The Effect of Audit & Feedback on Prescribing Behaviour and Engagement with Data on OpenPrescribing.net - A Randomised Controlled Trial Protocol

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1. SYNOPSIS

Study Title	The Effect of Audit & Feedback on Prescribing Behaviour and Engagement with Data on OpenPrescribing.net - A Randomised Controlled Trial Protocol	
Internal ref. no.	OPAF1	
Study Setting	The study setting is NHS GP practices in England. In May 2017, there were 58.4 million residents registered at 7,463 general practices, organised into 207 Clinical Commissioning Groups (CCGs). The study will be carried out at the Evidence-Based Medicine DataLab at the University of Oxford.	
Study Design	Cluster-randomised, controlled parallel-group trial. Participants will be allocated to intervention or control group in a 1:1 ratio, block-randomised by CCG. Those in the intervention group will be allocated to receive one of two different styles of intervention, block-randomised by CCG. Practices will receive three communications at regular intervals. We are seeking to investigate superiority of any intervention over control, and to explore the relative impact of two different interventions.	
Study Participants	GP Practices in England	
Planned Sample Size	1400 practices	
Planned Study Period	15 weeks	
	Objectives	**Outcome Measures**
Primary	P1. Our overall objective is to determine whether receipt of data feedback highlighting potential for improvement in antibiotic prescribing prompts practices to Improve performance in prescribing and increase their engagement with prescribing data.	ENGAGEMENT: Difference in the proportion of practices having their dashboard viewed during the 15 week intervention period, between intervention and control groups. PRESCRIBING: Difference in the proportion of antibiotics prescribed which were broad-spectrum, during the follow-up period, between intervention and control groups.
Secondary	Our secondary objectives are to identify: S1. Whether behavioural change techniques affect the level of engagement; S2. Which method of communication is most effective (email, letter,	ENGAGEMENT: ● Difference in the proportion of practices having their dashboard viewed during the 15 week intervention period, and in the proportion of broad-spectrum antibiotics

	fax) at prompting practices to engage and improve performance; S3. Whether the intervention can lead to a wider impact on prescribing behaviours.	prescribed, between groups A and B (Objective S1). ● Difference in the mean dashboard views per practice during the 15 week intervention period, for intervention versus control groups, and for group A versus B (Objective P1, S1). ● Number of practices accessing at least one link provided in the intervention, as a proportion of all practices contacted, for group A versus B (Objective S1). ● Number of links accessed at least once as a proportion of all links delivered by each method of contact (email, fax, letter) (Objective S2). ● Proportion of emails opened overall; and total number of links accessed from emails as a proportion of those opened, during the follow-up period, for intervention A versus B (Objective S2). ● Exploratory descriptive analysis of browsing sessions arising from each link accessed: number of browsing sessions, number of different IP addresses, and number of pages viewed per session (to explore sharing of links among professionals) (Objectives S1-3, contamination). PRESCRIBING: ● From the primary outcome measure we will estimate the overall effect of the intervention on the number of broad-spectrum antibiotics prescribed during the follow-up period. This will be calculated as the total difference between the observed number of

		broad-spectrum antibiotics per practice and the expected number had they been in the control group, using the regression model. ● To assess wider impact on prescribing behaviours (Objective S3), we will also calculate the difference in other national antibiotic prescribing measures (a-c below) during the follow-up period, between intervention and control groups. These will be analysed using multivariable linear regression as per the primary outcome, except where otherwise stated. a) Rate of total antibiotic prescribing per adjusted population unit, Antibiotic STAR-PU (Specific Therapeutic group Age-sex Related Prescribing Unit) (EBM-DataLab 2017b). As this is a rate we will use a poisson regression model for analysis. b) Mean number of daily doses per prescription for uncomplicated urinary tract infections (UTIs), measured as the mean number of average daily quantities (ADQs) per item, of trimethoprim 200mg tablets, nitrofurantoin 50mg tablets/capsules, nitrofurantoin 100mg M/R capsules and pivmecillinam 200mg

		tablets (EBM-DataLab 2017c). c) Mean number of trimethoprim items prescribed as a percentage of all nitrofurantoin and trimethoprim items, per practice (EBM-DataLab 2017a). ● Each of the primary and secondary outcomes will also be compared between intervention groups A and B (Objective S1).

2. ABBREVIATIONS

ADQ	Average Daily Quantity
CCG	Clinical Commissioning Group
CI	Chief Investigator
CTRG	Clinical Trials & Research Governance, University of Oxford
CUREC	Central University Research Ethics Committee
GCP	Good Clinical Practice
GP	General Practitioner
IDREC	Interdisciplinary Research Ethics Committee
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PI	Principal Investigator
SOP	Standard Operating Procedure
STAR-PU	Specific Therapeutic group Age-sex Related Prescribing Unit

3. BACKGROUND AND RATIONALE

Prescribing medications in primary care involves keeping in line with a large number of guidelines. However, decisions are often made locally and can be slow to respond to changes in evidence. OpenPrescribing.net, an openly accessible service which transforms the monthly national prescribing datasets into meaningful charts on key measures of prescribing safety, efficacy and cost-effectiveness, demonstrates the huge variation across (and within) practices and their parent organisations (CCGs). Although CCGs have medicines optimisation teams to facilitate and promote best practice in prescribing in their local regions, there is clear need for a more coordinated approach. Appropriate prescribing of antibiotics is one critical public health issue which varies across the country.

On the OpenPrescribing site we have four measures of appropriate antibiotic prescribing, based upon national guidelines intended to minimise the development of resistant bacteria (NICE 2015). The use of broad-spectrum antibiotics is one of the most crucial of the national targets, as these should be reserved for "last resort" treatment, and are rarely indicated in primary care settings.

We aim to test an "audit and feedback" methodology, sending practices tailored information on their recent broad-spectrum antibiotic prescribing compared to their peers, in an attempt to both engage participants with their data and impact their behaviour.

Audit and feedback has been shown to be capable of changing behaviour of practitioners of primary care, to a limited extent (Ivers et al. 2012). However, the optimal way to communicate audit and feedback interventions is not yet clear. Labour-intensive complex methods such as pharmacist assistance or face-to-face meetings at every practice can be an effective part of audit and feedback; however, they are costly and not currently feasible to roll out on a national level, so we aim to test the effect of written communications. Interventions previously having the most impact have been individualised, frequent and give clear actions to be taken (Brehaut et al. 2016). Unfortunately the data currently available only allows monitoring at whole-practice level rather than individual prescribers, but the selected measure allows us to provide a simple action plan, and we can send frequent (approximately monthly) updates on performance.

There have been a variety of attempts to change prescribing behaviour for antibiotics, but none have led to routine continuation or national expansion. Our intervention, if effective, can be easily rolled out for multiple prescribing behaviours and supplied on an ongoing basis. One previous trial, using computer-based decision aids to improve antibiotic prescribing for respiratory tract infections (RTIs), has been expanded to a larger-scale follow-up study (Gulliford et al. 2014; Juszczyk et al. 2016), but only practices in the Clinical Practice Research Datalink (CPRD) are included, and they must opt in. Moreover, the earlier trial together with its partner study required grant funding of £338,000 to set up. Our trial has much smaller cost implications given the data and website infrastructure already in place, lack of opt-in procedure and no requirement to install software on participants' systems.

Our trial will be similar in scope to another recent trial which provided feedback on total antibiotics to the 20% of GP prescribers with the highest baseline levels and made a small but significant impact (Hallsworth et al. 2016). A similar methodology targeting dentists was also successful in changing behaviour (Elouafkaoui et al. 2016). We will also contact the highest-prescribing 20%, approximately 1,400 of 7,000 active practices in England, half of which will be randomised to the control group and receive no intervention. Our methods will differ in that the intervention will be sent from a University research group rather than an NHS body, be delivered by fax and email as well as postal mail, and we will

investigate whether an impact can be made upon more than one area of prescribing through increased engagement with data.

We will also test two different styles of intervention by randomising intervention practices again into two arms, A and B. Group A will receive a behaviour-change optimised series of three interventions: (1) antibiotic feedback; (2) antibiotic feedback plus provision of evidence that feedback is effective at changing clinical behaviour; (3) feedback on another prescribing measure available at OpenPrescribing.net, inviting recipients to access the site to monitor their data. This sequence will allow us to supply clear messages to recipients. Group B will instead receive three interventions which are all similar, highlighting their performance on antibiotics, but also inviting them to use the OpenPrescribing site to monitor their data.

Within every intervention, practices will be supplied with a link to their practice dashboard on OpenPrescribing.net, with a slight difference according to wave (Intervention 1,2,3) and method of sending (email, fax, letter). In addition to measuring engagement, we will measure the impact of the interventions on antibiotic prescribing performance and the wider impact on other measures of prescribing quality, to test whether practices act upon other areas of performance displayed on the website.

If the trial is found to be effective, we will also roll out the most impactful intervention to the control group at the end of the trial for three interventions (or less if found to be sufficient), and roll out to other measures in order to provide a routine audit and feedback service for improvement of prescribing in primary care.

Objectives

P1. Our overall objective is to determine whether receipt of data feedback highlighting potential for improvement in antibiotic prescribing prompts practices to Improve performance in prescribing and increase their engagement with prescribing data.

Our secondary objectives are to identify:

S1. Whether behavioural change techniques affect the level of engagement;
S2. Which method of communication is most effective (email, letter, fax) at prompting practices to engage and improve performance;
S3. Whether the intervention can lead to a wider impact on prescribing behaviours.

Our null hypothesis is that feedback on current prescribing performance has no impact on information-seeking or prescribing behaviour.

Risks and Benefits to Participants

Risks: (1) Time burden on busy GPs. How minimised: Participants can choose whether or not to engage with the intervention at all and if so, how much time they wish to spend on it. We also give them the option to opt out of further communications. (2) Participants unaware they are in a trial. How minimised: No individuals will be identifiable. Can ignore or opt-out freely. Data in public arena already. Engagement rates are an important outcome for the study and contacting practices for consent would bias this. In addition, it is not necessary to obtain consent from practices to use practice-level prescribing data because it is already publicly available and licensed for this purpose. We will not be collecting any

identifiable personal information directly from the practices beyond that which is already in the public domain. Any feedback that is received will be anonymised so it will not be possible to identify which individual at a GP practice provided it. (3) Change of care of patients as a result of the intervention. How minimised: The prescribers involved in the trial will remain responsible for the safe and appropriate care of their patients using their professional judgement. Our intervention will only reiterate existing national guidelines, and not advise changing the care of any specific patients. No additional risk of harm is anticipated in relation to the trial. Prescribers are also responsible for keeping up to date with the latest drug safety alerts and other relevant information when prescribing. If we detect signals of actively dangerous prescribing by individual practices, we will alert their local CCG Medicines Optimisation team.

Benefits: Increased awareness of their prescribing behaviour in comparison to national trends and of price variations of drugs they prescribe. Increased awareness of national guidelines on prescribed medications. Empowerment to improve the safety, efficacy and cost-effectiveness of their prescribing choices.

4. OBJECTIVES AND OUTCOME MEASURES

4.1. Core Outcomes

Objectives	**Outcome Measures**	**Timepoint(s) of evaluation of this outcome measure (if applicable)**
Primary Objective P1. Our overall objective is to determine whether receipt of data feedback highlighting potential for improvement in antibiotic prescribing prompts practices to Improve performance in prescribing and increase their engagement with prescribing data.	ENGAGEMENT: Difference in the proportion of practices having their dashboard viewed during the 15 week intervention period, between intervention and control groups. PRESCRIBING: Difference in the proportion of antibiotics prescribed which were broad-spectrum, during the follow-up period, between intervention and control groups.	ENGAGEMENT: Follow-up period: 5 weeks following each wave, including day of sending (total 15 weeks). Baseline period: 15 weeks prior to first intervention. PRESCRIBING: Follow-up period: corresponding six month period, one year on from baseline period. Baseline period: latest available six months of data at start of study.

Our secondary objectives are to identify: S1. Whether behavioural change techniques affect the level of engagement; S2. Which method of communication is most effective (email, letter, fax); S3. Whether the intervention can lead to a wider impact on prescribing behaviours.	ENGAGEMENT: ● Difference in the proportion of practices having their dashboard viewed during the 15 week intervention period, and in the proportion of broad-spectrum antibiotics prescribed, between groups A and B (Objective S1). ● Difference in the mean dashboard views per practice during the 15 week intervention period, for intervention versus control groups, and for group A versus B (Objective P1, S1). ● Number of practices accessing at least one link provided in the intervention, as a proportion of all practices contacted, for group A versus B (Objective S1). ● Number of links accessed at least once as a proportion of all links delivered by each method of contact (email, fax, letter) (Objective S2). ● Proportion of emails opened overall; and total number of links accessed from emails as a proportion of those opened, during the follow-up period, for intervention A versus B (Objective S2). ● Exploratory descriptive analysis of browsing sessions arising from each link accessed: number of browsing sessions, number of different IP addresses, and number of pages viewed per session (to explore sharing of links among professionals) (Objectives S1-3, contamination). PRESCRIBING: ● From the primary outcome measure we will estimate the overall effect of the intervention on the number of broad-spectrum antibiotics prescribed during the follow-up period. This will be calculated as the total difference between the observed number of broad-spectrum antibiotics per practice and the expected number had they been in the control group, using the regression model. ● To assess wider impact on prescribing behaviours (Objective S3), we will also calculate the difference in other national antibiotic prescribing measures (a-c below) during the follow-up period, between intervention and control groups.	See above.

	These will be analysed using multivariable linear regression as per the primary outcome, except where otherwise stated. a) Rate of total antibiotic prescribing per adjusted population unit, Antibiotic STAR-PU (Specific Therapeutic group Age-sex Related Prescribing Unit) (EBM-DataLab 2017b). As this is a rate we will use a poisson regression model for analysis. b) Mean number of daily doses per prescription for uncomplicated urinary tract infections (UTIs), measured as the mean number of average daily quantities (ADQs) per item, of trimethoprim 200mg tablets, nitrofurantoin 50mg tablets/capsules, nitrofurantoin 100mg M/R capsules and pivmecillinam 200mg tablets (EBM-DataLab 2017c). c) Mean number of trimethoprim items prescribed as a percentage of all nitrofurantoin and trimethoprim items, per practice (EBM-DataLab 2017a). ● Each of the primary and secondary outcomes will also be compared between intervention groups A and B (Objective S1).	

4.2. Other Analyses

Sub-group analyses:

The primary and secondary prescribing outcome measures will also be compared between the sub-groups interacting with the link supplied, versus those not interacting; and for the sub-group which excludes those opting-out of the intervention.

Qualitative measures:

The responses to the feedback question asked upon following the link in any of the interventions will be analysed against prior and post usage of the site. Any other feedback supplied by participants will also be collected (anonymously) and key themes compiled.

Detection of contamination:

Contamination is most likely to occur between practices belonging to the same CCGs, as practices are subject to management of prescribing by CCG Medicines Optimisation teams. However, this will be controlled for by block-randomising practices by CCG. Contamination beyond CCG boundaries may also occur through wider organisations or personal communications. However, provision of tailored advice

should minimise the possibility for contamination among peer groups. By tracking links and web page access, rarely for an RCT we will be able to measure the extent of contamination by some routes:

- Link sharing (links and pages accessed by multiple IP addresses)
- Number of non-intervention practices having their OpenPrescribing.net pages viewed during sessions arising from links being clicked. This could either arise from participants observing other practices' behaviour after their own, or sharing the links with others who then look for their own practice.

4.3. Strengths and Limitations

ENGAGEMENT:

Measuring visits to practice dashboards allows us to monitor any overall change in levels of interaction with prescribing data which may result from the intervention, for example recipients may sign up for a routine alert, and access the site through that method. In order to be counted in the primary outcome, users must click elsewhere on the page after following a link provided, to indicate they are exploring data beyond antibiotics. However, site traffic may be affected by other factors such as media attention, which may cause some contamination. This should affect both the intervention and control groups equally, but we can also assess the level of contamination as described below. Practice dashboards may be accessed by persons not directly involved with provision of care at that practice, such as patients, drug company representatives or members of CCGs. However, this should also be divided amongst control and intervention practices. The provision of links allows a high level of precision in the measurement of direct interaction with the intervention, as visits to the site through all other sources can be excluded for this measure. Practices may act upon the feedback without accessing the links provided; this will be captured in the measurement of prescribing behaviour. Page views by members of the research group will be excluded by installing tools which block activity from being tracked.

PRESCRIBING:

The change in the selected antibiotic measure as the primary outcome gives a simple and comprehensible figure of percentage point change, comparable to similar audit & feedback studies. We will also assess the effect across other national antibiotic measures, to estimate the wider impact. These measures are consistent with national targets, of which prescribers should be aware. A potential weakness of the primary outcome measure is that a high measure value could result from occasional (perhaps appropriate) prescribing of broad-spectrum items in practices which are strict guardians of all antibiotics (and therefore prescribe all antibiotics in very low numbers). However, this should be evenly distributed between intervention and control groups.

5. STUDY DESIGN

Cluster-randomised, controlled parallel-group trial. Participants will be allocated to intervention or control group in a 1:1 ratio, block-randomised by CCG. Those in the intervention group will be allocated to receive one of two different styles of intervention, block-randomised by CCG. Practices will receive three communications at regular 5-week intervals. We are seeking to investigate superiority of any intervention over control, and to explore the relative impact of two different interventions. A follow-up letter will be sent to intervention practices 6-12 months after the end of the trial, to summarise any

improvements in prescribing behaviour and also to serve as a reminder of how to use the OpenPrescribing site to monitor other prescribing behaviours.

Interventions will be delivered every 5 weeks for 15 weeks. The first intervention will be delivered on the first Friday of the month at the start of the intervention (such that the baseline data used is as recent as possible). The second and third will be 5 weeks and 10 weeks later, respectively. Sending on Fridays helps to ensure that all interventions arriving by different routes are likely to be accessed by participants at a similar time (i.e. Monday). Sending every five weeks ensures that an updated monthly dataset will be available for each intervention.

Engagement data will be accessed via Google Analytics as per standard practice for any website. Practice-level prescribing data will be obtained from national datasets published monthly by NHS Digital, with approximately two months' lag time (NHS-Digital 2017). This is generated from claims for items dispensed from pharmacies so cannot be altered by practices except by changes in prescribing behaviour. It is routinely compiled and loaded into our database. We will also collect responses to a simple feedback question. The first time each link is ever accessed (by any IP address), a single (anonymous) feedback question will be asked: "Did the message we sent give you new information about your prescribing?" to which an answer ("Yes" or "No") should be selected.

6. PARTICIPANT IDENTIFICATION AND RECRUITMENT

6.1. Study Participants

Participants will be GP Practices in England (and any staff involved in prescribing therein) ranking in the worst 20% for prescribing broad-spectrum antibiotics. The initial set of lowest-ranked practices will continue to be included in the trial, i.e. the highest prescribers of broad spectrum antibiotics will not be re-identified during the trial. However, if new quarterly organisation data is released from NHS Digital during the intervention period, practices which have changed status or become dormant may be excluded from further interventions.

6.2. Inclusion and Exclusion Criteria

The eligibility criteria are set out in Table 1.

Table 1. Eligibility criteria for practices.

GP Practice Eligibility Criteria	**Rationale**	**Data source / timepoint**
Standard GP practices (Setting type 4) in England	Exclude non-standard settings such a walk-in centres, prisons etc.	Latest release of NHS Digital organisation data
At least one method of contact (postal address, fax number and/or email address)	Required for intervention to be sent.	At time of randomisation
Active status	Exclude dormant and closed practices.	Latest release of NHS Digital organisation data
Opened at least 6 months before start	Completeness of baseline data.	Latest release of NHS

of trial		Digital organisation data
>= 1,000 registered patients (with 10-85% aged 25-64)	Exclude non-standard practices. Limit noise in data. Exclude practices in process of closing.	Latest release of NHS Digital organisation data
>= 1000 total items prescribed per month	Limit noise in data. Low volume may be a sign of impending closure.	Latest month of prescribing baseline
>= 60 total antibiotic items prescribed in 6 months	Limit noise in data. Low volume can be a sign of missing pharmacy claims data.	Whole prescribing baseline period
Individual practices and whole CCGs not involved in preliminary testing	Prior exposure to intervention. This will exclude from the study the CCG in which RC is employed.	Prior to intervention
Worst 20% of prescribers of broad-spectrum antibiotics of all antibiotics	Target those with poorest performance.	Whole prescribing baseline period

7. STUDY PROCEDURES

7.1. Recruitment

All GP Practices in England will be identified in the latest release of NHS Digital organisation data. No recruitment strategies will be employed because all practices will be screened, and those included will be sent information without prior contact, in order to measure real-world impact of a large-scale intervention. However, practices will be free to ignore the correspondence and supplied with instructions on opting-out.

7.2. Screening and Eligibility Assessment

GP practices will be screened against the eligibility criteria using the latest release of NHS Digital organisation data and prescribing data. This will be carried out by the research team using a pre-written script at the same time as recruitment (included within Appendix A).

7.3. Informed Consent

Informed consent will not be sought. This study is similar to two previous studies where the participants were healthcare professionals and the intervention involved sending information to practices, with no face-to-face contact, and the need for consent was waived: Hallsworth et al 2016 (England) and Guthrie et al 2016 (Scotland).

Similar to those studies, our intervention is a supply of non-sensitive, publicly available information relevant only to the recipients. Recipients will receive information in their professional capacity in the NHS, and routinely receive comparable material from other sources. Our intervention adds no additional burden unless participants choose to engage further; participants are free to simply ignore the communications or opt-out if they wish. Further, our aim is to measure the impact of a wide-scale, low-cost audit & feedback intervention; obtaining consent would invalidate this process as, much like an

Intention To Treat analysis, engagement rates are an important outcome for the study and contacting practices for consent would bias this.

In addition, it is not necessary to obtain consent from practices to use practice-level prescribing data because it is already publicly available and licensed for this purpose. We will not be collecting any identifiable personal information directly from the practices beyond that which is already in the public domain. Any feedback that is received will be anonymised so it will not be possible to identify which individual at a GP practice provided it.

7.4. Randomisation

We will identify practices, apply eligibility criteria and assign to intervention and control groups, block-randomised by CCG concurrently, as indicated in Figure 1. This will all be implemented together in pre-prepared software (Appendix A). Outcome measurement and statistical analysis will be performed using pre-prepared scripts (Appendix B), so it is not necessary for researchers to be blinded to allocation. Participants will not be informed that they are in a trial.

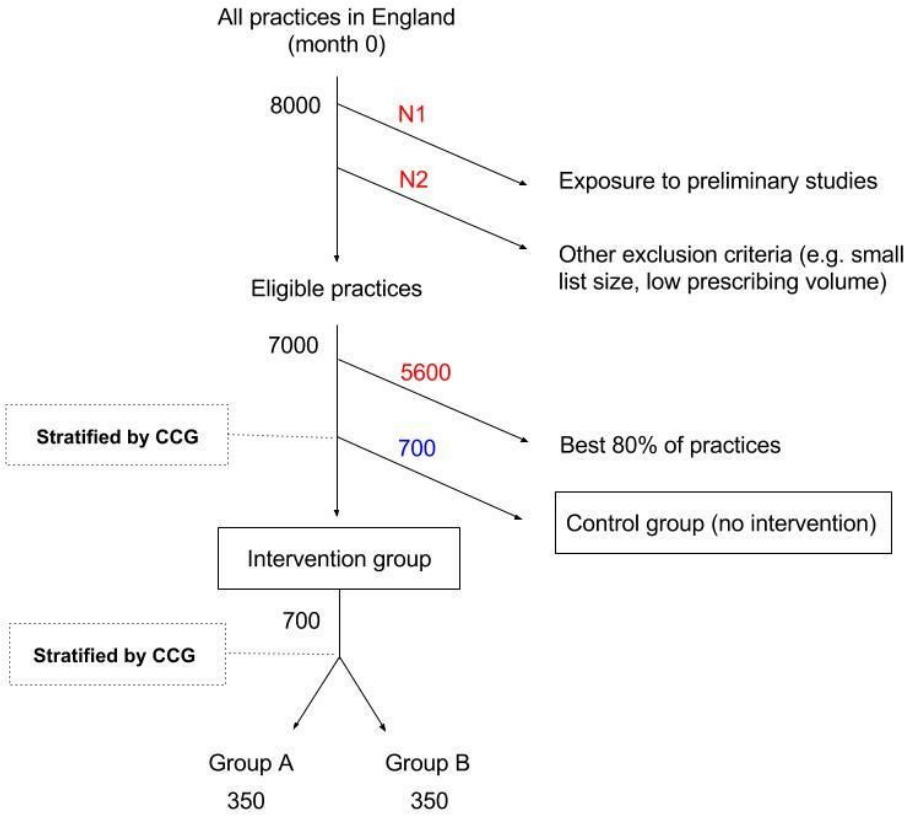

Figure 1. *Indicative participant identification and allocation procedure, with approximate sample sizes.*

7.5. Baseline Assessments

At the time of randomisation we will measure the baseline proportion of antibiotics prescribed which were broad-spectrum, in order to identify the highest 20% of practices. All other baseline measurements will be carried out in the data analysis process, using pre-prepared scripts (Appendix B).

7.6. Follow-Up Data collection

Follow-up data for prescribing outcomes will be collected from the publicly available prescribing data, when published by NHS Digital approximately two months after the end of the prescribing follow-up period. For engagement outcomes, follow-up data will be extracted from Google Analysis services immediately after completion of the engagement follow-up period. Data extraction and follow-up measurements will be carried out as in the pre-written scripts in Appendix B. Any feedback received from participants will be recorded (anonymously) in a spreadsheet.

7.7. Discontinuation/Withdrawal of Participants from Study

The whole intervention, or specified method(s) of contact, will be discontinued upon practice request, but those practices will be included in the analysis of engagement and prescribing outcomes. A record will be kept of practices opting out. Interventions will be forwarded to new contact details if provided. Any practices which are found to have changed status (from being a standard practice) or become dormant/closure during the intervention will be excluded from further interventions and be excluded from analysis. Our intervention is not expected to influence overall items prescribed, number of patients, change of status or closure/dormancy of practices. Outcome measures will not be monitored through the trial, so the intervention will not be modified or discontinued for any other foreseeable reason. Withdrawn participants will not be replaced.

7.8. Definition of End of Study

The end of study is the date of the last intervention being sent.

7.9. Improving and Monitoring Adherence

There will be no attempt to improve adherence beyond the intervention itself, but engagement with the intervention will be monitored (see Outcomes).

7.10. Concomitant Management

While participating in the trial, intervention practices will also subject to usual management, such as other local or national guidelines or interventions, and use the other information available on OpenPrescribing.net. Individual members of some practices may be subscribed to monthly email alerts from OpenPrescribing, but these are expected to be equally distributed between the intervention and control groups.

8. INTERVENTIONS / INVESTIGATIONS

The 'intervention' will be the delivery of tailored written feedback to each practice, which details their recent performance on the selected measure in a graphical form and invites recipients to access the other services available at OpenPrescribing.net via a unique link for their practice.

Participants will be randomly allocated to receive no communication, variant A, or variant B:

A. Behaviour-change optimised series of three different interventions (attached files): (1) antibiotic feedback, designed to provide enough information to allow prescribers to assess and change their antibiotic prescribing behaviour without needing to access the website; (2) antibiotic feedback "reminder", plus provision of link to evidence showing how feedback has been effective at changing antibiotic prescribing behaviour; (3) more information about the other data available at OpenPrescribing.net, potential cost savings highlighted, an example of another measure on which they rank poorly amongst other practices, and inviting recipients to access the site to monitor their prescribing data.

B. All-In-One: practices in this group will instead receive three interventions which are all similar, highlighting their performance on antibiotics, but also inviting them to use the OpenPrescribing site to monitor their data.

Interventions will be delivered to practices by all available routes concurrently (email, letter and fax). Addresses are freely available from NHS Digital. Fax and email addresses were obtained via FOI requests sent to CCGs, and from practice websites on NHS Choices. Practice email addresses are primarily either generic with no named recipient, or contain the name of the practice manager (or other administrative function). Where multiple details were available for the same practices, all will be used.

Within every intervention, practices will be supplied with a link to their practice dashboard on OpenPrescribing.net. The first time each link is ever accessed (by any IP address), a single (anonymous) feedback question will be asked: "Did the message we sent give you new information about your prescribing?" After an answer ("Yes" or "No") is selected, the dashboard will appear, with the selected measure highlighted. On the dashboard, practices can find more detail on this measure and others, along with interactive charts. Users will also be able to see how other practices/CCGs perform and access all the usual features of the website such as custom analyses.

9. STATISTICS AND ANALYSIS

9.1. Description of Statistical Methods

Data analysis will be carried out using pre-prepared scripts (Appendix B).

Engagement outcomes:

- We will extract data on "Unique Pageviews" (separate browsing sessions) for practice dashboards from Google Analytics, for all practices eligible for the study. Aggregated measure values for each baseline and follow-up period will be calculated by summing the relevant outcomes for all practices in each group.

- Primary and secondary outcomes measured as proportions will be compared with confidence intervals (CIs) and chi-squared tests; except:
    - For the proportion of links accessed by each method of contact, a McNemar paired-sample test will be used, because these measurements are not independent, e.g. a practice using the link supplied by email may be less likely to access the link in the letter. We will also perform a sensitivity analysis where we restrict analysis to only practices contacted by all three methods, to assess bias, e.g. practices with a discoverable fax number may be less responsive to email.
    - Analysis of browsing sessions, which will be discussed by distribution and basic descriptive statistics.
- Missing data: engagement data will be gathered from Google Analytics, therefore is expected to be complete except where users of the website have installed tools to prevent their activity being collected. This is likely to be uncommon, and equally distributed between intervention and control groups.

Prescribing outcomes:

- Aggregated measure values for the six-month baseline and follow-up periods will be calculated for each practice, by summing items/ADQs prescribed (and averaging STAR-PU) then calculating proportions.
- Primary, secondary outcomes and subgroup analyses will be compared using regression models, with baseline value and intervention group as dependent variables. For the rate of antibiotic prescribing per STAR-PU, we will offset for STAR-PU to account for size.
- Practices in the intervention group will be included in analysis whether or not they opt out of the intervention. Prescribing datasets are highly complete, but missing data (i.e. no prescribing) may occur in the case of practices closing before the start of the follow-up period. Such practices will be excluded from analysis, as this should not be influenced by our intervention; and during the course of closure they are likely to have substantially reduced prescribing levels and limited capacity to interact with the intervention.
- We will investigate whether the level of engagement/improvement is affected by list size by including this as an additional variable in the linear regression model.
- Subgroup analyses will be carried out by repeating the regression analysis of the primary variable on the intervention group, with membership of subgroup as a dependent variable (in addition to baseline performance).

9.2. The Number of Participants

All practices in England meeting eligibility criteria will be included. This is the complete set of all available participants. Selecting the worst-performing 20% gives approximately 1,400 practices.

An illustrative power calculation has been conducted showing we have 80% power to detect a difference of 0.53% on our primary prescribing outcome at 95% significance (the mean for the worst 20% of

practices in 2016 (Jan-Jun) changed from 13.7% to 12.1% in 2017). Additionally we have 80% power to detect a change of 7.42% on our primary engagement outcome at 95% significance, based upon current level of approximately 48%. This represents 52 out of 700 interventions leading to a dashboard page view.

All 1,400 practices that are randomised will be included in the analysis (except where detailed in Section 7.7), as part of the study is looking at engagement rates.

10. DATA MANAGEMENT

10.1. Access to Data

Direct access will be granted to authorised representatives from the University of Oxford and any host institution for monitoring and/or audit of the study to ensure compliance with regulations.

10.2. Data Handling and Record Keeping

Practice-level prescribing data is obtained from national datasets published monthly by NHS Digital, with approximately two months' lag time (NHS-Digital 2017). It is routinely compiled and loaded into our database in Google BigQuery. Baseline measurement of broad-spectrum antibiotic prescribing will be made (alongside allocation) using Python script in Appendix A.

Follow-up data will be subject to analysis as pre-defined in Appendix B. Website access data will be collected via Google's Analysis services. Any other information arising from participant feedback (e.g. emails, telephone calls and letters) will be entered into an Excel spreadsheet, with participants identified by practice ID only. The name and any other identifying detail will NOT be included in any study data electronic file.

Data for any participants who opt out will remain included in the intervention group for outcome measurement.

11. QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

The study will be conducted in accordance with the current approved protocol, relevant regulations and standard operating procedures. We perform routine checks and analysis on the data which will highlight any issues with completeness or quality. Any errors noticed after interventions are sent will be corrected by a statement provided in the following intervention and alert on the landing pages. Interim analyses specific to trial outcomes will not be performed, although the data will be available for use. The trial will not be under any stopping guidelines.

All analysis scripts and datasets will be made available for scrutiny. We will keep a clear log of (anonymised) communications received, issues raised and actions taken which will also be made freely available. During the trial we will obtain confirmation that letters have been successfully printed and posted by the external service provider. We will also perform checks that emails and faxes are being sent successfully. Access will be provided for external audits and inspections.

12. ETHICAL AND REGULATORY CONSIDERATIONS

12.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

12.2. Approvals

The protocol and associated documents will be submitted to the Medical Sciences IDREC, and host institution for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

12.3. Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by practice ID number on all study documents and any electronic database. All data collected and reported will be at practice level only and is publicly available, with the exception of some email addresses and fax numbers used to contact practices, which will be suppressed in publication; and comments/feedback, which will be anonymised.

All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

12.4. Expenses and Benefits

Participants will not be paid for their participation in the research.

12.5. Annual Progress Report

The CI shall submit on request, a Progress Report to the Medical IDREC with a copy to CTRG.

12.6. Other Ethical Considerations

No additional risks to individual patients or clinicians are anticipated in relation to the trial. The standard measures are based upon existing national guidelines, of which prescribers should already be aware. Prescribers will, as always, consider the risks of making changes to ongoing medications on an individual patient basis. Prescribers are also responsible for keeping up to date with the latest drug safety alerts and other relevant information when prescribing. If we detect signals of actively dangerous prescribing by individual practices, we will alert their local CCG Medicines Optimisation team.

Protocol amendments

Important protocol modifications will be explained clearly in the submitted article, and communicated to CUREC, the Trial Steering Committee, investigators, and where appropriate on the registry entry. A copy

of the protocol with a complete change log from study commencement will be available at study completion.

Consent

Consent for participation will not be required; practices in intervention groups will be disseminated information but not aware they are in a trial. Practices and prescribers may choose whether or not they wish to act upon the information received. The decision to change any prescriptions for individual patients remains the responsibility of the healthcare practitioner as part of their ongoing care. Practice-level prescribing data is already publicly available for use in research studies.

Ancillary and post-trial care:

The healthcare professionals and prescribers involved in the trial will remain responsible for the safe and appropriate care of their patients throughout and beyond the trial. Choices of medication, brand and formulation are a routine part of prescribing decisions made in general practice so no additional risk of harm is anticipated in relation to the trial. The intervention will include generic contact details for the OpenPrescribing group, should any participants wish to raise queries. We will later send a follow-up communication to the intervention groups after the end of the trial, summarising any changes in prescribing.

13. FINANCE AND INSURANCE

13.1. Funding

This RCT is funded by the Health Foundation; the OpenPrescribing project has also received funding from: NIHR Biomedical Research Centre, Oxford, NIHR School of Primary Care Research (SPCR), West of England Academic Health Science Network (AHSN) and NHS England.

13.2. Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London).

14. PUBLICATION POLICY

The results will be published in a scientific journal for dissemination and results reported in the ISRCTN registry. There may be further publicising of results in line with any restrictions imposed by the journal publishing the study. The full protocol, practice-level dataset and statistical code will all be publicly accessible.

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged. No professional writers will be used and

all authors will approve the final manuscript. Authors will acknowledge that the study was funded by the Health Foundation.

Participants in the intervention group will be sent a follow-up letter 6-12 months after the end of the intervention, including information from results of the study available at the time.

15. CONTRIBUTIONS AND ACKNOWLEDGEMENTS

BG conceived the study. HC and BG designed the methods with input from all authors. HC, BG and RP designed the analysis with input from AW. HC drafted the manuscript. All authors contributed to and approved the final manuscript. BG supervised the project and is guarantor. The authors acknowledge the support received from Emma-Jane Morbey and Lydia Berry in setting up the trial.

Conflict of Interest Statement

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare the following: BG has received research funding from the Laura and John Arnold Foundation, the Wellcome Trust, the Biomedical Research Centre, Oxford, the NHS National Institute for Health Research School of Primary Care Research, the Health Foundation, and the World Health Organisation; he also receives personal income from speaking and writing for lay audiences on the misuse of science. HC, AW, RC and SB are employed on BG's grants for the OpenPrescribing project. RC is also employed by a CCG to optimise prescribing (this CCG will be excluded from the trial), and has received income as a paid member of advisory boards for Martindale Pharma, Menarini Farmaceutica Internazionale SRL and Stirling Anglian Pharmaceuticals Ltd. CH has received expenses and fees for media work, expenses from the WHO and holds grant funding from the NIHR, the NIHR School of Primary Care Research, The Wellcome Trust and the WHO. He has received financial remuneration from an asbestos case. He has also received income from the publication of a series of toolkit books published by Blackwells. On occasion, he receives expenses for teaching EBM and is also paid for his GP work in NHS out of hours and as editor in Chief of the BMJ EBM Journal. CEBM jointly runs the EvidenceLive Conference with the BMJ and the Overdiagnosis Conference with some international partners based on a non-profit making model. KM reports funding from the National Institute for Health Research (NIHR) School for Primary Care Research and Health Technology Assessment programme. RP, MH and HH declare no competing interests.

16. REFERENCES

Brehaut, Jamie C., Heather L. Colquhoun, Kevin W. Eva, Kelly Carroll, Anne Sales, Susan Michie, Noah Ivers, and Jeremy M. Grimshaw. 2016. “Practice Feedback Interventions: 15 Suggestions for Optimizing Effectiveness.” *Annals of Internal Medicine* 164 (6): 435–41.

EBM-DataLab. 2017a. “Antibiotics Trimethoprim Measure.” *GitHub*. https://github.com/ebmdatalab/openprescribing/blob/master/openprescribing/frontend/management/commands/measure_definitions/trimethoprim.json.

———. 2017b. “KTT9 Antibiotics per STAR-PU Measure.” *GitHub*. https://github.com/ebmdatalab/openprescribing/blob/master/openprescribing/frontend/management/commands/measure_definitions/ktt9_antibiotics.json.

———. 2017c. “KTT9 Antibiotics UTI Measure.” *GitHub*. https://github.com/ebmdatalab/openprescribing/blob/master/openprescribing/frontend/management/commands/measure_definitions/ktt9_uti_antibiotics.json.

Elouafkaoui, Paula, Linda Young, Rumana Newlands, Eilidh M. Duncan, Andrew Elders, Jan E. Clarkson, Craig R. Ramsay, and Translation Research in a Dental Setting (TRiaDS) Research Methodology Group. 2016. “An Audit and Feedback Intervention for Reducing Antibiotic Prescribing in General Dental Practice: The RAPiD Cluster Randomised Controlled Trial.” *PLoS Medicine* 13 (8): e1002115.

Gulliford, Martin C., Tjeerd van Staa, Alex Dregan, Lisa McDermott, Gerard McCann, Mark Ashworth, Judith Charlton, Paul Little, Michael V. Moore, and Lucy Yardley. 2014. “Electronic Health Records for Intervention Research: A Cluster Randomized Trial to Reduce Antibiotic Prescribing in Primary Care (eCRT Study).” *Annals of Family Medicine* 12 (4): 344–51.

Hallsworth, Michael, Tim Chadborn, Anna Sallis, Michael Sanders, Daniel Berry, Felix Greaves, Lara Clements, and Sally C. Davies. 2016. “Provision of Social Norm Feedback to High Prescribers of Antibiotics in General Practice: A Pragmatic National Randomised Controlled Trial.” *The Lancet* 387 (10029): 1743–52.

Ivers, Noah, Gro Jamtvedt, Signe Flottorp, Jane M. Young, Jan Odgaard-Jensen, Simon D. French, Mary Ann O’Brien, Marit Johansen, Jeremy Grimshaw, and Andrew D. Oxman. 2012. “Audit and Feedback: Effects on Professional Practice and Healthcare Outcomes.” *Cochrane Database of Systematic Reviews* , no. 6 (June): CD000259.

Juszczyk, Dorota, Judith Charlton, Lisa McDermott, Jamie Soames, Kirin Sultana, Mark Ashworth, Robin Fox, et al. 2016. “Electronically Delivered, Multicomponent Intervention to Reduce Unnecessary Antibiotic Prescribing for Respiratory Infections in Primary Care: A Cluster Randomised Trial Using Electronic Health Records-REDUCE Trial Study Original Protocol.” *BMJ Open* 6 (8): e010892.

NHS-Digital. 2017. “Primary Care Prescribing.” https://digital.nhs.uk/article/6735/Primary-care-prescribing.

NICE. 2015. “Antimicrobial Stewardship: Prescribing Antibiotics.” https://www.nice.org.uk/advice/ktt9/chapter/Prescribing-data.

17. APPENDIX A: ENROLMENT AND ALLOCATION SCRIPTS

Final allocation script is accessible here:
https://gist.github.com/HelenCEBM/1735caa31276c88ff1b0fe0a6cd87f4b

18. APPENDIX B: DATA ANALYSIS SCRIPTS

Engagement outcomes scripts accessible here, with change log for updates:
https://gist.github.com/HelenCEBM/529525b355508b5a5575f156c56acbfe

Prescribing outcomes script to follow.

19. APPENDIX C: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	1.2	2/2/19	HC	● Corrected Objective P1 which had "engagement" aspect missed off (outcome measures not affected as these were correct). ● Completed ethical approval details. ● Change of eligibility criteria from" >= 500 registered patients" to ">= 1,000 registered patients (with 10-85% aged 25-64)" as used in trial ● Link to allocation and analysis script added.