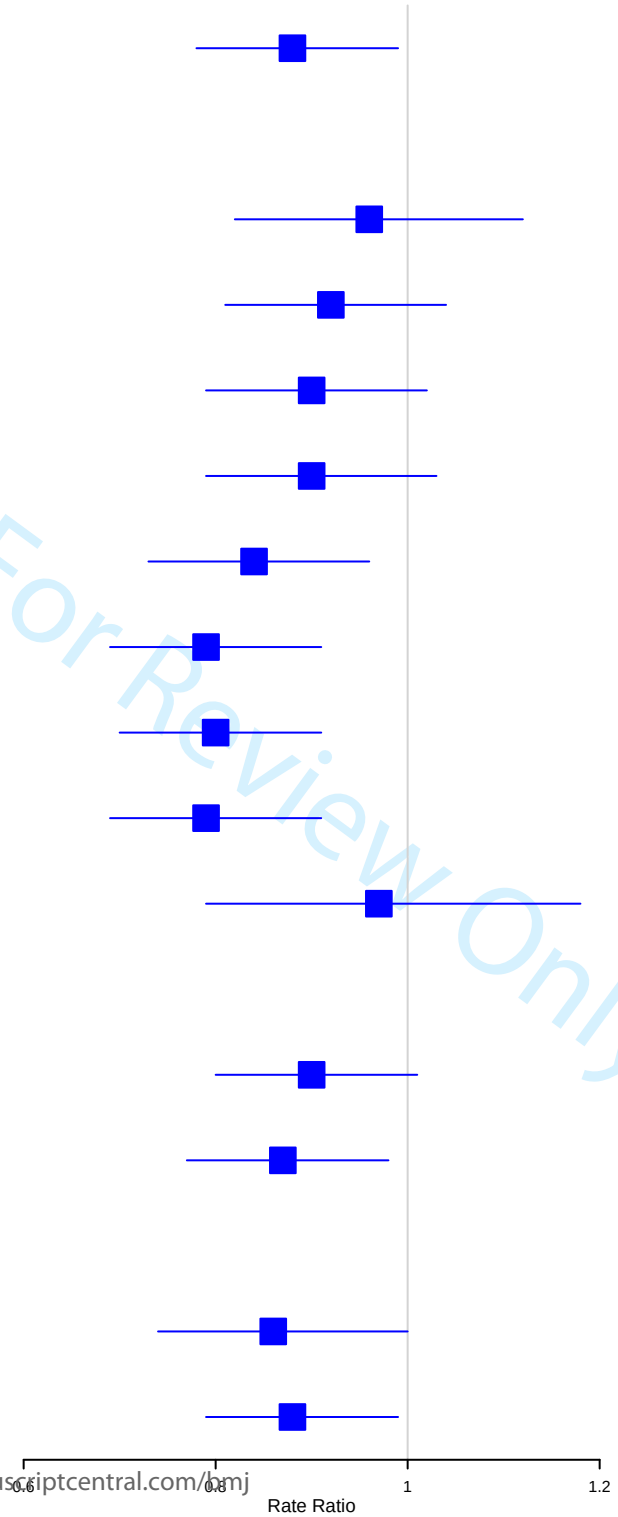
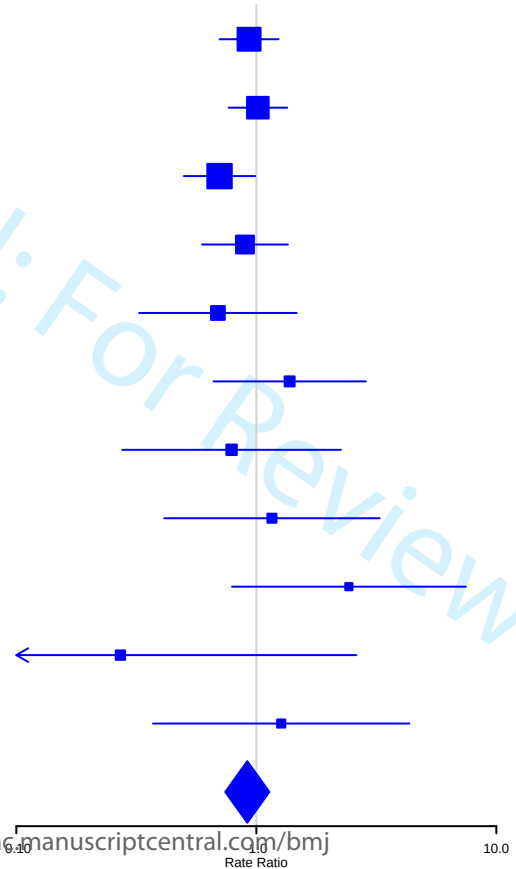
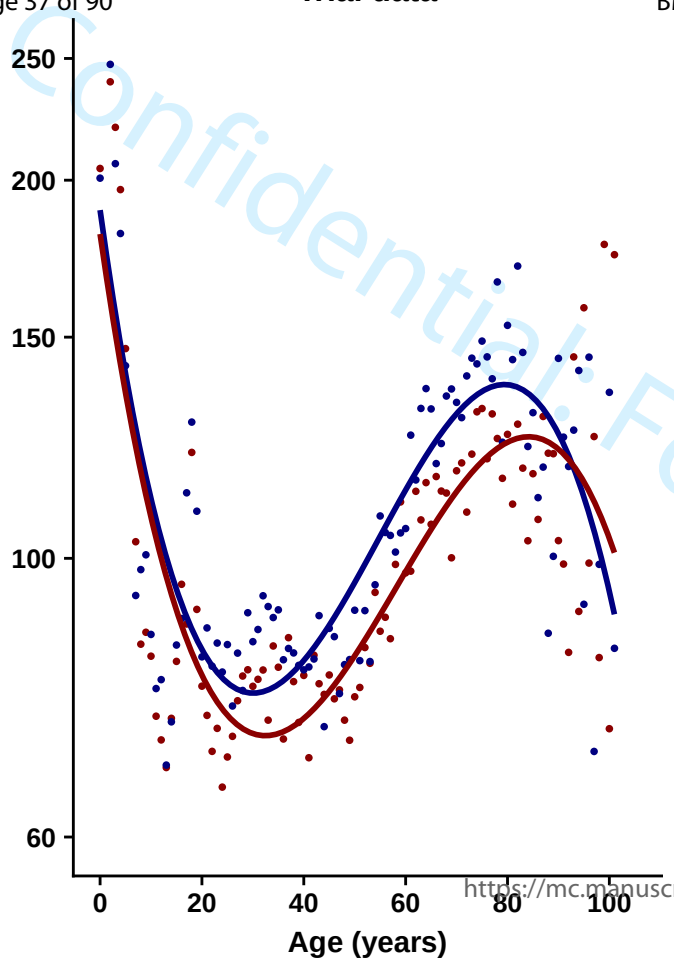
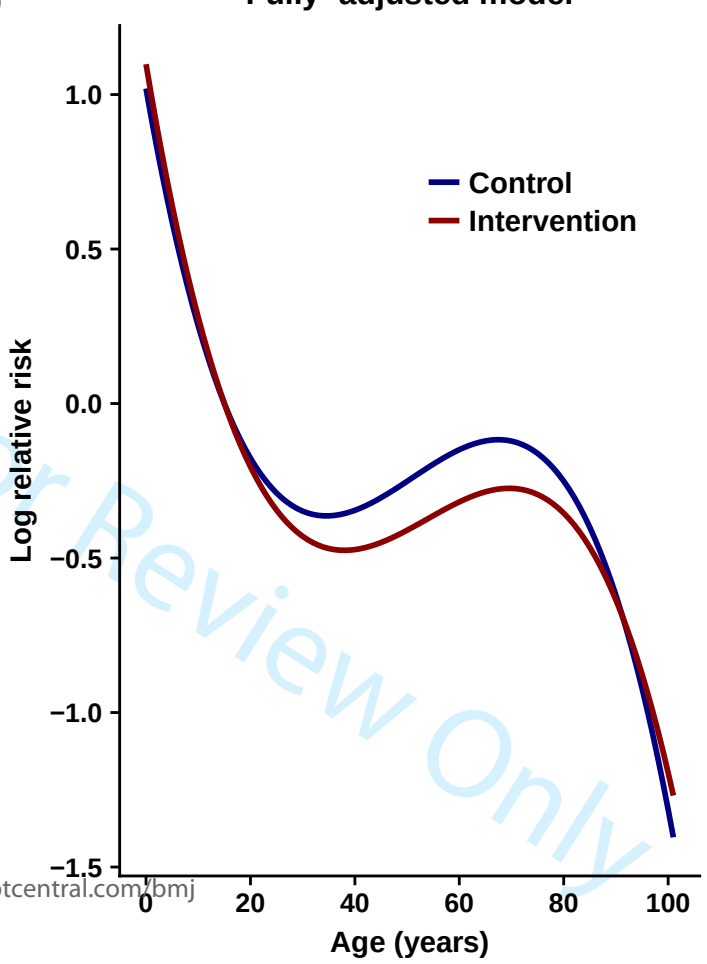


Figure 3

Condition	AMS	Usual Care	RR (95%CI)
Person Years	323,155	259,520	
Pneumonia	367	299	0.93 (0.70 to 1.24)
Pyelonephritis	115	84	1.01 (0.77 to 1.34)
Scarlet Fever	60	72	0.70 (0.50 to 0.99)
Peritonsillar Abscess	49	42	0.90 (0.59 to 1.35)
Septic Arthritis	13	14	0.69 (0.32 to 1.47)
Osteomyelitis	21	11	1.38 (0.66 to 2.86)
Mastoiditis	7	7	0.79 (0.28 to 2.25)
Meningitis	9	6	1.16 (0.41 to 3.27)
Empyema	13	4	2.43 (0.79 to 7.46)
Intracranial Abscess	1	3	0.27 (0.03 to 2.61)
Septicaemia	7	4	1.27 (0.37 to 4.34)
All	**662**	**546**	**0.92 (0.74 to 1.13)**







REDUCE Trial: Supplementary Data.

Supplementary Table 1: Results of sensitivity analysis comparing analysis with different time-windows for excluding secondary consultations.

	Measure	AMS intervention (323,155·4 person-years)	Usual care (259,519·7 person-years)	Adjusted RR (95% confidence interval)[a]	P Value
Base case: 14-day time window					
	RTI consultations	78,324	66,114		
	AB prescriptions	31,907	27,923		
	AB Prescription rate (per 1000 person-years)	98.7	107.6	0.88 (0.78 to 0.99)	0.04
10-day time window					
	RTI consultations	80,160	67,695		
	AB prescriptions	32,643	28,567		
	AB Prescription rate (per 1000 person-years)	101.0	110.1	0.88 (0.78 to 0.99)	0.04
No time window					
	RTI consultations	86,473	72,717		
	AB prescriptions	35,271	30,549		
	AB Prescription rate (per 1000 person-years)	109.1	117.7	0.88 (0.77 to 0.99)	0.04

AB, antibiotic; AMS, antimicrobial stewardship; RR, rate ratio; RTI, self-limiting respiratory tract infection

[a]adjusted for random effect of general practice and fixed effects of gender, age-group, comorbidity, region, quarter in study, practice-specific baseline rate and interaction with period of randomisation

Supplementary Table 2: Effect of intervention on secondary outcome measures. Figures are frequencies except where indicated.

	Measure	Antimicrobial stewardship intervention	Usual care	RR (95% confidence interval)[a]	P Value
RTI Consultation Rate	RTI consultations	78,324	66,114	0.94 (0·86 to 1·03)	0·19
	Person-years	323,155·4	259,519·7		
	Crude rate (per, 1000)	242·4	254·8		
Proportion of RTI consultations with AB prescribed	AB prescriptions	31,907	27,923	0·96 (0·89 to 1·03)	0·25
	RTI consultations	78,324	66,114		
	Proportion (%)	40·7	42·2		
Rate of AB Prescribing for all indications	AB prescriptions	185,924	150,539	0·93 (0·83 to 1·04)	0·18
	Person-years	323,155·4	259,519·7		
	Crude rate (per, 1000)	575·3	581·0		

AB, antibiotic; RR, rate ratio; RTI, self-limiting respiratory tract infection

[a]adjusted for random effect of general practice and fixed effects of gender, age-group, comorbidity, region, quarter in study, practice-specific baseline rate and interaction with period of randomisation

Supplementary Table 3: Effect of intervention on primary outcome for children, adults and people aged 85 and older separately.

	AMS intervention AB / Person-time	Usual care AB / Person-time	RR (95%CI)[a]
Children 0:14 years	7,497 / 53,826·3	6,432 / 46,019·6	0·96 (0·82 to 1·12)
Adults 15:84 years	23,551 / 261,841·3	20,811 / 207,611·4	0·84 (0·75 to 0·95)
Adults 85+ years	859 / 7,487·8	680 / 5,888·7	0·97 (0·79 to 1·18)

AB, antibiotic prescriptions; AMS, antimicrobial stewardship; RR, rate ratio; RTI, self-limiting respiratory tract infection consultations
[a]adjusted for random effect of general practice and fixed effects of gender, age-group, comorbidity, region, quarter in study, practice-specific baseline rate and interaction with period

Supplementary Table 4: Effect of intervention by sub-groups of practice-level covariates. Figures are frequencies except where indicated.

Practice-level covariate		AMS intervention AB / Person-time	Usual care AB / Person-time	RR (95%CI)[a]	P Interaction[b]
Region	South and East	5,460 / 67,062·7	6,674 / 61,281·7	0·73 (0·61 to 0·87)	0·03
	London	2,693 / 36,421·0	1,316 / 24,176·8	1·46 (0·53 to 4·06)	
	South West	3,225 / 39,329·9	2,158 / 23,026·7	0·81 (0·65 to 1·02)	
	North and Midlands	1,752 / 17,067·6	3,341 / 32,210·1	1·23 (1·03 to 1·48)	
	Wales	4,172 / 52,810·3	4,999 / 50,643·0	0·86 (0·70 to 1·06)	
	Scotland	8,396 / 76,041·1	5,076 / 42,807·1	0·71 (0·53 to 0·95)	
	Northern Ireland	6,209 / 34,422·9	4,359 / 25,374·3	1·00 (0·87 to 1·14)	
AB Prescribing Quartile	Lowest	5,516 / 109,110·8	1,882 / 39,425·9	0·87 (0·62 to 1·22)	0·48
	2	6,139 / 74,090·7	6,017 / 71,910·6	0·75 (0·55 to 1·01)	
	3	7,051 / 62,127·4	9,381 / 78,259·7	0·92 (0·75 to 1·13)	
	Highest	13,201 / 77,826·6	10,643,69,923·5	0·97 (0·86 to 1·10)	

AB, antibiotic prescriptions; AMS, antimicrobial stewardship; RR, rate ratio; RTI, self-limiting respiratory tract infection consultations

[a]adjusted for random effect of general practice and fixed effects of gender, age-group, comorbidity, region, quarter in study, practice-specific baseline rate and interaction with period

[b]test for interaction of trial arm with covariate

Supplementary Table 5: Antibiotic (AB) prescribing by type of RTI. (Cons., consultations; Pres., prescriptions).

Type of RTI	Intervention		Control		RR (95% CI)[a]
	Cons.	AB pres.	Cons.	AB pres.	
Colds and URTI	15,571	3,304	12,892	3,072	1·00 (0·69 to 1·44)
Cough and bronchitis	38,337	15,152	32,743	13,109	0·85 (0·71 to 1·03)
Otitis media	5,932	3,282	4,486	2,647	0·93 (0·75 to 1·14)
Rhinosinusitis	3,214	2,552	2,921	2,391	0·90 (0·69 to 1·18)
Sore throat	15,270	7,617	13,072	6,704	0·92 (0·79 to 1·08)

AB, antibiotic prescriptions for RTI; RR, rate ratio

[a]adjusted for random effect of general practice and fixed effects of gender, age-group, comorbidity, region, quarter in study, practice-specific baseline rate and interaction with period

Supplementary Figure 1: example of antibiotic prescribing report.

Reduce Trial

Practice Prescribing Report: February 2017

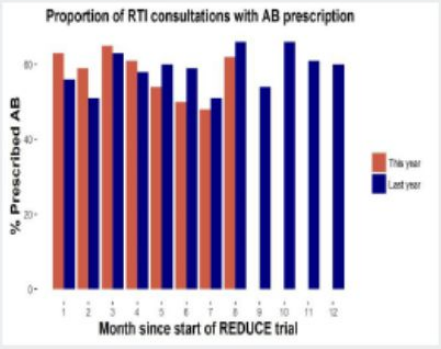
This is the ninth in a series of reports on your practice that you will receive during the REDUCE Trial. Collecting all 13 reports will provide evidence of audit suitable for use in appraisal.

Information about antibiotic prescribing at your Practice:

During the first six months of the Trial in your practice:

- There were 1714 consultations for RTI compared with 1882 in the same period last year
- The proportion of consultations with antibiotics prescribed was 57% compared with 58% in the same period last year
- There has been a a 1% reduction in antibiotic prescribing since the same time last year

	May 2015	Jun 2015	Jul 2015	Aug 2015	Sep 2015	Oct 2015	Nov 2015	Dec 2015	Jan 2016	Feb 2016	Mar 2016	Apr 2016	Total
RTI Consultations	176	210	163	160	230	259	337	347	314	276	304	245	3021
Antibiotic prescribed	99	107	103	93	139	154	172	229	170	181	184	147	1778
Percentage prescribed AB	56	51	63	58	60	59	51	66	54	66	61	60	59
	May 2016	**Jun 2016**	**Jul 2016**	**Aug 2016**	**Sep 2016**	**Oct 2016**	**Nov 2016**	**Dec 2016**	**Jan 2017**	**Feb 2017**	**Mar 2017**	**Apr 2017**	**Total**
RTI Consultations	232	207	149	184	206	220	258	258					1714
Antibiotic prescribed	147	123	97	112	111	110	123	160					983
Percentage prescribed AB	63	59	65	61	54	50	48	62					57
Change since last year (%)	7	8	2	3	-6	-9	-3	-4					-1



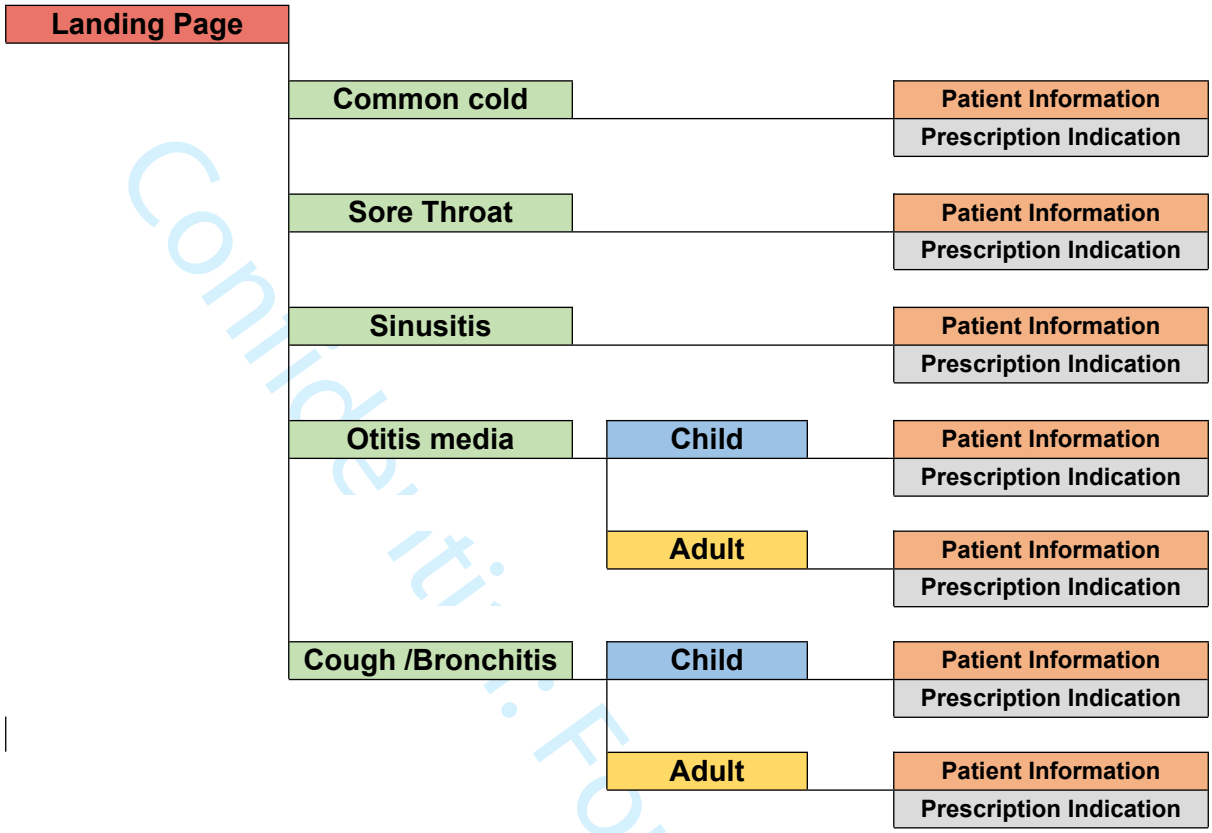
How to plan changes in antibiotic prescribing for your Practice

Patients can also be reassured that clinical trials and other research studies have shown that antibiotic prescription has little or no effect on the duration of illness or the severity of symptoms.

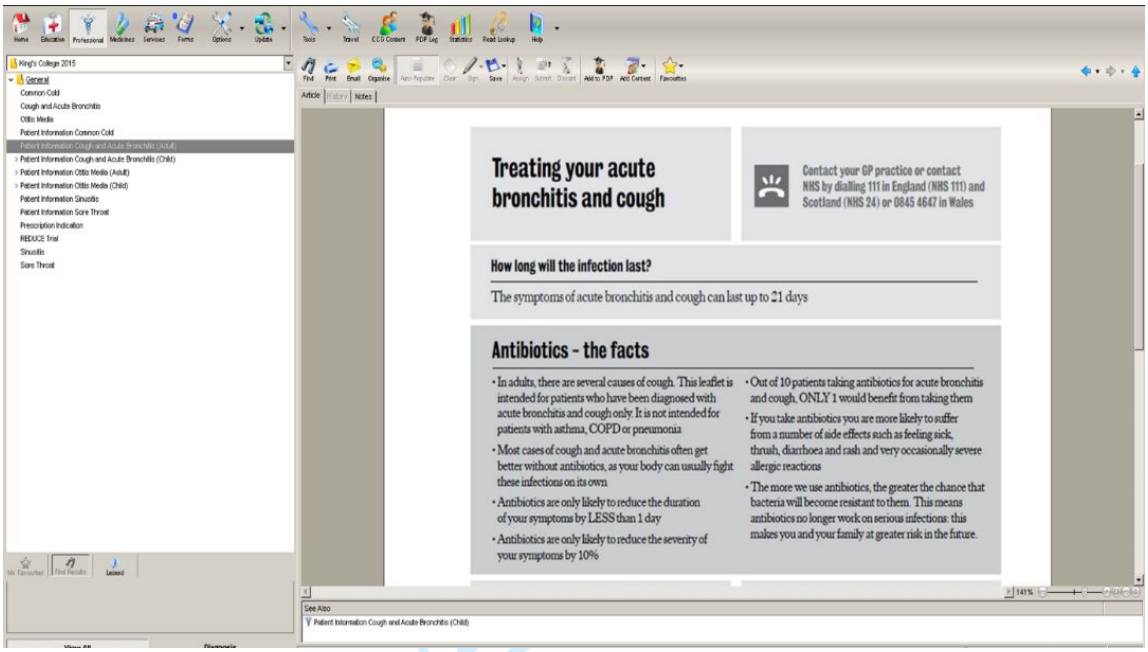
To help support patients, you can access the **Reduce Trial Support Tools** via DXS to print individualised information for patients.

For more information about this prescribing report please contact Professor Martin Gulliford at King's College London martin.gulliford@kcl.ac.uk.

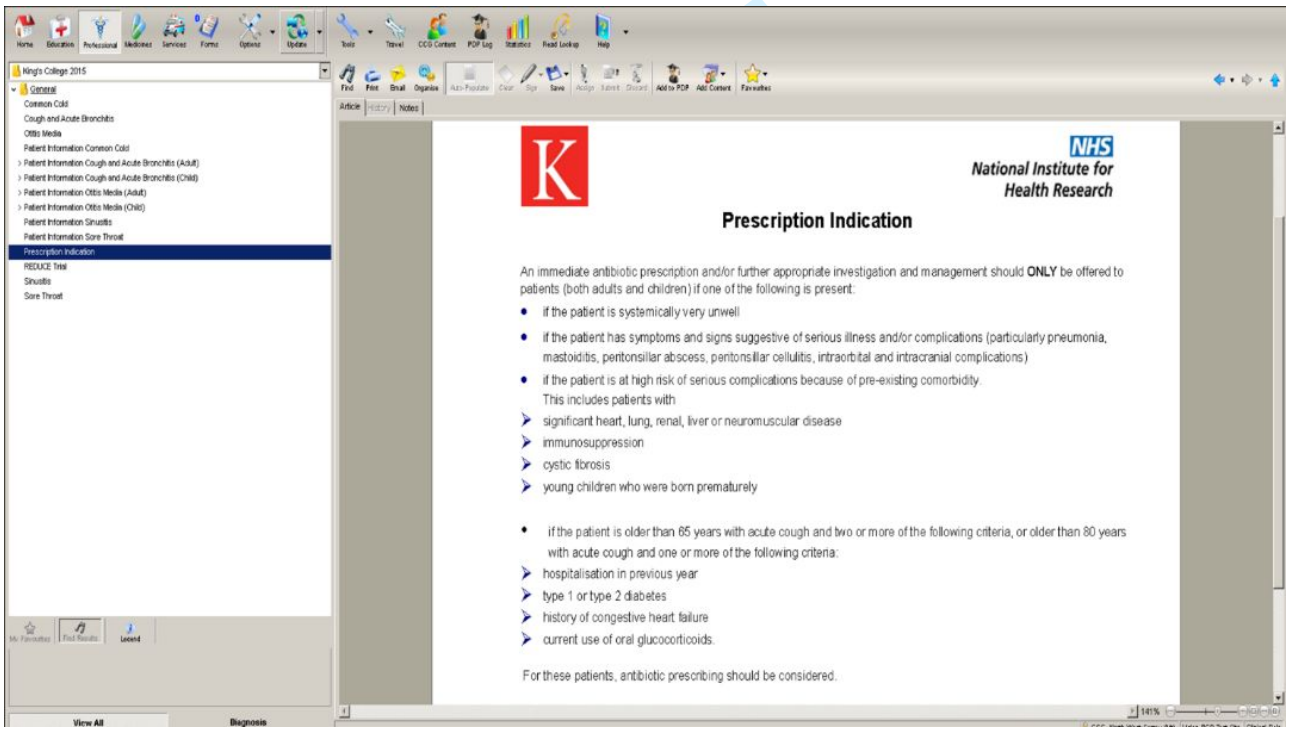
Supplementary Figure 2: Map of decision support tools.



Supplementary Figure 3: Part of one of the REDUCE Trial patient information leaflets.



Supplementary Figure 4: Screenshot showing the REDUCE Trial prescription indication page.



readcode	readterm	class
1656	Feverish cold	colds, influenza and URTI
16L..00	Influenza-like symptoms	colds, influenza and URTI
H0...00	Acute respiratory infections	colds, influenza and URTI
H00..00	Acute nasopharyngitis	colds, influenza and URTI
H00..11	Common cold	colds, influenza and URTI
H00..12	Coryza - acute	colds, influenza and URTI
H00..13	Febrile cold	colds, influenza and URTI
H00..14	Nasal catarrh - acute	colds, influenza and URTI
H00..15	Pyrexial cold	colds, influenza and URTI
H00..16	Rhinitis - acute	colds, influenza and URTI
H05..00	Other acute upper respiratory infections	colds, influenza and URTI
H051.00	Acute upper respiratory tract infection	colds, influenza and URTI
H054.00	Recurrent upper respiratory tract infection	colds, influenza and URTI
H05y.00	Other upper respiratory infections of multipl	colds, influenza and URTI
H05z.00	Upper respiratory infection NOS	colds, influenza and URTI
H05z.11	Upper respiratory tract infection NOS	colds, influenza and URTI
H05z.12	Viral upper respiratory tract infection NOS	colds, influenza and URTI
H06z111	Respiratory tract infection	colds, influenza and URTI
H07..00	Chest cold	colds, influenza and URTI
H0y..00	Other specified acute respiratory infections	colds, influenza and URTI
H0z..00	Acute respiratory infection NOS	colds, influenza and URTI
H27..00	Influenza	colds, influenza and URTI
H271.00	Influenza with other respiratory manifestatic	colds, influenza and URTI
H271z00	Influenza with respiratory manifestations NC	colds, influenza and URTI
H27y.00	Influenza with other manifestations	colds, influenza and URTI
H27y100	Influenza with gastrointestinal tract involver	colds, influenza and URTI
H27yz00	Influenza with other manifestations NOS	colds, influenza and URTI
H27z.00	Influenza NOS	colds, influenza and URTI
H27z.11	Flu like illness	colds, influenza and URTI
H27z.12	Influenza like illness	colds, influenza and URTI
H29..00	Avian influenza	colds, influenza and URTI
H2A..00	Influenza due to Influenza A virus subtype H1	colds, influenza and URTI
H2A..11	Influenza A (H1N1) swine flu	colds, influenza and URTI
Hyu0.00	[X]Acute upper respiratory infections	colds, influenza and URTI
Hyu0300	[X]Other acute upper respiratory infections/r	colds, influenza and URTI
Hyu0500	[X]Influenza+other manifestations,influenza	colds, influenza and URTI
Hyu0600	[X]Influenza+oth respiratory manifestatns,vir	colds, influenza and URTI
Hyu0700	[X]Influenza+other manifestations, virus not	colds, influenza and URTI
14B3.11	H/O: bronchitis	cough and bronchitis
171..00	Cough	cough and bronchitis
171..11	C/O - cough	cough and bronchitis
1712	Dry cough	cough and bronchitis
1713	Productive cough -clear sputum	cough and bronchitis
1714	Productive cough -green sputum	cough and bronchitis
1715	Productive cough-yellow sputum	cough and bronchitis
1716	Productive cough NOS	cough and bronchitis
1716.11	Coughing up phlegm	cough and bronchitis
1717	Night cough present	cough and bronchitis
1719	Chesty cough	cough and bronchitis

1719.11	Bronchial cough	cough and bronchitis
171A.00	Chronic cough	cough and bronchitis
171B.00	Persistent cough	cough and bronchitis
171C.00	Morning cough	cough and bronchitis
171D.00	Evening cough	cough and bronchitis
171E.00	Unexplained cough	cough and bronchitis
171F.00	Cough with fever	cough and bronchitis
171G.00	Bovine cough	cough and bronchitis
171H.00	Difficulty in coughing up sputum	cough and bronchitis
171J.00	Reflux cough	cough and bronchitis
171K.00	Barking cough	cough and bronchitis
171Z.00	Cough symptom NOS	cough and bronchitis
173B.00	Nocturnal cough / wheeze	cough and bronchitis
H06..00	Acute bronchitis and bronchiolitis	cough and bronchitis
H060.00	Acute bronchitis	cough and bronchitis
H060.11	Acute wheezy bronchitis	cough and bronchitis
H060000	Acute fibrinous bronchitis	cough and bronchitis
H060100	Acute membranous bronchitis	cough and bronchitis
H060200	Acute pseudomembranous bronchitis	cough and bronchitis
H060300	Acute purulent bronchitis	cough and bronchitis
H060400	Acute croupous bronchitis	cough and bronchitis
H060500	Acute tracheobronchitis	cough and bronchitis
H060600	Acute pneumococcal bronchitis	cough and bronchitis
H060700	Acute streptococcal bronchitis	cough and bronchitis
H060800	Acute haemophilus influenzae bronchitis	cough and bronchitis
H060900	Acute neisseria catarrhalis bronchitis	cough and bronchitis
H060A00	Acute bronchitis due to mycoplasma pneumo	cough and bronchitis
H060B00	Acute bronchitis due to coxsackievirus	cough and bronchitis
H060C00	Acute bronchitis due to parainfluenza virus	cough and bronchitis
H060D00	Acute bronchitis due to respiratory syncytial	cough and bronchitis
H060E00	Acute bronchitis due to rhinovirus	cough and bronchitis
H060F00	Acute bronchitis due to echovirus	cough and bronchitis
H060v00	Subacute bronchitis unspecified	cough and bronchitis
H060w00	Acute viral bronchitis unspecified	cough and bronchitis
H060x00	Acute bacterial bronchitis unspecified	cough and bronchitis
H060z00	Acute bronchitis NOS	cough and bronchitis
H061.00	Acute bronchiolitis	cough and bronchitis
H061000	Acute capillary bronchiolitis	cough and bronchitis
H061100	Acute obliterating bronchiolitis	cough and bronchitis
H061200	Acute bronchiolitis with bronchospasm	cough and bronchitis
H061300	Acute exudative bronchiolitis	cough and bronchitis
H061500	Acute bronchiolitis due to respiratory syncyti	cough and bronchitis
H061600	Acute bronchiolitis due to other specified org	cough and bronchitis
H061z00	Acute bronchiolitis NOS	cough and bronchitis
H06z.00	Acute bronchitis or bronchiolitis NOS	cough and bronchitis
H30..00	Bronchitis unspecified	cough and bronchitis
H30..11	Chest infection - unspecified bronchitis	cough and bronchitis
H300.00	Tracheobronchitis NOS	cough and bronchitis
H30z.00	Bronchitis NOS	cough and bronchitis
H310100	Smokers' cough	cough and bronchitis

Hyu1000	[X]Acute bronchitis due to other specified or	cough and bronchitis
Hyu1100	[X]Acute bronchiolitis due to other specified	cough and bronchitis
R062.00	[D]Cough	cough and bronchitis
1C3..00	Earache symptoms	otitis-media
1C32.00	Unilateral earache	otitis-media
1C33.00	Bilateral earache	otitis-media
1C3Z.00	Earache symptom NOS	otitis-media
1c3..00		otitis-media
A552.00	Postmeasles otitis media	otitis-media
F51..00	Nonsuppurative otitis media + eustachian tul	otitis-media
F510.00	Acute non suppurative otitis media	otitis-media
F510000	Acute otitis media with effusion	otitis-media
F510011	Acute secretory otitis media	otitis-media
F510100	Acute serous otitis media	otitis-media
F510200	Acute mucoid otitis media	otitis-media
F510300	Acute sanguinous otitis media	otitis-media
F510z00	Acute nonsuppurative otitis media NOS	otitis-media
F514.00	Unspecified nonsuppurative otitis media	otitis-media
F514100	Serous otitis media NOS	otitis-media
F514200	Catarrhal otitis media NOS	otitis-media
F514300	Mucoid otitis media NOS	otitis-media
F514z00	Nonsuppurative otitis media NOS	otitis-media
F52..00	Suppurative and unspecified otitis media	otitis-media
F520.00	Acute suppurative otitis media	otitis-media
F520000	Acute suppurative otitis media tympanic mer	otitis-media
F520100	Acute suppurative otitis media tympanic mer	otitis-media
F520300	Acute suppurative otitis media due to diseas	otitis-media
F520z00	Acute suppurative otitis media NOS	otitis-media
F524.00	Purulent otitis media NOS	otitis-media
F524000	Bilateral suppurative otitis media	otitis-media
F525.00	Recurrent acute otitis media	otitis-media
F526.00	Acute left otitis media	otitis-media
F527.00	Acute right otitis media	otitis-media
F528.00	Acute bilateral otitis media	otitis-media
F52z.00	Otitis media NOS	otitis-media
F52z.11	Infection ear	otitis-media
F540.00	Acute myringitis without otitis media	otitis-media
F540z00	Acute myringitis NOS	otitis-media
FyuP000	[X]Other acute nonsuppurative otitis media	otitis-media
FyuP200	[X]Other chronic suppurative otitis media	otitis-media
FyuP300	[X]Otitis media in bacterial diseases classifiec	otitis-media
FyuP400	[X]Otitis media in viral diseases classified else	otitis-media
FyuP500	[X]Otitis media in other diseases classified el	otitis-media
SN30.11	Aero-otitis media	otitis-media
H01..00	Acute sinusitis	rhinosinusitis
H01..11	Sinusitis	rhinosinusitis
H010.00	Acute maxillary sinusitis	rhinosinusitis
H010.11	Antritis - acute	rhinosinusitis
H011.00	Acute frontal sinusitis	rhinosinusitis
H012.00	Acute ethmoidal sinusitis	rhinosinusitis

H013.00	Acute sphenoidal sinusitis	rhinosinusitis
H014.00	Acute rhinosinusitis	rhinosinusitis
H01y.00	Other acute sinusitis	rhinosinusitis
H01y000	Acute pansinusitis	rhinosinusitis
H01yz00	Other acute sinusitis NOS	rhinosinusitis
H01z.00	Acute sinusitis NOS	rhinosinusitis
H130.12	Maxillary sinusitis	rhinosinusitis
H131.11	Frontal sinusitis	rhinosinusitis
H135.00	Recurrent sinusitis	rhinosinusitis
H13y100	Pansinusitis	rhinosinusitis
Hyu0000	[X]Other acute sinusitis	rhinosinusitis
SN31.11	Aerosinusitis	rhinosinusitis
1C9..00	Sore throat symptom	sorethroat
1C9..11	Throat soreness	sorethroat
1C92.00	Has a sore throat	sorethroat
1C93.00	Persistent sore throat	sorethroat
1C9Z.00	Sore throat symptom NOS	sorethroat
1CB3.00	Throat pain	sorethroat
1CB3.11	Pain in throat	sorethroat
2DB6.00	O/E - follicular tonsillitis	sorethroat
2DC2.00	O/E - granular pharyngitis	sorethroat
2DC3.00	Inflamed throat	sorethroat
A34..00	Streptococcal sore throat and scarlatina	sorethroat
A340.00	Streptococcal sore throat	sorethroat
A340100	Streptococcal laryngitis	sorethroat
A340200	Streptococcal pharyngitis	sorethroat
A340300	Streptococcal tonsillitis	sorethroat
A340z00	Streptococcal sore throat NOS	sorethroat
A34z.00	Streptococcal sore throat with scarlatina NOS	sorethroat
A383000	Fusobacterial necrotising tonsillitis	sorethroat
AA12.00	Vincent's pharyngitis	sorethroat
AA1z.11	Vincent's laryngitis	sorethroat
AA1z.12	Vincent's tonsillitis	sorethroat
AA25.11	Rhinopharyngitis mutilans	sorethroat
H02..00	Acute pharyngitis	sorethroat
H02..11	Sore throat NOS	sorethroat
H02..12	Viral sore throat NOS	sorethroat
H02..13	Throat infection - pharyngitis	sorethroat
H020.00	Acute gangrenous pharyngitis	sorethroat
H021.00	Acute phlegmonous pharyngitis	sorethroat
H022.00	Acute ulcerative pharyngitis	sorethroat
H023.00	Acute bacterial pharyngitis	sorethroat
H023000	Acute pneumococcal pharyngitis	sorethroat
H023100	Acute staphylococcal pharyngitis	sorethroat
H023z00	Acute bacterial pharyngitis NOS	sorethroat
H024.00	Acute viral pharyngitis	sorethroat
H02z.00	Acute pharyngitis NOS	sorethroat
H03..00	Acute tonsillitis	sorethroat
H03..11	Throat infection - tonsillitis	sorethroat
H03..12	Tonsillitis	sorethroat

H030.00	Acute erythematous tonsillitis	sorethroat
H031.00	Acute follicular tonsillitis	sorethroat
H032.00	Acute ulcerative tonsillitis	sorethroat
H033.00	Acute catarrhal tonsillitis	sorethroat
H034.00	Acute gangrenous tonsillitis	sorethroat
H035.00	Acute bacterial tonsillitis	sorethroat
H035000	Acute pneumococcal tonsillitis	sorethroat
H035100	Acute staphylococcal tonsillitis	sorethroat
H035z00	Acute bacterial tonsillitis NOS	sorethroat
H036.00	Acute viral tonsillitis	sorethroat
H037.00	Recurrent acute tonsillitis	sorethroat
H03z.00	Acute tonsillitis NOS	sorethroat
H04..00	Acute laryngitis and tracheitis	sorethroat
H040.00	Acute laryngitis	sorethroat
H040000	Acute oedematous laryngitis	sorethroat
H040100	Acute ulcerative laryngitis	sorethroat
H040200	Acute catarrhal laryngitis	sorethroat
H040300	Acute phlegmonous laryngitis	sorethroat
H040400	Acute haemophilus influenzae laryngitis	sorethroat
H040600	Acute suppurative laryngitis	sorethroat
H040w00	Acute viral laryngitis unspecified	sorethroat
H040x00	Acute bacterial laryngitis unspecified	sorethroat
H040z00	Acute laryngitis NOS	sorethroat
H041.00	Acute tracheitis	sorethroat
H041000	Acute tracheitis without obstruction	sorethroat
H041100	Acute tracheitis with obstruction	sorethroat
H041z00	Acute tracheitis NOS	sorethroat
H042.00	Acute laryngotracheitis	sorethroat
H042.11	Laryngotracheitis	sorethroat
H042000	Acute laryngotracheitis without obstruction	sorethroat
H042100	Acute laryngotracheitis with obstruction	sorethroat
H042z00	Acute laryngotracheitis NOS	sorethroat
H043.00	Acute epiglottitis (non strep)	sorethroat
H043.11	Viral epiglottitis	sorethroat
H043000	Acute epiglottitis without obstruction	sorethroat
H043100	Acute epiglottitis with obstruction	sorethroat
H043200	Acute obstructive laryngitis	sorethroat
H043211	Croup	sorethroat
H043z00	Acute epiglottitis NOS	sorethroat
H044.00	Croup	sorethroat
H04z.00	Acute laryngitis and tracheitis NOS	sorethroat
H050.00	Acute laryngopharyngitis	sorethroat
H052.00	Pharyngotracheitis	sorethroat
H053.00	Tracheopharyngitis	sorethroat
H055.00	Pharyngolaryngitis	sorethroat
H121100	Atrophic pharyngitis	sorethroat
H121200	Granular pharyngitis	sorethroat
H121300	Hypertrophic pharyngitis	sorethroat
H121400	Pharyngitis keratosa	sorethroat
H14y600	Lingular tonsillitis	sorethroat

H271000	Influenza with laryngitis	sorethroat
H271100	Influenza with pharyngitis	sorethroat
H301.00	Laryngotracheobronchitis	sorethroat
Hyu0100	[X]Acute pharyngitis due to other specified o	sorethroat
Hyu0200	[X]Acute tonsillitis due to other specified org	sorethroat
R041.00	[D]Throat pain	sorethroat

readcode	readterm	class
H50..00	Empyema	Empyema
H501100	Thorax abscess NOS	Empyema
H50z.00	Empyema NOS	Empyema
H501200	Pleural empyema	Empyema
H501400	Purulent pleurisy	Empyema
H500100	Empyema with bronchopleural fistula	Empyema
H501000	Pleural abscess	Empyema
H501500	Pyopneumothorax	Empyema
H501300	Lung empyema NOS	Empyema
H500.00	Empyema with fistula	Empyema
H501600	Pyothorax	Empyema
H501.00	Empyema with no fistula	Empyema
H500400	Empyema with pleural fistula NOS	Empyema
H500000	Empyema with bronchocutaneous fistula	Empyema
F040011	Cerebral abscess	ICRA
F040.11	Brain abscess	ICRA
F040.00	Intracranial abscess	ICRA
F040111	Cerebellar abscess	ICRA
F040000	Cerebral intracranial abscess	ICRA
F040511	Subdural intracranial abscess	ICRA
F040400	Extradural intracranial abscess	ICRA
F040311	Epidural intracranial abscess	ICRA
F040100	Cerebellar intracranial abscess	ICRA
F040500	Subdural intracranial abscess	ICRA
F040211	Otogenic intracranial abscess	ICRA
F040z00	Intracranial abscess NOS	ICRA
F040200	Otogenic intracranial abscess	ICRA
F040300	Epidural intracranial abscess	ICRA
A383011	Lemierre's syndrome	Lemierre
F53z.00	Mastoiditis NOS	MAS
F53..00	Mastoiditis and related conditions	MAS
F530.00	Acute mastoiditis	MAS
F531.00	Chronic mastoiditis	MAS
F531z00	Chronic mastoiditis NOS	MAS
F530.11	Abscess of mastoid	MAS
F530z00	Acute mastoiditis NOS	MAS
F530000	Acute mastoiditis without complications	MAS
F530100	Subperiosteal mastoid abscess	MAS
F530300	Acute mastoiditis with other complication	MAS
FyuP700	[X]Other mastoiditis and related conditions	MAS
F530.12	Empyema of mastoid	MAS
A360.00	Meningococcal meningitis	Meningitis
F00..00	Bacterial meningitis	Meningitis
A362.00	Meningococcal septicaemia	Meningitis
F001.00	Pneumococcal meningitis	Meningitis
F000.00	Haemophilus meningitis	Meningitis
A36..00	Meningococcal infection	Meningitis
F005.00	Meningitis - meningococcal	Meningitis
A366.00	Meningococcal meningitis with meningococcal sep	Meningitis

A365.00	Meningococcal meningitis with acute meningococc	Meningitis
F002.00	Streptococcal meningitis	Meningitis
A361.00	Meningococcal encephalitis	Meningitis
F033011	Meningococcal encephalitis	Meningitis
F00z.00	Bacterial meningitis NOS	Meningitis
A36z.00	Meningococcal infection NOS	Meningitis
A362000	Acute meningococcaemia	Meningitis
F033000	Encephalitis due to meningococcus	Meningitis
F00y.00	Other specified bacterial meningitis	Meningitis
F00yz00	Other specified bacterial meningitis NOS	Meningitis
Fyu0000	[X]Other bacterial meningitis	Meningitis
H15..11	Quinsy	PTA
H15..00	Peritonsillar abscess - quinsy	PTA
7531100	Drainage of peritonsillar abscess	PTA
7531111	Drainage of quinsy	PTA
2DB5.11	O/E - quinsy present	PTA
2DB5.00	O/E - tonsils - quinsy present	PTA
A341.00	Scarlet fever - scarlatina	ScarletFever
A341.11	Scarlet fever	ScarletFever
A341.12	Scarlatina	ScarletFever
65V7.00	Notification of scarlet fever	ScarletFever
1414	H/O: scarlatina	ScarletFever
A34..00	Streptococcal sore throat and scarlatina	ScarletFever
A34z.00	Streptococcal sore throat with scarlatina NOS	ScarletFever
A57y400	Pseudoscarlatina	ScarletFever
A57y300	Parascarlatina	ScarletFever
N300.00	Acute osteomyelitis	osteomyelitis
N302.00	Unspecified osteomyelitis	osteomyelitis
N302000	Unspecified osteomyelitis of unspecified site	osteomyelitis
N300600	Acute osteomyelitis of the lower leg	osteomyelitis
N302500	Unspecified osteomyelitis of the pelvic region and t	osteomyelitis
N300511	Hip acute osteomyelitis	osteomyelitis
N300700	Acute osteomyelitis of the ankle and foot	osteomyelitis
N302z00	Unspecified osteomyelitis NOS	osteomyelitis
N300z00	Acute osteomyelitis NOS	osteomyelitis
J064.12	Osteomyelitis - jaw	osteomyelitis
N302700	Unspecified osteomyelitis of the ankle and foot	osteomyelitis
N302600	Unspecified osteomyelitis of the lower leg	osteomyelitis
N300Q00	Acute osteomyelitis-femur	osteomyelitis
N300500	Acute osteomyelitis of the pelvic region and thigh	osteomyelitis
N300000	Acute osteomyelitis of unspecified site	osteomyelitis
N300S00	Acute osteomyelitis-tibia	osteomyelitis
N300Y00	Acute osteomyelitis-phalanx of toe	osteomyelitis
N300800	Acute osteomyelitis of other specified site	osteomyelitis
N302800	Unspecified osteomyelitis of other specified site	osteomyelitis
N300100	Acute osteomyelitis of the shoulder region	osteomyelitis
N300Z00	Acute haematogenous osteomyelitis	osteomyelitis
N300400	Acute osteomyelitis of the hand	osteomyelitis
N300712	Foot - acute osteomyelitis	osteomyelitis
A022400	Salmonella osteomyelitis	osteomyelitis

N300X00	Acute osteomyelitis-metatarsal	osteomyelitis
N302400	Unspecified osteomyelitis of the hand	osteomyelitis
NyuC300	[X]Other osteomyelitis	osteomyelitis
N300C00	Acute osteomyelitis-lumbar spine	osteomyelitis
N300N00	Acute osteomyelitis-phalanx of finger/thumb	osteomyelitis
N300200	Acute osteomyelitis of the upper arm	osteomyelitis
F4G0400	Orbital osteomyelitis	osteomyelitis
N300711	Ankle - acute osteomyelitis	osteomyelitis
N302a00	Osteomyelitis of vertebra	osteomyelitis
N309.00	Subacute osteomyelitis	osteomyelitis
N300U00	Acute osteomyelitis-calcaneum	osteomyelitis
N302100	Unspecified osteomyelitis of the shoulder region	osteomyelitis
N300300	Acute osteomyelitis of the forearm	osteomyelitis
N300T00	Acute osteomyelitis-fibula	osteomyelitis
N302200	Unspecified osteomyelitis of the upper arm	osteomyelitis
N302300	Unspecified osteomyelitis of the forearm	osteomyelitis
N300H00	Acute osteomyelitis-humerus	osteomyelitis
N300J00	Acute osteomyelitis-radius	osteomyelitis
N300F00	Acute osteomyelitis-clavicle	osteomyelitis
N300A00	Acute osteomyelitis-cervical spine	osteomyelitis
N300B00	Acute osteomyelitis-thoracic spine	osteomyelitis
N300P00	Acute osteomyelitis-pelvis	osteomyelitis
N300512	Pelvis acute osteomyelitis	osteomyelitis
N300513	Thigh acute osteomyelitis	osteomyelitis
N300R00	Acute osteomyelitis-patella	osteomyelitis
N300V00	Acute osteomyelitis-talus	osteomyelitis
N300M00	Acute osteomyelitis-metacarpal	osteomyelitis
N300D00	Acute osteomyelitis-sacrum	osteomyelitis
N302900	Unspecified osteomyelitis of multiple sites	osteomyelitis
NyuC000	[X]Other acute osteomyelitis	osteomyelitis
N300K00	Acute osteomyelitis-ulna	osteomyelitis
J064400	Acute osteomyelitis of jaw	osteomyelitis
N300W00	Acute osteomyelitis-other tarsal bone	osteomyelitis
N300E00	Acute osteomyelitis-coccyx	osteomyelitis
N300900	Acute osteomyelitis of multiple sites	osteomyelitis
H26..00	Pneumonia due to unspecified organism	pneumonia
H25..00	Bronchopneumonia due to unspecified organism	pneumonia
H21..00	Lobar (pneumococcal) pneumonia	pneumonia
H260.00	Lobar pneumonia due to unspecified organism	pneumonia
H261.00	Basal pneumonia due to unspecified organism	pneumonia
H2B..00	Community acquired pneumonia	pneumonia
H28..00	Atypical pneumonia	pneumonia
H260000	Lung consolidation	pneumonia
H231.00	Pneumonia due to mycoplasma pneumoniae	pneumonia
H22z.00	Bacterial pneumonia NOS	pneumonia
H2C..00	Hospital acquired pneumonia	pneumonia
H22..00	Other bacterial pneumonia	pneumonia
H25..11	Chest infection - unspecified bronchopneumonia	pneumonia
H23..00	Pneumonia due to other specified organisms	pneumonia
H263.00	Pneumonitis, unspecified	pneumonia

H223.00	Pneumonia due to streptococcus	pneumonia
H22y200	Pneumonia - Legionella	pneumonia
H26..11	Chest infection - pnemonia due to unspecified orga	pneumonia
H22..11	Chest infection - other bacterial pneumonia	pneumonia
H224.00	Pneumonia due to staphylococcus	pneumonia
H23z.00	Pneumonia due to specified organism NOS	pneumonia
H22yz00	Pneumonia due to bacteria NOS	pneumonia
H220.00	Pneumonia due to klebsiella pneumoniae	pneumonia
H262.00	Postoperative pneumonia	pneumonia
H221.00	Pneumonia due to pseudomonas	pneumonia
H24y200	Pneumonia with pneumocystis carinii	pneumonia
H222.00	Pneumonia due to haemophilus influenzae	pneumonia
H233.00	Chlamydial pneumonia	pneumonia
H243.00	Pneumonia with whooping cough	pneumonia
H24..00	Pneumonia with infectious diseases EC	pneumonia
H243.11	Pneumonia with pertussis	pneumonia
H22y.00	Pneumonia due to other specified bacteria	pneumonia
H21..11	Chest infection - pneumococcal pneumonia	pneumonia
H23..11	Chest infection - pneumonia organism OS	pneumonia
H24..11	Chest infection with infectious disease EC	pneumonia
H246.00	Pneumonia with aspergillosis	pneumonia
H24y000	Pneumonia with actinomycosis	pneumonia
H223000	Pneumonia due to streptococcus, group B	pneumonia
H222.11	Pneumonia due to haemophilus influenzae	pneumonia
H22y000	Pneumonia due to escherichia coli	pneumonia
H24z.00	Pneumonia with infectious diseases EC NOS	pneumonia
H247000	Pneumonia with candidiasis	pneumonia
H24y.00	Pneumonia with other infectious diseases EC	pneumonia
H242.00	Pneumonia with ornithosis	pneumonia
H22y011	E.coli pneumonia	pneumonia
H24y400	Pneumonia with salmonellosis	pneumonia
H24y300	Pneumonia with Q-fever	pneumonia
H22yX00	Pneumonia due to other aerobic gram-negative ba	pneumonia
H24yz00	Pneumonia with other infectious diseases EC NOS	pneumonia
H24y600	Pneumonia with typhoid fever	pneumonia
H232.00	Pneumonia due to pleuropneumonia like organism	pneumonia
H24y100	Pneumonia with nocardiasis	pneumonia
H230.00	Pneumonia due to Eaton's agent	pneumonia
H22y100	Pneumonia due to proteus	pneumonia
H247z00	Pneumonia with systemic mycosis NOS	pneumonia
H244.00	Pneumonia with tularaemia	pneumonia
H247100	Pneumonia with coccidioidomycosis	pneumonia
H24y500	Pneumonia with toxoplasmosis	pneumonia
K101.00	Acute pyelonephritis	pyelonephritis
K10y000	Pyelonephritis unspecified	pyelonephritis
K101z00	Acute pyelonephritis NOS	pyelonephritis
K10yz00	Unspecified pyelonephritis NOS	pyelonephritis
K10y.00	Pyelonephritis and pyonephrosis unspecified	pyelonephritis
K101000	Acute pyelonephritis without medullary necrosis	pyelonephritis
N010.11	Septic arthritis	SepticArthritis

N010.00	Pyogenic arthritis	SepticArthritis
N010y00	Pyogenic arthritis of other specified sites	SepticArthritis
N010600	Pyogenic arthritis of the lower leg	SepticArthritis
N010611	Knee pyogenic arthritis	SepticArthritis
N010800	Staphylococcal arthritis and polyarthritis	SepticArthritis
N010500	Pyogenic arthritis of the pelvic region and thigh	SepticArthritis
N010700	Pyogenic arthritis of the ankle and foot	SepticArthritis
N010z00	Pyogenic arthritis NOS	SepticArthritis
N010511	Hip pyogenic arthritis	SepticArthritis
N010100	Pyogenic arthritis of the shoulder region	SepticArthritis
N010400	Pyogenic arthritis of the hand	SepticArthritis
N010211	Elbow pyogenic arthritis	SepticArthritis
N010300	Pyogenic arthritis of the forearm	SepticArthritis
N010311	Wrist pyogenic arthritis	SepticArthritis
N010000	Pyogenic arthritis of unspecified site	SepticArthritis
N010200	Pyogenic arthritis of the upper arm	SepticArthritis
N010711	Ankle pyogenic arthritis	SepticArthritis
N010x00	Pyogenic arthritis of multiple sites	SepticArthritis
N010900	Pneumococcal arthritis and polyarthritis	SepticArthritis
A38z.00	Septicaemia NOS	TSSSepticaemia
A381.00	Staphylococcal septicaemia	TSSSepticaemia
A380.00	Streptococcal septicaemia	TSSSepticaemia
A382.00	Pneumococcal septicaemia	TSSSepticaemia
A384200	Escherichia coli septicaemia	TSSSepticaemia
A384211	E.coli septicaemia	TSSSepticaemia
A3Ay100	Toxic shock syndrome	TSSSepticaemia
A384.00	Septicaemia due to other gram negative organisms	TSSSepticaemia
A021.00	Salmonella septicaemia	TSSSepticaemia
A38y.00	Other specified septicaemias	TSSSepticaemia
A381000	Septicaemia due to Staphylococcus aureus	TSSSepticaemia
A380100	Septicaemia due to streptococcus, group B	TSSSepticaemia
A384300	Pseudomonas septicaemia	TSSSepticaemia
A384000	Gram negative septicaemia NOS	TSSSepticaemia
A384100	Haemophilus influenzae septicaemia	TSSSepticaemia
A380300	Septicaemia due to streptococcus pneumoniae	TSSSepticaemia
A380400	Septicaemia due to enterococcus	TSSSepticaemia
A380000	Septicaemia due to streptococcus, group A	TSSSepticaemia
L090z00	Septicaemia NOS following abortive pregnancy	TSSSepticaemia
A383.00	Septicaemia due to anaerobes	TSSSepticaemia
Ayu3J00	[X]Septicaemia, unspecified	TSSSepticaemia
A270100	Listeria septicaemia	TSSSepticaemia
A381100	Septicaemia due to coagulase-negative staphyloco	TSSSepticaemia
R055200	[D]Endotoxic shock	TSSSepticaemia
A380500	Vancomycin resistant enterococcal septicaemia	TSSSepticaemia
Ayu3F00	[X]Streptococcal septicaemia, unspecified	TSSSepticaemia
A384z00	Other gram negative septicaemia NOS	TSSSepticaemia
Ayu3G00	[X]Septicaemia due to other gram-negative organis	TSSSepticaemia
A271100	Erysipelothrix septicaemia	TSSSepticaemia
Ayu3E00	[X]Other streptococcal septicaemia	TSSSepticaemia
Ayu3H00	[X]Other specified septicaemia	TSSSepticaemia

ISAC APPLICATION FORM
PROTOCOLS FOR RESEARCH USING THE CLINICAL PRACTICE RESEARCH DATALINK (CPRD)

ISAC use only:		**IMPORTANT**
Protocol Number	.....	**If you have any queries, please contact ISAC Secretariat:**
Date submitted	.....	ISAC@cprd.com

1. Study Title

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

2. Principal Investigator (full name, job title, organisation & e-mail address for correspondence regarding this protocol)

Martin Gulliford

3. Affiliation (full address)

King's College London, Department of Primary Care and Public Health Sciences

4. Protocol's Author (if different from the principal investigator)

5. List of all investigators/collaborators (*please list the names, affiliations and e-mail addresses* of all collaborators*, other than the principal investigator)

Mark Ashworth mark.ashworth@kcl.ac.uk , Senior Lecturer in General Practice
Judith Charlton, Judith.charlton@kcl.ac.uk, Research Associate
Paul Little, p.little@soton.ac.uk, Professor of Primary Care Research, University of Southampton
Lisa McDermott, Lisa.mcdermott@kcl.ac.uk , Research Associate
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Rathi Ravindrarajah, rathi.ravindrarajah@kcl.ac.uk Research Associate

Please note that your ISAC application form and protocol **must be copied to all e-mail addresses listed above at the time of submission of your application to the ISAC mailbox. Failure to do so will result in delays in the processing of your application.*

6. Type of Institution (please tick one box below)

Academia	☒	Research Service Provider	☐	Pharmaceutical Industry	☐
NHS	☐	Government Departments	☐	Others	☐

7. Financial Sponsor of study

Pharmaceutical Industry *(please specify)*	☐	Academia*(please specify)*	☒ *NIHR HTA support requested*
Government / NHS *(please specify)*	☐	None	☐
Other *(please specify)*	☐		

8. Data source *(please tick one box below)*

Sponsor has on-line access	☒	Purchase of ad hoc dataset	☐
Commissioned study	☐		
Other	☐ *(please specify)*		

9. Has this protocol been peer reviewed by another Committee?

Yes*	☒	No	☐

** Please state in your protocol the name of the reviewing Committee(s) and provide an outline of the review process and outcome. NIHR HTA programme board, provisionally supported subject to comments.*

10. Type of Study *(please tick all the relevant boxes which apply)*

Adverse Drug Reaction/Drug Safety	☐	Drug Use	☐	Disease Epidemiology	☐
Drug Effectiveness	☐	Pharmacoeconomic	☐	Other	☒

Cluster randomised trial

11. This study is intended for:

Publication in peer reviewed journals	☒	Presentation at scientific conference	☒
Presentation at company/institutional meetings	☐	Other	

12. Does this protocol also seek access to data held under the CPRD Data Linkage Scheme?

Yes ☒ No ☐

13. If you are seeking access to data held under the CPRD Data Linkage Scheme*, please select the source(s) of linked data being requested.

☒ Hospital Episode Statistics ☐ Cancer Registry Data**
☐ MINAP ☐ ONS Mortality Data
☒ Index of Multiple Deprivation/ Townsend Score
☐ Mother Baby Link ☐ Other: (please specify)

** As part of the ISAC review of linkages, the protocol may be shared - in confidence - with a representative of the requested linked data set(s) and summary details may be shared - in confidence - with the Confidentiality Advisory Group of the Health Research Authority.*

***Please note that applicants seeking access to cancer registry data must provide consent for publication of their study title and study institution on the UK Cancer Registry website. Please contact the CPRD Research Team on +44 (20) 3080 6383 or email kc@cprd.com to discuss this requirement further.*

14. If you are seeking access to data held under the CPRD Data Linkage Scheme, have you already discussed your request with a member of the Research team?

Yes ☒ No* ☐

**Please contact the CPRD Research Team on +44 (20) 3080 6383 or email kc@cprd.com to discuss your requirements before submitting your application.*

Please list below the name of the person/s at the CPRD with whom you have discussed your request.
Gerard McCann

15. If you are seeking access to data held under the CPRD Data Linkage Scheme, please provide the following information:

The number of linked datasets requested: 1

A synopsis of the purpose(s) for which the linkages are required:
We are seeking linked HES data in order to estimate hospital utilisation by trial participants.

Is linkage to a local dataset with <1 million patients being requested?

Yes* ☐ No ☒

** If yes, please provide further details:*

16. If you have requested linked data sets, please indicate whether the Principal Investigator or any of the collaborators listed in response to question 5 above, have access to any of the linked datasets in a patient identifiable form, or associated with a patient index.

Yes* ☐ No ☒

** If yes, please provide further details:*

17. Does this protocol involve requesting any additional information from GPs?

Yes* ☒ No ☐

** Please indicate what will be required:*

Completion of questionnaires by the GP[ψ] Yes ☐ No ☐

Provision of anonymised records (e.g. hospital discharge summaries) Yes ☐ No ☐

Other (please describe)

GPs will be asked to participate in a process evaluation of the trial. Research Ethics Committee approval will be obtained for this. This will not require any individual patient data.

[ψ] Any questionnaire for completion by GPs or other health care professional must be approved by ISAC before circulation for completion.

18. Does this protocol describe a purely observational study using CPRD data (this may include the review of anonymised free text)?

Yes* ☐ No** ☒

** Yes: If you will be using data obtained from the CPRD Group, this study does not require separate ethics approval from an NHS Research Ethics Committee.*
*** No: You may need to seek separate ethics approval from an NHS Research Ethics Committee for this study. The ISAC will provide advice on whether this may be needed.*

19. Does this study involve linking to patient *identifiable* data from other sources?

Yes ☐ No ☒

20. Does this study require contact with patients in order for them to complete a questionnaire?

Yes ☐ No ☒

N.B. Any questionnaire for completion by patients must be approved by ISAC before circulation for completion.

21. Does this study require contact with patients in order to collect a sample?

Yes* ☐ No ☒

** Please state what will be collected*

22. Experience/expertise available

Please complete the following questions to indicate the experience/expertise available within the team of researchers actively involved in the proposed research, including analysis of data and interpretation of results

	Previous GPRD/CPRD Studies	Publications using GPRD/CPRD data
None	☐	☐
1-3	☐	☐
> 3	☒	☒

	Yes	No
Is statistical expertise available within the research team?	☒	☐
If yes, please outline level of experience	*Professor of Medical Statistics*	
Is experience of handling large data sets (>1 million records) available within the research team?	☒	☐

If yes, please outline level of experience	*Several previous CPRD studies*	
Is UK primary care experience available within the research team?	☒	☐
If yes, please outline level of experience	*3 practising GPs*	

23. References relating to your study

Please list up to 3 references (most relevant) relating to your proposed study.

1: Gulliford MC, van Staa TP, McDermott L, McCann G, Charlton J, Dregan A; eCRT Research Team. Cluster randomized trials utilizing primary care electronic health records: methodological issues in design, conduct, and analysis (eCRT Study). Trials. 2014 Jun 11;15(1):220. doi: 10.1186/1745-6215-15-220. PubMed PMID: 24919485; PubMed Central PMCID: PMC4062282.

2: Dregan A, van Staa TP, McDermott L, McCann G, Ashworth M, Charlton J, Wolfe CD, Rudd A, Yardley L, Gulliford MC. Point-of-Care Cluster Randomized Trial in Stroke Secondary Prevention Using Electronic Health Records. Stroke. 2014 Jul;45(7):2066-2071. Epub 2014 Jun 5. PubMed PMID: 24903985.

3. Electronic Health Records for Intervention Research: A Cluster Randomized Trial to Reduce Antibiotic Prescribing in Primary Care (eCRT Study) *Ann Fam Med 2014 July 14 (forthcoming)*

PROTOCOL CONTENT CHECKLIST

In order to help ensure that protocols submitted for review contain adequate information for protocol evaluation, ISAC have produced instructions on the content of protocols for research using CPRD data. These instructions are available on the CPRD website (www.cprd.com/ISAC). All protocols using CPRD data which are submitted for review by ISAC must contain information on the areas detailed in the instructions. IF you do not feel that a specific area required by ISAC is relevant for your protocol, you will need to justify this decision to ISAC.

Applicants must complete the checklist below to confirm that the protocol being submitted includes all the areas required by ISAC, or to provide justification where a required area is not considered to be relevant for a specific protocol. Protocols will not be circulated to ISAC for review until the checklist has been completed by the applicant.

Please note, your protocol will be returned to you if you do not complete this checklist, or if you answer 'no' and fail to include justification for the omission of any required area.

	Included in protocol?		
Required area	Yes	No	If no, reason for omission
Lay Summary (max.200 words)	☒	☐	
Background	☒	☐	
Objective, specific aims and rationale	☒	☐	
Study Type *Descriptive* *Hypothesis Generating* *Hypothesis Testing*	 ☐ ☐ ☒	 ☐ ☐ ☐	
Study Design	☒	☐	
Sample size/power calculation (Please provide justification of sample size in the protocol)	☒	☐	
Study population (including estimate of expected number of relevant patients in the CPRD)	☒	☐	
Selection of comparison group(s) or controls	☒	☐	
Exposures, outcomes and covariates *Exposures are clearly described* *Outcomes are clearly described*	☒ ☒ ☒	☐ ☐ ☐	
Use of linked data (if applicable)	☒	☐	
Data/ Statistical Analysis Plan *There is plan for addressing confounding* *There is a plan for addressing missing data*	☒ ☒ ☒	☐ ☐ ☐	
Patient/ user group involvement [†]	☒	☐	
Limitations of the study design, data sources and analytic methods	☒	☐	
Plans for disseminating and communicating study results	☒	☐	

[†] ***It is expected that many studies will benefit from the involvement of patient or user groups in their planning and refinement, and/or in the interpretation of the results and plans for further work. This is particularly, but not exclusively true of studies with interests in the impact on quality of life. Please indicate whether or not you intend to engage patients in any of the ways mentioned above.***

Voluntary registration of ISAC approved studies:

Epidemiological studies are increasingly being included in registries of research around the world, including those primarily set up for clinical trials. To increase awareness amongst researchers of ongoing research, ISAC encourages voluntary registration of epidemiological research conducted using MHRA databases. This will not replace information on ISAC approved protocols that may be published in its summary minutes or annual report. It is for the applicant to determine the most appropriate registry for their study. Please inform the ISAC secretariat that you have registered a protocol and provide the location.

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.

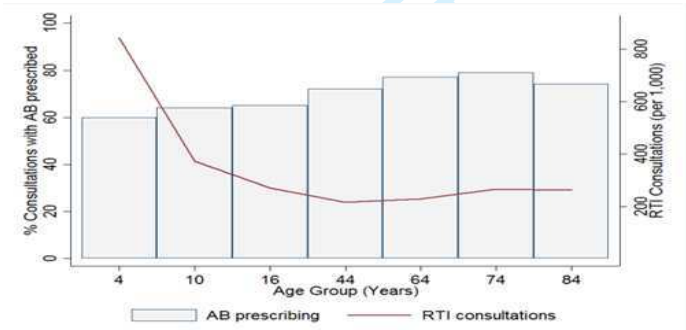


Figure 1: Age-specific consultation rates for respiratory tract infections and proportion of RTI consultations with antibiotics prescribed in CPRD, 2000. Source: Ashworth et al. (2006).

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.

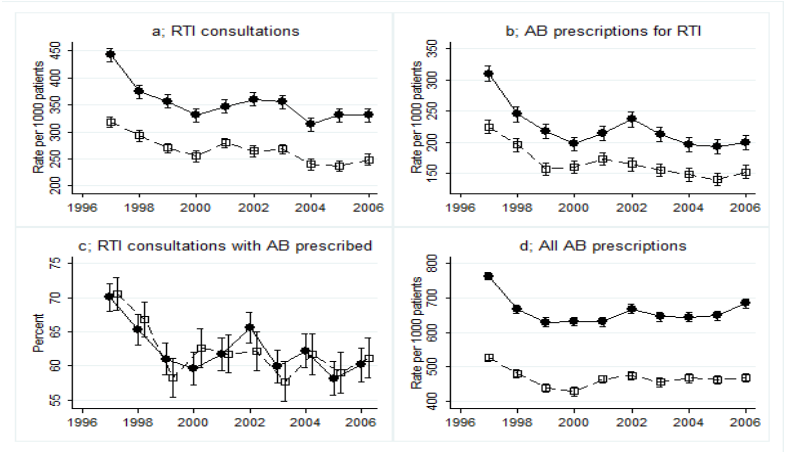


Figure 2: Data from CPRD for RTI consultations and antibiotic prescriptions from 1996 to 2006. Source: Gulliford et al. (2009).

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.

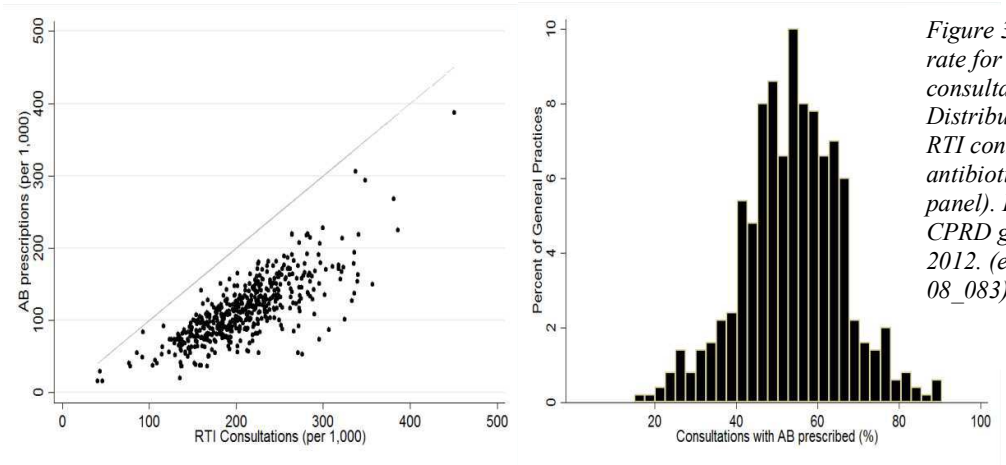


Figure 3: Antibiotic prescribing rate for RTI plotted against RTI consultation rate (left panel). Distribution for proportion of RTI consultations with antibiotic prescribed (right panel). Data are for 500 UK CPRD general practices in 2012. (eCRT Trial data 08_083).

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.

Trial 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.

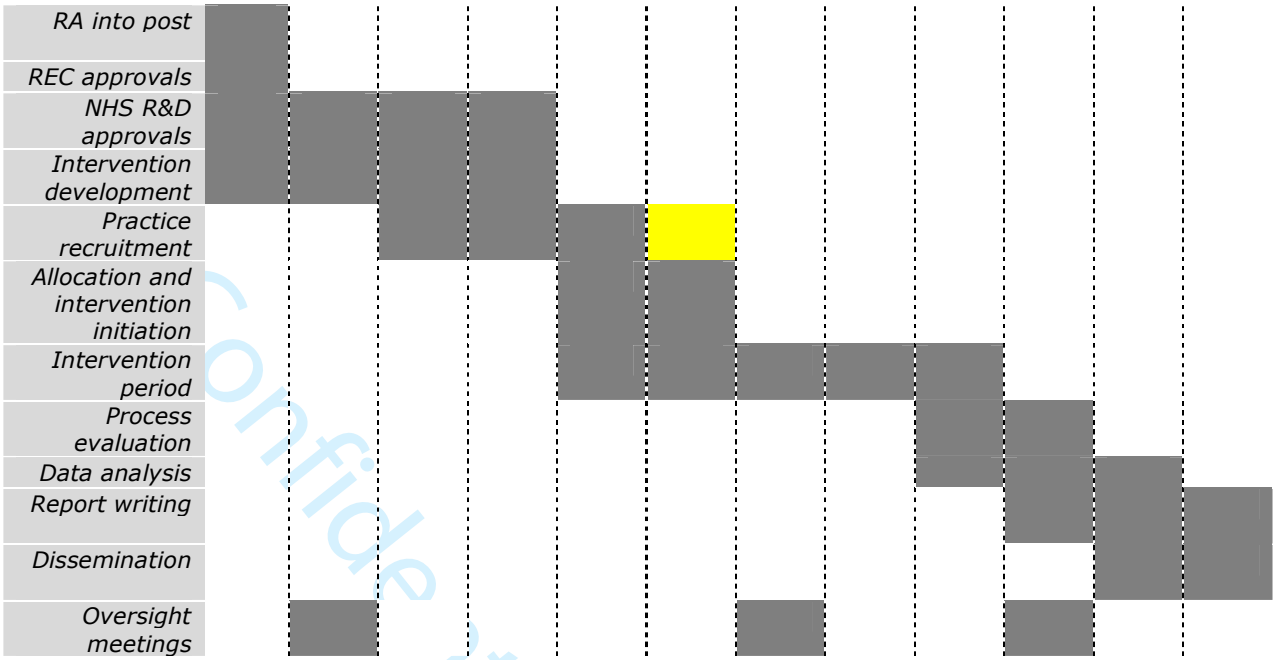
We have discussed the proposal with the behavioural insights team at Public Health England (PHE) who have indicated their interest in the project as potentially providing evidence on scalable behaviour change strategies that may be used to support the government's strategy on antimicrobial resistance (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

Year 1				Year2				Year 3			
Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4



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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Amendment 1. Dated 26th August 2015.

This amendment is to modify the definition of safety outcomes for the trial and to specify the pre-trial (baseline) assessment of safety outcomes.

On page 19, the safety outcomes are listed as 'Pneumonia and lower respiratory tract infections, peritonsillar abscess, mastoiditis, skin infections and bacterial infections'. Following review of recent NICE guidance (NG15, 2015), 'intracranial abscess' and 'empyema' will be included as safety outcomes. 'Bacterial infections' will now be omitted as lacking specificity.

On page 15 (first paragraph), where it reads '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.'

We now wish to specify that the period of study for these analyses will be 2005 to 2014. Analysis of safety outcomes will be included in these analyses. Antibiotic prescribing will be evaluated in terms of the antibiotic prescribing rate for RTI for 1,000 registered patients (Primarily) and according to the antibiotic prescribing proportion (secondarily). In order to effect the analysis, CPRD practices will be divided into quartiles of high/medium/low antibiotic prescribing practices but, if there appears to be a linear effect, then the antibiotic prescribing measures may also be fitted as linear predictors in secondary analyses. In the primary analysis, a composite comprising any of the safety outcomes will be evaluated. In secondary analyses, each safety outcome will be evaluated separately. As there are six safety outcomes a Bonferroni correction will be applied.

Amendment 2 dated 17th November 2015

This amendment is to add to the safety outcomes being monitored for the trial. It is also to request linked practice-level deprivation score data to aid in interpretation of analyses.

At the trial Data Monitoring Committee held on 20th October 2015, it was recommended to include the following conditions as safety outcomes to be monitored during the trial and reported to the DMC: 'Scarlet Fever, pyelonephritis, septic arthritis, osteomyelitis, meningitis, toxic shock syndrome and septicaemia'. This amendment is to add these to the measures being evaluated in safety analyses as outlined in Amendment 1.

We are also requesting access to practice level IMD 2010 score data. This is understand whether antibiotic prescribing and infection risk are association with deprivation, and to adjust for deprivation as a confounder in analyses. As we have extensive previous experience of analysing IMD data, we have not contacted CPRD staff for this request as yet. However, Helen Strongman is a member of the DMC.

Thank you for considering this amendment.

Major amendment 3: - dated 19th July 2016

This amendment concerns the revised sample size and revised timeline of the study.

Present situation

The Reduce Trial had an initial recruitment target of 120 CPRD general practices to be recruited by March 2016. At present we have 76 CPRD general practices randomised to the study. (Two intervention trial arm practices have withdrawn from CPRD). It now appears unlikely that the target of 120 general practices can be achieved since the number of general practices that are currently contributing to CPRD has declined rapidly from 562 in January 2013 to 311 in June 2016. This results from a national trend of general practices moving away from using the Vision software used by CPRD practices. Consequently, we are recruiting from a much smaller pool of eligible general practices. We have recruited about 24.4% of active CPRD practices. We have considered the option of recruiting general practices outside of CPRD, but there are practical difficulties of obtaining monthly uploads of data from non-CPRD practices, whose data may not be well quality assured.

In order to complete the trial on schedule and within-budget, we propose to complete recruitment at the end of July 2016, by which time we hope that close to 80 general practices may be included in the trial. This suggests a proposed alteration to the sample size statement. There will be now be 80% power to detect a 15 per 1000 difference in prescribing rate and 90% power to detect a 3.5% difference in AB prescribing proportion if 80 practices are recruited, even allowing for 4 of the 80 practices to withdraw. The study will be completed by January 2018 as initially planned.

On 11th July 2016 we have attended HTA Monitoring Hub Visit to discuss our progress on general practice recruitment to the REDUCE Trial. The HTA programme wanted to be clear that there was no alternative to recruiting more practices and emphasized that would like to see the study succeed. The HTA programme agreed to the revised sample size and revised timeline proposed by the study team.

Thank you for considering this amendment.

Major amendment 4 dated 12th June 2017

This amendment concerns the statistical analysis plan (SAP) for the trial. The SAP has been written by the Trial Statistician (A Prevost) and the Principal Investigator (M Gulliford). The SAP has been reviewed and approved by the independent Data Monitoring Committee (meeting on 20th April 2017) and the Trial Steering Committee (meeting on 8th June 2017).

Unit of analysis

The 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.

Method of analysis

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 month following the intervention start date. 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 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. A similar approach will be employed for each of the secondary outcomes.

Use of cluster-level analysis

Cluster-level analyses will now be implemented as secondary analyses using data aggregated to general practice level, using the family practice-specific rates or proportions as observations. We will compare the results of cluster-level analyses that include the 69 practices that completed 12 months of follow-up, with individual-level analyses that include data for the same 69 practices. This will allow us to evaluate whether the different analytical approaches lead to any difference of interpretation.

ISAC EVALUATION OF PROTOCOLS FOR RESEARCH INVOLVING CPRD DATA

FEEDBACK TO APPLICANTS

CONFIDENTIAL	**by e-mail**		
PROTOCOL NO:	*14_130A4*		
PROTOCOL TITLE:	Electronically delivered, multi-component intervention to reduce unnecessary antibiotic prescribing in primary care. Cluster randomised trial using electronic health records (eCRT2)		
APPLICANT:	Martin Gulliford King's College London, Department of Primary Care and Public Health Sciences		
APPROVED ☒	**APPROVED WITH COMMENTS (resubmission not required)** ☐	**REVISION/ RESUBMISSION REQUESTED** ☐	**REJECTED** ☐

INSTRUCTIONS:

Please include your response/s to the Reviewer's feedback below only if you are required to Revise/ Resubmit your protocol.

Protocols with an outcome of 'Approved' or 'Approved with comments' do not require resubmission to the ISAC.

Protocol 14_130A4 is approved.

DATE OF ISAC FEEDBACK:	15/06/2017
DATE OF APPLICANT FEEDBACK:	

For protocols approved from 01 April 2014 onwards, applicants are required to include the ISAC protocol in their journal submission with a statement in the manuscript indicating that it had been approved by the ISAC (with the reference number) and made available to the journal reviewers. If the protocol was subject to any amendments, the last amended version should be the one submitted.

***** Please refer to the ISAC advice about protocol amendments provided below*****

Amendments to protocols approved by ISAC Version June 2015

During the course of some studies, it may become necessary to deviate from a protocol which has been approved by ISAC. Any deviation to an ISAC approved protocol should be clearly documented by the applicant but not all such amendments need be submitted for ISAC review and approval. The general principles to be applied in regard to the need for submission are as follows:

- Major amendments should be submitted
- Minor amendments need not be submitted (but must still be documented by the applicant and should normally be mentioned at the publication stage)

In cases of uncertainty, the applicant should contact the ISAC secretariat for advice quoting the original reference number and providing a brief explanation of the nature of the amendment(s) and underlying reason(s).

Major Amendments

We consider an amendment as major if it substantially changes the study design or analysis plan of the proposed research. An amendment should be considered major if it involves the following (although this is not necessarily an exhaustive list):

- A change to the primary hypothesis being tested in the research
- A change to the design of the study
- Additional outcomes or exposures unrelated to the main focus of the approved study*
- Non-trivial changes to the analysis strategy
- Not performing a primary outcome analysis
- Omissions from the analysis plan which may impact on important validity issues such as confounding
- Change of Chief Investigator
- Use of additional linkages to other databases
- Any new proposal involving contact with health professionals or patient or change in regard to such matters

* N.B. extensive changes in this respect will require a new protocol rather than an amendment - if in doubt please consult the Secretariat

Minor Amendments

Examples of amendments which can generally be considered minor include the following:

- Change of personnel other than the Chief Investigator (these should be notified to the Secretariat)
- A change to the definition of the study population, providing the change is mentioned and justified in the paper/output [NB previously major]
- Extension of the time period in relation to defining the study population
- Changes to the definitions of outcomes or exposures of interest, providing the change is mentioned and justified in the paper/output [NB previously major]
- Not using linked data which are part of the approved protocol, unless the linked data are considered critical in defining exposures or outcomes (in which case this would be a major amendment)
- Limited additional analysis suggested by unexpected findings, provided these are clearly presented as post-hoc

- Additional methods to further control for confounding or sensitivity analysis provided these are to be reported as secondary to the main findings
- Validation and data quality work provided additional information from GPs is not required

To submit an amendment of protocol to the ISAC, please submit the following documents to the ISAC mailbox (isac@cprd.com)

1. A covering letter providing justification for the request
2. A completed and, if necessary, updated application form with all changes highlighted; if new linkages are required the current version of the ISAC application form must be completed. Otherwise, the original form may be amended as necessary
3. **The updated protocol document containing the heading 'Amendment' at the end of it.** Please include all amendments to the protocol under this heading. No other changes should be made to the already approved document.