Knowledge support to General Practitioners and patients: evaluation of the effectiveness of periodic feedback, decision support during consultations and peer comparisons in multi-arm cluster randomised trial (BRIT2)

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ABSTRACT (300 words ethics)

The Learning Healthcare System approach has been proposed to better integrate research into clinical practice[1][1]. It involves iterative phases including data analytics, feedback to clinicians and implementation of quality improvement activities by the clinicians. In this project, this approach will be applied to two different clinical areas in general practice, one concerning antibiotic prescribing for common infections and the other concerning treatments for frail elderly. The overall research question will be to evaluate whether the Learning Healthcare System improves prescribing without increasing the risks of complications. The study will be a multi-arm pragmatic cluster randomised controlled trial with randomisation of practices to various interventions and also include an observational arm. General practices participating in the trial will be randomised to the following interventions: periodic practice-level feedback using dashboards only, practice + individual prescriber feedback, and (in antibiotic sub-study only) periodic practice + individual feedback+ knowledge support system (KSS). This KSS will consist of a display on the GP's computer while seeing the ill patient; the GP will need to enter answers to standard questions about the patient's condition and then presented with information on e.g. patient's risk of complications due to the infection). We will develop individualised patient leaflets that the GP can provide to patients during consultation after KSS activation. Data from large national data sources will be used to get better understanding of the drivers for heterogeneity in care and for the effectiveness of different treatment strategies (benchmarking). The results will provide the baseline content for the dashboards. This will be followed by analyses of anonymised patient-level data from local participating practices. These data and the dashboard infrastructure will be held in secure Trustworthy Research Environments. The number of practices will be at least 202 in the antibiotic sub-study and at least 100 in the frailty sub-study.

INTRODUCTION

Translating research findings into daily clinical practice is a major challenge. There is considerable need for clinical decisions to be based on the best available evidence, but often this evidence is incomplete as, for example, patients with complex multimorbidity or polypharmacy are excluded from trials. The Learning Healthcare System approach has been proposed to better integrate research into clinical practice [1]. It involves iterative phases including data analytics (data to knowledge), feedback to clinicians (knowledge to performance) and implementation of quality improvement activities by the clinicians (performance to data) [2]. The cycle of the Learning Healthcare System starts again by evaluating the effectiveness of these quality improvement activities. The analytics phase includes a detailed data analysis of the opportunities and challenges in current clinical practice and the local site (such as analysis of the effectiveness of current activities). The analyses may identify practices that could potentially improve clinical care. The second phase involves review by the clinicians of these results and decide which have sufficient credibility to generate recommendations for change, ideally customised to its own specific circumstances. The third phase involves clinicians implementing these recommendations [2].

The Learning Healthcare System (LHS) involves analysis of data from local healthcare organisations followed by feedback to clinicians. An example of feedback is the UK's Quality and Outcomes Framework (QOF) which was introduced in 2004 to provide financial rewards to general practices for meeting a range of performance indicators, primarily relating to the management of chronic conditions [3]. However, the effectiveness of feedback of indicators has not been uniform. Recent research reported that QOF, despite the large financial investment, did not have major impact on clinical outcomes such as hospitalisation for incentivised conditions. Material deprivation and urbanicity were found to be the stronger predictors of the variation in hospitalisation rates for all QOF incentivised conditions across England [4]. On the other hand, a cluster trial by Guthrie et al found that periodic feedback of prescribing safety data was effective at reducing high risk prescribing in general practices [5]. A potential reason for this variable effectiveness of periodic feedback may be that top-down performance indicators such as QOF are not sensitive to local context and clinical challenges.

In the LHS, feedback to clinicians can either be provided periodically through e.g. internet dashboards or during consultation with patients using Decision Support Systems (KSSs). KSSs have been widely tested in hospitals. A systematic review of 81 studies reported that these systems significantly improved the adequacy of antibiotic coverage, lowered antibiotic utilisation, increased compliance with antibiotic guidelines and led to reductions in antimicrobial resistance [AMR] [6]. It has been proposed that a KSS could also be used to provide evidence for the GP to consider; the KSS would be activated within the electronic health record (EHR) during consultation with the patient [7]. By a simple click of an icon on a computer screen, it provides clinicians access to information on "patients like mine" (e.g., the risks of developing clinical complications in

similar patients), tailored recommendations (e.g., best not prescribe amoxicillin given this patient's frequent prior use) and an individualised patient leaflet. The information on similar patients could be drawn from several sources such as historic data on clinical outcomes from comparable patient groups [7].

The LHS approach is not just about analysis of data and feedback of results to clinicians. An important aspect is around understanding and changing behaviours which is a focus of behavioural sciences [8]. An example of this is the provision of social norm practice-level feedback (i.e., comparing a clinician to other peers). In a UK cluster randomised controlled trial (cRCT), this approach was found to substantially reduce antibiotic prescribing. Every GP in the feedback intervention group was sent a letter from England's Chief Medical Officer [9]. A US cRCT tested the effects of several behavioural interventions and found that peer comparisons resulted in lower rates of inappropriate antibiotic prescribing for acute respiratory tract infection. These comparisons consisted of emails sent to clinicians that compared their antibiotic prescribing rates with those of "top performers" (those with the lowest inappropriate prescribing rates) [10].

The LHS approach can be used in numerous clinical areas. In this project, the LHS approach will be applied to two different clinical areas in general practice, one concerning antibiotic prescribing for common infections and the other concerning treatments for frail elderly. Primary care accounts for 81% of antibiotic prescribing in England. Overuse of antibiotics is a major public health concern as it could lead to antimicrobial resistance. The NHS 2019 Long Term plan states as priority to continue to optimise use, reduce the need for and unintentional exposure to antibiotics. The 5-year Government plan aims to reduce UK antimicrobial use in humans by 15% by 2024. Research by the applicants has included qualitative semi-structured interviews with 41 GPs working in North-West England to understand contextual factors related to GPs antibiotic prescribing behaviour. Participating practices were purposively sampled from practices with low, medium and high antibiotic prescribing rates. The study found that optimising antibiotic prescribing creates tensions for GPs, particularly in doctor-patient communication during a consultation. GPs balanced patient expectations and their own decision-making in their communication. In low prescribing practices, GPs reported that increasing dialogue with colleagues, having consistent patterns of prescribing within the practice, supportive practice policies and enough resources such as longer consultation time were important supports when not prescribing antibiotics. With respect to the communication with patients, GPs from all prescribing groups reported how they discussed their decision-making with patients, while participants from low and medium prescribing practices in particular described highly detailed and individualised explanations that were helpful in getting across decisions not to prescribe antibiotics [11].

Approximately 10% of those aged over 65 years have frailty, rising to 25-50% in the over 85s. NHS England estimates that older people with frailty account for around £15 billion of NHS and social care expenditure. The Office for National Statistics project that by 2068 there will be an additional 8.2 million people aged 65+ years in the UK. At current rates this means a minimum of 800,000 additional people with frailty; this would

place an unprecedented burden on health and social care systems. Frail patients can deteriorate dramatically following minor events, such as infection or new prescriptions, which may result in hospitalisation or even death. The NHS long term plan highlights the need to improve the care of people with frailty and maintain care in the community.

Research questions

The overall research question will be to evaluate whether the LHS approach (i.e., detailed data analysis followed by feedback to clinicians) improves prescribing without increasing the risks of complications. The specific research questions will be to evaluate the effectiveness of periodic practice-level feedback (in an observational study) and to evaluate the effectiveness of individual prescriber feedback and of the KSS (in a randomised cluster trial). This project will be conducted in UK general practices involving two different populations, one including frail elderly and one including patients consulting for common infections who could be treated with oral antibiotics. The analytical strategy will be to use large national datasets (benchmarking) to evaluate heterogeneity in care and patients and drivers for clinical effectiveness followed by detailed analyses of the anonymised data from participating general practices. This will allow an evaluation of the local challenges as well as benchmarking of the participating general practices compared to the national analyses. The results of these analyses will then be used to inform the periodic feedback to clinicians about their practice (through regularly updated dashboards) as well as to inform the content of information provided in a KSS during consultation.

METHODS AND ANALYSIS

Study design, participating sites and overview of interventions

The randomised part of the study will be a multi-arm pragmatic cluster randomised controlled trial with randomisation of practices to various interventions and also include an observational arm. Figure 1 provides an overview of the design of the study. In the antibiotic sub-study, study sites will be randomised to the following three interventions:

(i) A: Periodic practice-level feedback

(ii) A+B: Practice-level + individual prescriber feedback

(iii) A+B+C: Practice-level + individual prescriber feedback + KSS during consultation with the GP providing content (such as information leaflet) that is individualised to the patient.

In the frailty sub-study, practices will be randomised to the following two interventions:

(i) A: Periodic practice-level feedback

(ii) A+B: Practice-level + individual prescriber feedback.

The observational arm will consist of local practices that are not participating in the study but with research access provided to the anonymised patient-level and data from large national datasets (Clinical Practice

Research Datalink GOLD and AURUM). Separate research approval will be obtained from the national dataset and practices from the areas in which this study is being conducted will be excluded.

The feedback will be provided in secure internet dashboards that can be accessed by practice staff. In addition, summary level data will be sent by email and postal letters in a frequency similar between intervention groups.

In order to evaluate the effect of practice-level dashboards, there will also be an observational control group of practices. This will include practices from the North of England that are not participating in the cluster-randomised trial. In case of small numbers available for this control group in the North of England:

- data will be obtained through the Clinical Practice Research Datalink (www.cprd.com); this national resource contains anonymised patient-level data from general practices across the UK.
- Practices from North-England will be *excluded* as identification of BRIT2 practices is not possible in the Clinical Practice Research Datalink.

In case of large interest of practices, a separate observational arm will be included offering practice-level and individual GP-level feedback. Separate research approvals will be sought for these observational comparisons.

The study sites will be general practices located in the North of England who provide anonymised patient-level data to one of the regional Shared Care Record data centres (that collate data from various local organisations with the objectives to support direct clinical care and, after appropriate approvals, to support research). Clinical decision-making about individual patient care will remain the sole responsibility of the clinicians in the practices. Informed consent by patients is, thus, not required.

Identification of sites

All general practices that provide data to the data centre will have access to their practice dashboards as a quality improvement tool. This will be communicated via the data centre, local Clinical Commissioning Group, and primary care network communications channels. We will also work with the clinical research network primary care teams to support recruitment to the study. Information about this study will be posted on the data centre and university websites and interested parties may also contact us directly. Permission for data to be used for secondary purposes is provided by Clinical Commissioning Groups who hold contracts with the datacentres. Any practice who becomes a study site will have this permission in place or they will not be eligible to become a site. This will be confirmed by the datacentre, and data will only be provided for analysis on this basis. Practices can chose to deliver one or both parts of the study and a randomisation process will then determine the interventions in the practices. Practices who have access to the dashboards but not wish to

take part in any of the arms of the study will be included in the observational control group with just practice-level dashboards.

Recruitment of participants for workshops

Invitations to workshops for GPs, pharmacists and other interested parties will be sent out through the data centre communications channels, the local clinical research network and to existing participants in the ACTION study. Interested participants will be send an email with an information sheet and link to an online consent form. Once this is returned, details of how to access the online workshop will be sent. Participants will be free to leave the workshop at any time.

Benchmarking

Data from large national data sources have been and will be used to get better understanding of the drivers for heterogeneity in care and for the effectiveness of different treatment strategies. The results will provide the baseline content for the dashboards.

Antibiotic sub-study

A previous project piloted and implemented the IT infrastructure for the Learning Healthcare System (i.e., data analytics, feedback to clinicians) on antibiotic prescribing care in UK primary care, This project (BRIT: Building Rapid Interventions to reduce AMR and over-prescribing of antibiotics) was part of the £20 million Department of Health & Social Care (DHSC) funded Connected Health Cities programme (https://www.connectedhealthcities.org/). The data analytics activities in BRIT consisted of benchmarking current practice in primary care, evaluating the levels of suboptimal antibiotic prescribing and identifying opportunities for improvement. Large variability in antibiotic prescribing was observed between practices and within practices: Change points in prescribing did not reflect updates to national guidelines. Prescribing levels within practices were not consistent for different infectious conditions. BRIT also found high levels of prescribing of potentially inappropriate type of antibiotics which were highest for otitis externa (67.3%) and upper respiratory tract infection (38.7%). BRIT found that that over the last 15 years antibiotic prescribing in primary care was not risk-based: patients with very low risk of infection-related hospital admissions were as likely to receive an antibiotic as patients with higher risks. BRIT also evaluated the effectiveness of treating common infections with antibiotics. The findings also indicate that incidental use of antibiotics is effective in reducing infection-related hospital admissions while repeated courses of antibiotics may have limited benefit and be indicative of adverse outcomes. Of 5.1 million antibiotics prescribed in UK primary care, only 14.8% were given to patients without any antibiotic prescribing in the previous three years and 43.6% are for patients who already received 5+ antibiotic prescriptions in the previous three years. These BRIT findings indicate that optimal antibiotic prescribing in primary care is a complex interplay of a patient's symptoms, age and co-morbidity and previous history of antibiotic use. While incidental use of an antibiotic may reduce the risk of infection-related complications, it may also decrease the effectiveness of the antibiotic for future infections

(possibly due to the development of resistance in the patient [12]). This highlights the importance for patient-specific communication, information and algorithms that recommend best course of action.

Recent research found considerable variability between GPs in the case mix of patients consulting and large variability in antibiotic prescribing habits. The majority of clinicians (> 95%) prescribed at least one antibiotic measure that was above the medians of their peers. It concluded that there is a need for a wider range of objectives (using a variety of measures without ranking of clinicians based on a single metric), varying engagement strategies with feedback tailored to each clinician, local context including bespoke recommendations that could be implemented and proactive support from colleagues and local organisations [manuscript submitted].

Frail elderly sub-study

Research is currently ongoing in the Clinical Practice Research Datalink to evaluate the heterogeneity in outcomes and treatments in frail elderly. Research approval has been obtained for this study with data from 2000 to 2020 [https://cprd.com/protocol/evaluation-drivers-heterogeneity-unplanned-hospital-admissions-and-mortality-frail-and]. This study will identify opportunities to better target clinical improvement activities for frail multi-morbid elderly patients in general practice. Anonymised electronic health records of frail elderly patients will be used. The outcomes of interest will be death (irrespective of the cause), emergency hospital admissions (and reasons), infection-related complications, Accident and Emergency Attendance and care home admission. The medicines that were prescribed to frail elderly patients will be evaluated for their associations with increased or decreased risk of these outcomes. Of particular interest will be to look at treatment strategies that vary between general practices and identify those that could suggest potential for improvement. Experts will review the clinical importance of these predictors. These variables will include characteristics such as extent and type of how many medicines a frail person receives and the complexity of a medication regimen. The results of this study will be used to provide feedback to GPs (using dashboards in a secure internet infrastructure) which can help to identify opportunities to better target clinical improvement activities to frail patients in their practice. The study includes about 4.2 million patients aged 65+, of whom about 600,000 to 1 million patients can be considered frail.

Details of study interventions

Intervention A

Periodic practice-level feedback

The standard intervention (A) will consist of practice-level feedback on antibiotic prescribing (as previously developed as part of the BRIT project) and/or prescribing to frail elderly. A variety of dashboards for antibiotic prescribing has been developed previously together with clinical stakeholders. They currently include dashboards that provide information on practice comparisons of levels and drivers of antibiotic

prescribing (overall and by indication), analyses of prescribing of inappropriate types of antibiotic and extent of risk-based prescribing (Appendix 1 shows examples of dashboards).

Development of dashboards

The purpose of dashboards is to integrate large volumes of routine data into a simple accessible format and provide clinicians with actionable of areas in quality of care may be improved. We will conduct usability evaluation of proposed dashboards using the think aloud method [13]. This evaluation will consist of asking the clinical stakeholders (such as GPs or prescribing advisors) to express their thoughts when reviewing parts of the dashboard as well as overall feedback [13,14]. This will involve a small group of clinical stakeholders (about 10-20 participants) which will be conducted online. Participants will be asked to record their thoughts in the chat box of the online conferencing tool. We will map the feedback comments into similar groups and classify these into the usability problem as used by Peute et al [13]. The frequency of the feedback comments will be noted. Any subsequent improvement and changes in the dashboards will be discussed with the participants. Personal data will not be collected from the study participants and informed consent from participants will be obtained for recording the chats in the online conferencing tool.

Intervention B

Periodic feedback on individual prescribing and peer comparisons

In each individual-GP feedback practice, an AMR champion will be identified who will be the point of contact with the study team (e.g. the prescribing advisor or practice manager). This AMR champion will receive (by post and email summary) information on GP-level prescribing within the practice and be able to re-identify the GPs. This contact person will decide whether people outside the practice (e.g., the Clinical Commissioning Group) should be forwarded study material. They will also be responsible for checking with each GP in the practice and providing advice / support. The study intervention will be delivered in the following steps:

(i) Letters containing a localised ‘league table’ (comparing each anonymised clinician to others within the practice and others within comparable practices) and with red coloured font will be sent to the practice AMR champion (one letter for each clinician). The ‘league table’ will be based on most recent analyses of the practice EHRs. The AMR champion will be requested to organise a practice face-to-face training meeting and feedback to the research team of any reasons for higher level of individual GP-level prescribing and of any additional analyses that may be useful. The letters will be sent by post and email.

(ii) The practices will have access to the BRIT2 feedback infrastructure with detailed personalised dashboards on the analytics of the individual GP prescribing. The CCG and practice prescribing advisor will have access to the BRIT dashboards subject to approvals by the practice (as data guardian).

(iii) Educational material for each of the antibiotic prescribing measures will be developed and made accessible in the BRIT IT infrastructure. This may include a 2-page handout and podcasts. This educational material will be developed in collaboration with PHE, NICE and clinicians as no educational material is currently available for these antibiotic prescribing measures (except for overall rate of antibiotic prescribing). This educational material will be developed for each of the antibiotic prescribing measures as being used in this study.

(iv) Letters for each clinician will be sent every three months to provide an update on the changes in antibiotic prescribing by clinicians (adjusted for seasonality) and to provide a 'league table' in improvements. These letters will be sent by post and email to the practice AMR champion. The usage by the practice of the BRIT infrastructure will be monitored (details of logging in). If there is no activity within the first six weeks of the study, the practice AMR champion will be contacted. If the practice AMR champion cannot be reached or is not interested, only one more batch of the three-monthly letters will be sent.

(v) Antibiotic prescribing measures will be assessed for each clinician individually and may include measures such as overall rate of prescribing, level of incidental prescribing, repeat prescribing within 30 days, number-needed-to-treat to prevent one hospital admission of patients prescribed incidental antibiotics and percentage of broad-spectrum antibiotics types of all antibiotics prescribed. Each GP letter will focus on the prescribing measure for which the clinician is comparatively highest.

The letters and information as sent by the research team will be blinded (i.e., only provides anonymised staff identifiers). There will be a re-identification process of GPs in the intervention practices. These anonymised staff identifiers will be used to populate the staff-level dashboards in the BRIT2 infrastructure and the 'league table' in the communications to the practices and CCGs. As outlined in Appendix 3, each practice will be able to re-identify the GPs within their practices (i.e., obtain the GMC code associated with the anonymised staff identifier). Only the practice will be able to do this. The researchers, other practices and CCGs will not have access to this information unless provided by the practice themselves.

<u>Intervention C [Antibiotic sub-study only]</u>

KSS intervention during consultation

A recent study by the researchers of this proposal evaluated the usability and acceptability of a KSS System prototype with 34 GPs. The majority of GPs (74%) found the KSS System to be useful. They considered the checklist of symptoms and the integration with the information recorded in the EHR to be most useful. However, half of the GPs felt that the KSS System changed their consultation style, by requiring them to code symptoms while interacting with the patient. The study concluded that to use the System effectively, GPs would need to adapt their consultation style (coding during rather than at the end of the consultation) [15]. It is

already recommended by the National Institute for Health and Care Excellence (NICE) that symptom scores for common infections are entered during consultation in order to support treatment decisions [16].

This project will utilise the KSS System as developed by Kings College London, for the European project TRANSFoRM [17]. TRANSFoRM implemented the digital infrastructure for the Learning Healthcare System including activation of a KSS during consultation. It includes rules that determine its activation and contents (step 0), which get manually curated and fed through the evidence service into the Clinical Evidence Repository (containing the evidence for different clinical scenarios as curated by the research team). In collaboration with the team who developed the KSS at Kings, the research team will adapt the system previously used in cancer studies for use in antibiotic prescribing. When the GP enters specific clinical codes into the EHR during consultation, a Case Report Form appears in order to enter symptoms and signs information. This symptom information can then be combined with information from the EHR including patient demographics, prior prescribing and clinical history. This is then sent to the evidence service (step 1), which queries the rules stored in the Clinical Evidence Repository (step 2), before sending back the patient-specific recommendations, annotated with levels of support and confidence for the presenting case. Upon exiting the tool, the coded evidence cues and current working diagnosis can be saved back to the patient EHR (step 3) [17]. The TRANSFoRM is currently functional within general practices that use the TPP SystemOne and Vision software (about 34% and 9% of practices in England and is being extended to EMIS (56%) [18]).

Content of KSS for GPs

The KSS in practices in the intervention group will be activated after GP entry of a common infection code. The KSS activation will be tailored to each GP or practice following analytics feedback on their prescribing (e.g., compared to their peers). When the KSS is activated, a computer screen will appear asking for entry of a small list of predefined symptoms (such as the symptoms used for the NICE risk scores); the GP will need to tick the symptoms or disregard the KSS. After completion of the symptom data entry, the GP will then be provided with a screen providing summary clinical information. This may include “patients like mine” (e.g., the risks of developing infection-related complications in similar patients), number-needed-to-prevent one hospital admission when treated with an antibiotic, benchmarking of treatment decisions by other GPs, tailored recommendations (e.g., best not to prescribe amoxicillin given resistance patterns locally), patient’s history of antibiotic use. The GP will also have access to a patient leaflet that is individualised to the patient (e.g., their individual risk of complications and information on the risks of developing resistance to the antibiotic). The GP will have the choice to print this leaflet and discuss this with the patient. GPs will be provided with feedback on opportunities in KSS usage in their practice (e.g., in patient groups in which antibiotic prescribed is different from their peers) and how they have used the KSS.

The summary information in the KSS will include: 1) an individualised risk prediction for the patient and /or an NNT value, 2) benchmarking of treatment and 3) an individualised patient information leaflet that can be printed during the consultation. This individualised risk score will be based on existing risk prediction models developed by the research team [19] and estimates from the recent study by Gulliford [20]. It will be calculated when the TRANSFoRM system extracts predefined parameters (such as patient demographics) from the EHR and combines these parameters with the estimated risk scores. This risk score will be adapted to incorporate symptom severity scores entered by the GP during the consultation. The individualised risk scores developed by the research team [19] and by Gulliford [20] included predictors such as age, gender, clinical and medication risk factors, ethnicity and socioeconomic status. There may be the following challenges with using the predicted risk scores. The first one is that patients with higher risks of infection-related complications (such as frail elderly) may have repeated episodes of common infections over time and thus regularly receive antibiotics over time. Repeated use of antibiotics has been associated with increased resistance [21] and lower effectiveness [22]. The second challenge may be that the risks of infection-related complications may change over time or vary by region (our risk prediction study found considerable risk differences between England and Wales [19]). The third challenge may be the inclusion of novel predictors (such as the symptom data from the KSS or post-Covid changes in risk). Model updating techniques [23] will be applied in order to limit the last two challenges.

The exact content of the treatment benchmarking (i.e., level of agreement between GPs in the treatment) will be developed through a series of GP focused workshops and online surveys. Benchmarking' clinical practice and integrating such data with national guidelines offers a way of establishing standards for use in clinical governance. Our approach will follow the methods as used by Mowle et al who presented different scenarios of children with otitis media and found that GP responders varied considerably in the likelihood (agreement) of prescribing antibiotics. By presenting a series of exemplar clinical scenarios, consistency and variations in clinical management can be identified [24]. BRIT has observed both consistencies and large discrepancies in clinical management for different scenarios. To scope the content of the KSS for clinical benchmarking, GP-focused workshops will review the variability of care patients receive given a specific ‘clinical scenario’. A data-driven approach will be adopted, analysing EHR data to derive clinically relevant scenario from the GPs own prescribing data. This analysis will focus on identifying more complex prescribing scenarios, which may include but is not limited to cases with diagnosis uncertainty, incidental prescribing, subsequent antibiotic treatment with the same/different type within 30 days of the initial antibiotic, a history of heavy repeated-intermittent-antibiotic use, as well as complex histories that are unsupported by clinical guidelines. Experts will review these clinical scenarios and suggest a treatment strategy (e.g., they would/wouldn’t treat with an antibiotic prescription) based on their clinical experience. Subsequent iterations of the workshop and online surveys will again present each complex scenario to experts to obtain their recommended treatment strategy, followed by a presentation of summary results from the previous workshop, allowing GPs to adapt their

recommendations accordingly. A series of workshop iterations will result in consensus of expert views regarding treatment strategies of some common, but complex scenarios using the Delphi method. This evidence will then be used to inform the KSS pop-up screen providing with peer-led advice on how to treat complex cases (for example: 80% of peers would not treat with an antibiotic in this scenario).

KSS content for patients

We will develop individualised patient leaflets that the GP can provide to patients during consultation after KSS activation. A recent Cochrane review found that people exposed to decision aids feel more knowledgeable, better informed and clearer about their values. It also found improved knowledge and accurate risk perceptions when decision aids are used within the consultation [25]. TARGET patient information leaflets are available to be shared with patients during the consultation. The leaflets include information on illness duration, self-care advice, prevention advice and advice on when to re-consult [https://www.rcgp.org.uk/clinical-and-research/resources/toolkits/amr/target-antibiotics-toolkit/leaflets-to-share-with-patients.aspx]. We will supplement these leaflets by including information of the risks and benefits that is tailored to the patient and that provide patient-specific estimates of e.g., the risks of being admitted to hospital for infection-related complications. This will be co-designed with members of the public. Recruitment of the members of the public will consider maximum variation according to age, gender and ethnicity. Internet survey distributed through patient groups and healthcare organisations will be used to identify information requirements. The survey tool may also request information about age, gender and socioeconomic status and education. Patients will be asked to rank, in order of importance, different information domains (such as likelihood of the patient developing complications, NNT for antibiotic treatment to avoid one case of infection-related complications and possible effects on future resistance). Results of this survey will then be discussed with the members of the public and possible designs of the patient information leaflets shared with them using the 'think-aloud' methodology for testing their usability. The subsequent design of the patient information leaflets will then be evaluated in a second internet survey which will compare the acceptability of current patient information leaflets [https://campaignresources.phe.gov.uk/resources/campaigns/58/resources/2133] with the individualised ones.

Other study-related activities

Online community of practice and professional training

An online community of practice (OCoP), also known as a virtual community of practice, will also be implemented for interested practice prescribing advisors and clinicians to share knowledge through education on the challenges within their clinics and the opportunities to improve prescribing. The OCoP will provide a critical resource to professionals who want and need recommendations, pointers, tips and tricks, best practices, insights and innovations for optimising prescribing.[26,27] The purpose of this OCoP is to facilitate

dialogue among experts and clinical stakeholders, present analysis results in order to collectively discuss the local challenges and opportunities for improving antibiotic prescribing that is relevant to the user.
The OCoP will focus on discussion of complex cases (e.g., patients who frequently but intermittently are prescribed antibiotics). It will also discuss the analytics of the local data and any actions that need to be implemented and evaluated locally – this will help researchers to understand the interpretation of the dashboard and provide feedback on the dashboard. The target users will be health professionals in the participating general practices as well as local healthcare (NHS) and public health organizations. The staff will include GPs, GP Research Leads, Practice Managers, Quality and Safety Pharmacists, Medicines Optimizations Pharmacists and Public Health Consultants. We have already spoken to some of the community to develop this and when developing the OCoP we will build on this to provide a platform that will suit the way this community works. We need some champions to encourage widespread adoption of the resource. We will include some workshops using video conferencing to gain some of the input for the OCoP as well as provide training.

Sample size (number of practices required to analyse sufficient patient records)

The number of practices will be at least 188 in the antibiotic sub-study and at least 100 in the frailty sub-study. Only the KSS arm (A+B+C) in the antibiotic sub-study will be limited to a maximum of 62 practices as this arm involves time and effort of GPs during consultation. In case of practice interest in the antibiotic sub-study after reaching the sample size of 188, recruitment will continue but with randomisation only between interventions A and A+B.

Antibiotic sub-study

The trial has two separate key objectives:

(i) to evaluate the effectiveness of in reducing the level of antibiotic prescribing when using periodic feedback on individual GP-prescribing and peer comparisons (B) plus periodic practice-level feedback relative (A) to using only peer comparisons plus periodic practice-level feedback (A) (i.e., the effectiveness of B+A relative to A: Figure 1)

(ii) to evaluate the effectiveness of in reducing the level of antibiotic prescribing when using KSS intervention during consultation (C) plus periodic feedback on individual GP-prescribing and peer comparisons (B) plus periodic practice-level feedback (A) relative to using only peer comparisons plus periodic practice-level feedback (A) (i.e., the effectiveness of A+B+C relative to A: Figure 1).

Moreover, comparisons will be made hierarchically, so a *formal* test for (i) will be made if and only if a statistically significant result is found when the test for (ii) is performed; as a result, no correction for multiple comparisons has been made. Therefore, for these two objectives, sample size calculations have been performed separately, based on the primary outcome of practice rate of antibiotic prescribing (per 1000

patients). For efficiency purposes (as both comparisons use the same comparator i.e. A only) including limiting the trial costs (as the cost of implementing the KSS intervention is a limiting factor), a 2:1:1 allocation ratio in favour of the control will be used.

In CPRD, the mean practice list size was 7981 and the overall rate of the number of antibiotic prescriptions (for any indication) was 598 per 1000 patients per year (standard deviation 155). An Australian trial that fed back individual prescribing measures found a reduction in prescribing of 14%[28], suggesting that a 10% reduction in the periodic practice-level feedback arm (A) would be plausible, leading to an antibiotic prescribing rate of 538 per 1000 patients per year. A 10% reduction due to either B or B+C would be important to detect and would lead to an antibiotic prescribing rate of 484 per 1000 patients per year. Assuming an unchanged SD of 155 and practice attrition rate of 5%, randomising 94 practices to A and 47 practices each to A+B and to A+B+C (i.e. a total of 188 practices, in a ratio of 2:1:1) will provide 90% power to detect a 10 % (i.e. 54 per 1000 patients per year) between-arm difference in the overall rate of antibiotic prescribing (two-sided α=0.05), assuming a conservative correlation of 0.82 (as used by Gulliford (2019)) between baseline and outcome antibiotic prescribing rate and analysing using ANCOVA with baseline prescribing rate as covariate. Should the reduction due to A be smaller than 10%, the power will be greater than 90%. Sample size calculations were performed in PASS 2019 software.

The minimum number of 47 practices in the A+B+C (KSS arm) will be increased to a target of 62 practices for pragmatic reasons and to allow for potential withdrawal of practices (as drop-out rates and effects of post-Covid on care are not known), leading to an overall target sample size of 248 practices. The target number of 62 practices is also based on the sample size calculation as provided to the funder NIHR which was based on 1:1 randomisation to the A+B+C and A+B trial arms stated: “Assuming an unchanged SD of 155 and practice attrition rate of 5%, randomising 62 practices to each of the high-intensity and low-intensity KS arms, will provide 90% power to detect a 10 % (54 per 1000 patients per year) between-arm difference in the overall rate of antibiotic prescribing (two-sided α=0.05), assuming a correlation of 0.82 between baseline and outcome antibiotic prescribing rate and analysing using ANCOVA with baseline prescribing rate as covariate.” Moreover, assuming no more than 8% post-randomisation attrition of practices, a the target sample size of 248 practices will provide over 96% power to detect a 54 per 1000 patients per year between arm difference (ANCOVA, two-sided α=0.05, SD=155 per 1000 patients per, year r=0.82).

Frail elderly sub-study

No sample size calculations can be conducted as the interventions (which medicines are being included into the feedback dashboards) have not been defined at this stage. We will use an approach of convenience sample size of 100 targeting to randomly allocate about 50 practices for intervention A and 50 practices for intervention A+B.

Outcomes in antibiotic sub-study

The unit of analysis in the antibiotic sub-study will be general practice.

Effects on consultation time

Use of KSS could increase consultation time by 1. EHR entry of the infection symptoms and 2. review of KSS content and 3. discussion with patient about information leaflet. In the BRIT qualitative study (comparing high and low prescribing practices), GPs noted the importance of sufficient support or resources to enable them to make a strong case for prescribing only when clinically needed and managing possible tension with patients' expectations [11]. In this project, we will monitor and evaluate the effects on duration of consultation time as recorded in the EHR. The KSS can be modified and part disabled if certain aspects are found to be too time-consuming (such as data entry of symptoms; it is planned to only enter symptoms as required in the NICE treatment guidelines). Furthermore, the EHR vendors are currently considering implementing a system in which patients in the waiting room can answer questionnaires on a device which is then loaded into the EHR. This would reduce the burden on GPs.

Clinical effectiveness

Outcomes: The primary outcome will be the overall rate of antibiotic prescribing. One secondary outcome will be the safety outcome of infection-related complications as recorded in the primary care records such as pneumonia and lower RTIs, peritonsillar abscess, mastoiditis, intracranial abscess, empyema, scarlet fever, pyelonephritis, septic arthritis, osteomyelitis, meningitis, toxic shock syndrome and septicaemia, and Lemierre syndrome (as defined by Gulliford et al [29]). As described in the Appendix (Page 19), BRIT found that GP-recorded infection-related complications provided comparable results as those recorded in linked hospital admission data. Another safety outcome will be the rate of hospital admission for infection-related complications (linked hospital data are likely to be available within the LHCREs. The primary and safety secondary outcome will be similar to a recent cRCT of generic decision support with a leaflet in UK primary care [30]. Another secondary outcome will be the level of risk-based prescribing. For each patient who has been prescribed an antibiotic and who has a recent EHR record of urinary tract infection, upper or lower respiratory tract infection, the predicted risk for infection-related complications as based on the risk prediction scores as developed and validated in the BRIT project [19] will be estimated. These predicted risks will then be averaged by practice and compared between intervention and control arms. It is expected that any risk-based prescribing by GPs would lead to an increased mean predicted risk in the intervention arm.

The analyses will be adjusted for several practice-level covariates including region, study quarter, period of randomisation and baseline antibiotic prescribing, socioeconomic status, case-mix of patients and ethnicity distribution in each practice (including mean Charlson comorbidity score[31]), consultation rates for common infections, coding propensity and characteristics of patients with common infections. The coding propensity

will be the proportion of antibiotic prescriptions with recent clinical record for common infection. The characteristics of patients with common infections will include the averages in each practice for mean age, sex, and predictors for infection-related complication including clinical and medication risk factors [32]). Body mass index and smoking history will also be considered as potential predictors for infection-related complications; these will be discussed with the Study Steering Committee and will each be included in either the primary analysis, a sensitivity analysis or not included in the analysis. The primary analysis will be a complete case analysis (i.e. excluding practices who drop out of the trial), unless attrition is higher than expected (i.e. >10% overall or differential between-arm attrition of >10%). The Statistical Analysis Plan will contain full details on the planned analyses and will be developed by the Statistics Team and approved by the Study Steering Committee.

Sensitivity analyses

The Statistical Analysis Plan will include a series of sensitivity analyses which will include detailed considerations of possible sources of bias and analytical strategies to mitigate and assess the impact of these. One set of sensitivity analyses will evaluate the effects of non-fidelity (non-use of the KSS in the intervention arm) and missing outcome data (due to drop-out of practice). Multiple imputation will be used for missing data. Complier-average causal effect estimation will be conducted to assess the effects of the intervention with 100% fidelity by GPs [33]. Further sensitivity analysis will include the Study Project Steering Committee and detailed in the Statistical Analysis Plan prior to commencement of any (unblinded) statistical analysis.

Additional analyses

These will include subgroup analyses evaluating the overall rate of antibiotic prescribing in the intervention and control arm within different subgroups of patients. Subgroups of interest will include children, elderly, frailty and socioeconomic status; further subgroups may be included following discussions with the Study Steering Committee. We will also repeat the above the clinical effectiveness analysis, and any associated sensitivity analyses deemed appropriate and necessary, having included the observational control arm.

Cost-effectiveness

NICE has produced guidance on the type of economic analysis needed for digital health technologies, depending on the level of financial risk to the NHS [34,35]. For a digital health technology like KSS that has the potential to be cost-saving, the economic analysis level could be defined as ‘low financial commitment’ requiring at least a cost-consequence analysis (CCA) and a budget impact analysis (BIA). Given the potentially wide impact and the uncertainty about whether KSS will lead to cost-savings we suggest being more cautious, defining the level as ‘high financial commitment’, and accordingly we will carry out an

indicative cost-utility analysis to provide estimates of overall impact of KS, relevant to specific decision-makers' and commissioners' timeframes.

We will estimate economic impact of the KSS, from the perspective of the NHS/PSS. The primary analysis will be a within-trial CCA and BIA where the outcomes are overall rate of antibiotic prescribing and level of risk-based prescribing. As we do not have access to infection-related hospital admissions, we need to use a proxy for this aspect of resource use. Therefore, we will also carry out an indicative BRIT algorithm-based economic analysis where we will use the data summarised above plus estimates of the expected rate of infection-related hospital admissions based on the validated BRIT risk algorithms, to provide indicative estimates of overall costs associated with KSS.

Costs: The comparator arms will be either high- or low-intensity KSS. Resource use will be apportioned to each level of intervention. Original development costs will not be included as they are related to research funding rather than NHS and PSS resources. Costs will consist of the BRIT dashboards (both arms) and KSS during consultation (intervention arm only). Costs will include delivery, maintenance and updating, facilitating activities, training NHS staff. We will have data within EHR on duration of consultations. Direct downstream costs are for management of infections and antibiotic-related complications. Therefore, costs will include incidental prescribing, subsequent antibiotic treatment with the same/different type within 30 days of the initial antibiotic and costs of safety outcomes, infection-related complications as recorded in the primary care records (pneumonia, sepsis, quinsy, mastoiditis, or meningitis). Costs in the indicative analysis will also include the estimated costs of infection-related hospital admissions based on the validated BRIT risk algorithms. These data will be combined with BNF [36], NHS reference [37] and Personal Social Services Research Unit (PSSRU) [38] unit costs, and other sources as needed, to derive prescribing and healthcare costs.

Outcomes: In the primary CCA, we will use the primary outcome, overall level of antibiotic prescribing, level of risk-based prescribing, infection-related hospital admissions and infection-related complications, to estimate economic impact of KS. In the indicative analysis, we will use published estimates of QALY decrements associated with infection-related hospital admissions and safety outcomes to estimate differences in utility gain. Information on Quality of life (QOL) utility weights will be based on results of literature review. A recent study used several utility weights for a cost-effectiveness analysis for Acute Respiratory Infection [39]. Each utility value will then be used to adjust for the time spent in that health state per year to calculate an overall utility value for that health state.

Economic and budget impact analyses: Primary CCA will generate estimates of incremental costs and outcomes. BIA will estimate of the impact of KSS on decision-makers' budgets, where both costs and benefits

are monetised over at least two years, depending on length of follow-up available. We will develop provision of CCG-specific impact estimates based on local population and uptake characteristics.

Incremental cost-effectiveness ratios will be calculated in the indicative analysis in the event of KSS having higher costs and better outcomes than usual care. If there is a difference in outcomes, we will express costs incurred in terms of quality-adjusted life-years (QALY) gain. Uncertainty will be addressed by generating cost-effectiveness planes from bootstrapped resamples. Cost-effectiveness acceptability curves (CEACs) will be constructed to show the probability that the intervention is cost-effective for different QALY thresholds, along with net benefit estimation. As this will be an indicative estimate, costs and effects will be examined over one year only and discounting will not be needed.

Outcomes in frailty sub-study

The unit of analysis in the frailty sub-study will be general practice. The outcomes of interest will be based on prescribing rates in frail elderly. The precise definition of medication classes to be included in the outcome measurement will be based on findings in the benchmarking analyses of effectiveness of prescribing in frail elderly and the content of the dashboards. The selection will be made by the research team and approved by the Study Steering Committee which will include GPs and prescribing advisors.

Allocation and blinding

The random allocation to the various interventions will use anonymised practice identifiers with randomisation stratified by region and baseline rate of antibiotic prescribing (antibiotic arm) or level of polypharmacy (frail elderly arm). The data analysts will not be blinded to intervention allocation for practical reasons as they will be compiling the intervention-related dashboards. However, the Statistical Analysis Plan for the end-of-study analyses will be developed by the Lead Statistician from the Centre for Biostatistics (Co-Investigator CS) who will not have access to study data and practice names throughout the study, and he will also perform the checking of statistical results to ensure that they are performed in accordance with the approved Statistical Analysis Plan.

DATA MONITORING AND QUALITY ASSURANCE

We will establish an oversight committee, the Study Steering Committee, including senior representatives independent of the trial, comprising stakeholders in general practice, pharmacy, commissioning groups and patient representatives (6-monthly meetings) and statistician. This committee will act as a sounding and advisory board on the progress of this project; the principal investigator, project manager and one of data analysts will also attend. Professor Janusz Jankowski, clinician and healthcare policy expert, has agreed to chair this committee. We will follow NIHR guidance for programme steering committees [Research Governance Guidelines (nihr.ac.uk)]. The study will be subject to the audit and monitoring regime of the University of Manchester.

SAFETY CONSIDERATIONS AND ADVERSE EVENTS

Clinical decision-making about individual patient care will remain the sole responsibility of the clinicians in the practices. One secondary outcome in the statistical analysis in the antibiotic sub-study will be the safety outcome of infection-related complications as recorded in the primary care records. This will assess whether any reductions in antibiotic use are associated with increases in risks of infection-related complications.

PEER REVIEW

The proposals for this study have been reviewed by two funding panels from Health Data Research UK and National Institute for Health Research. The design of the study was developed by members of the research team, who have wide experience in the design and implementation of research projects using electronic health records and linked deidentified data, and randomised clinical trials. The multidisciplinary members of the research team independently reviewed the design to ensure quality and robustness.

ETHICAL and REGULATORY CONSIDERATIONS

Research Ethics Committee approval will be obtained before commencing research. The study will be conducted in full conformance with all relevant legal requirements and the principles of the Declaration of Helsinki, Good Clinical Practice (GCP) and the UK Policy Framework for Health and Social Care Research 2017.

There will no risks to patients related to this research. There may be increased burden in reviewing the feedback, dashboards and knowledge support system. However, we will undertake workshops with GPs to improve the design and usefulness of the feedback mechanisms so that GPs will see them as an advantage rather than burdensome.

STATEMENT OF INDEMNITY

The University has insurance available in respect of research involving human subjects that provides cover for legal liabilities arising from its actions or those of its staff or supervised students. The University also has insurance available that provides compensation for non-negligent harm to research subjects occasioned in circumstances that are under the control of the University.

FUNDING and RESOURCES

This work is supported by three independently funded grants. The first is funded by the National Institute for Health Research (HS&DR Project: NIHR130581) and concerns the cluster randomised trial to improve antibiotic prescribing in primary care. The second is funded by Health Data Research UK (HDR UK Better Care Programme for frail elderly) and concerns the analysis & feedback for frail elderly. The third is funded

by Public Health England and concerns the feedback in primary care to individual GPs on their individual antibiotic prescribing.

PUBLICATION POLICY

Dissemination of research outputs to participating clinical staff and policy and guideline developers will be an integral part of this project. In addition, we will promote dissemination to national policy makers, managers and clinical leaders, through project summaries and policy briefings. Through our partners in PHE and NICE, we will engage NHS England. We will continue to work closely with Wessex Academic Health Science Network (AHSN) which is the national lead for the AHSNs' Medicines Optimisation Programme and works collaboratively with the other 14 AHSNs to develop, share and spread good practice. Members within our team have been actively engaged with the AHSN network to support the national roll out of PINCER: Pharmacist-led information technology intervention for reducing clinically important errors in general practice prescribing. We will benefit from this engaged network of local, regional and national Medicines Optimisation groups including local primary care prescribing advisors, clinical pharmacy networks in general practice, and national advisory groups. Results of this study will also be published in peer-reviewed scientific journal (open access if funding is available) and presented at scientific conferences. The participating practices will be sent summary results of the study.

All study results will be reported in accordance to this study protocol and to the Consolidated Standards of Reporting Trials statement extended to cluster-randomised trials [40].

PATIENT AND PUBLIC INVOLVEMENT

We will recruit a patient advisory group of 5+ members via the NIHR Patient research ambassadors programme. The advisory group will have a lay Chair and will meet quarterly and will provide input to shape key study components and analysis and dissemination throughout the multiple work streams. Members of our PPPIE advisory group will also work with us to engage with relevant wider public and community groups including older people and carers in order to raise awareness about responsible antibiotic prescribing and use, and to ensure public perspectives feed into the project and development of appropriate outputs. We will work with community-based groups and conduct community engagement events in participating regions during the project. We will also include at least one PPI representatives on our Study Steering Committee.

COMPETING INTERESTS

The authors have no competing interests.

REFERENCES

1 Grossmann C, Sanders J, English RA, *et al.* Large Simple Trials and Knowledge Generation in a

Learning Health System - Workshop Summary. Washington: : National Academies Press 2013. http://www.iom.edu/Reports/2013/Large-Simple-Trials-and-Knowledge-Generation-in-a-Learning-Health-System.aspx

2 Friedman CP, Rubin JC, Sullivan KJ. Toward an Information Infrastructure for Global Health Improvement. *Yearb Med Inform* 2017;**26**:16–23. doi:10.15265/IY-2017-004

3 Roland M. Linking Physicians' Pay to the Quality of Care — A Major Experiment in the United Kingdom. *N Engl J Med* 2004;**351**:1448–54. doi:10.1056/NEJMhpr041294

4 Grigoroglou C, Munford L, Webb R, *et al.* Impact of a national primary care pay-for-performance scheme on ambulatory care sensitive hospital admissions: a small-area analysis in England. *BMJ Open* 2020;**10**:e036046. doi:10.1136/bmjopen-2019-036046

5 Guthrie B, Kavanagh K, Robertson C, *et al.* Data feedback and behavioural change intervention to improve primary care prescribing safety (EFIPPS): multicentre, three arm, cluster randomised controlled trial. *BMJ* 2016;**354**:i4079. doi:10.1136/BMJ.I4079

6 Curtis CE, Al Bahar F, Marriott JF. The effectiveness of computerised decision support on antibiotic use in hospitals: A systematic review. *PLoS One* 2017;**12**:e0183062. doi:10.1371/journal.pone.0183062

7 Longhurst CA, Harrington RA, Shah NH. A 'Green Button' For Using Aggregate Patient Data At The Point Of Care. *Health Aff* 2014;**33**:1229–35. doi:10.1377/hlthaff.2014.0099

8 Improving people's health: Applying behavioural and social sciences to improve population health and wellbeing in England. 2018. www.facebook.com/PublicHealthEngland (accessed 1 Feb 2020).

9 Hallsworth M, Chadborn T, Sallis A, *et al.* Provision of social norm feedback to high prescribers of antibiotics in general practice: a pragmatic national randomised controlled trial. *Lancet* 2016;**387**:1743–52. doi:10.1016/S0140-6736(16)00215-4

10 Meeker D, Linder JA, Fox CR, *et al.* Effect of behavioral interventions on inappropriate antibiotic prescribing among primary care practices a randomized clinical trial. *JAMA - J Am Med Assoc* 2016;**315**:562–70. doi:10.1001/jama.2016.0275

11 van der Zande MM, Dembinsky M, Aresi G, *et al.* General practitioners' accounts of negotiating antibiotic prescribing decisions with patients: a qualitative study on what influences antibiotic prescribing in low, medium and high prescribing practices. *BMC Fam Pract* 2019;**20**:172. doi:10.1186/s12875-019-1065-x

12 Costelloe C, Metcalfe C, Lovering A, *et al.* Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *BMJ* 2010;**340**:c2096.http://www.ncbi.nlm.nih.gov/pubmed/20483949 (accessed 15 Sep 2018).

13 Peute LWP, de Keizer NF, Jaspers MWM. The value of Retrospective and Concurrent Think Aloud in formative usability testing of a physician data query tool. *J Biomed Inform* 2015;**55**:1–10. doi:10.1016/j.jbi.2015.02.006

14 De Lusignan S, Liyanage H, Sherlock J, *et al.* Atrial fibrillation dashboard evaluation using the think

aloud protocol. *BMJ Heal Care Informatics* 2020;**27**:100191. doi:10.1136/bmjhci-2020-100191

15 Porat T, Delaney B, Kostopoulou O. The impact of a diagnostic decision support system on the consultation: perceptions of GPs and patients. *BMC Med Inform Decis Mak* 2017;**17**:79. doi:10.1186/s12911-017-0477-6

16 National Institute of Health and Care Excellence. Overview | Respiratory tract infections (self-limiting): prescribing antibiotics | Guidance | NICE. https://www.nice.org.uk/guidance/cg69 (accessed 30 May 2019).

17 Delaney BC, Curcin V, Andreasson A, *et al.* Translational Medicine and Patient Safety in Europe: TRANSFoRm-Architecture for the Learning Health System in Europe. *Biomed Res Int* 2015;**2015**:961526. doi:10.1155/2015/961526

18 Kontopantelis E, Stevens RJ, Helms PJ, *et al.* Spatial distribution of clinical computer systems in primary care in England in 2016 and implications for primary care electronic medical record databases: a cross-sectional population study. *BMJ Open* 2018;**8**:e020738. doi:10.1136/bmjopen-2017-020738

19 Mistry C, Palin V, Li Y, *et al.* Development and validation of a multivariable prediction model for infection-related complications in patients with common infections in UK primary care and the extent of risk-based prescribing of antibiotics. *BMC Med* 2020;**18**:118. doi:10.1186/s12916-020-01581-2

20 Gulliford MC, Charlton J, Winter JR, *et al.* Probability of sepsis after infection consultations in primary care in the United Kingdom in 2002–2017: Population-based cohort study and decision analytic model. *PLOS Med* 2020;**17**:e1003202. doi:10.1371/journal.pmed.1003202

21 Costelloe C, Metcalfe C, Lovering A, *et al.* Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *BMJ* 2010;**340**:c2096.http://www.ncbi.nlm.nih.gov/pubmed/20483949 (accessed 6 Sep 2018).

22 Van Staa TP, Palin V, Li Y, *et al.* The effectiveness of frequent antibiotic use in reducing the risk of infection-related hospital admissions: Results from two large population-based cohorts. *BMC Med* 2020;**18**:40. doi:10.1186/s12916-020-1504-5

23 Moons KGM, Kengne AP, Grobbee DE, *et al.* Risk prediction models: II. External validation, model updating, and impact assessment. Heart. 2012;**98**:691–8. doi:10.1136/heartjnl-2011-301247

24 Mowle S, Edwards A, Hood K, *et al.* Benchmarking using simulated clinical scenarios: a feasibility project. *Br J Gen Pract* 2001;**51**:658–60.http://www.ncbi.nlm.nih.gov/pubmed/11510396 (accessed 26 Jan 2020).

25 Stacey D, Légaré F, Lewis K, *et al.* Decision aids for people facing health treatment or screening decisions. *Cochrane Database Syst Rev* Published Online First: 12 April 2017. doi:10.1002/14651858.CD001431.pub5

26 Barnett S, Jones SC, Bennett S, *et al.* General practice training and virtual communities of practice - a review of the literature. *BMC Fam Pract* 2012;**13**:87. doi:10.1186/1471-2296-13-87

27 Bermejo-Caja CJ, Koatz D, Orrego C, *et al.* Acceptability and feasibility of a virtual community of practice to primary care professionals regarding patient empowerment: a qualitative pilot study. *BMC*

Health Serv Res 2019;**19**:403. doi:10.1186/s12913-019-4185-z

28 PMAC AGD of H&. Nudge vs Superbugs: a behavioural economics trial to reduce the overprescribing of antibiotics June 2018. ttps://www1.health.gov.au/internet/main/publishing.nsf/Content/Nudge-vs-Superbugs-behavioural-economics-trial-to-reduce-overprescribing-antibiotics-June-2018 (accessed 23 Nov 2019).

29 Gulliford MC, Juszczyk D, Prevost AT, *et al.* Electronically delivered interventions to reduce antibiotic prescribing for respiratory infections in primary care: Cluster RCT using electronic health records and cohort study. *Health Technol Assess (Rockv)* 2019;**23**:1–72. doi:10.3310/hta23110

30 Gulliford MC, Prevost AT, Charlton J, *et al.* Effectiveness and safety of electronically delivered prescribing feedback and decision support on antibiotic use for respiratory illness in primary care: REDUCE cluster randomised trial. *BMJ* 2019;**364**:l236. doi:10.1136/bmj.l236

31 Charlson M, Wells MT, Ullman R, *et al.* The Charlson comorbidity index can be used prospectively to identify patients who will incur high future costs. *PLoS One* 2014;**9**:e112479. doi:10.1371/journal.pone.0112479

32 Mistry C, Palin V, Li Y, *et al.* Development and validation of a multivariable prediction model for infection-related complications in patients with common infections in UK primary care and the extent of risk-based prescribing of antibiotics. *BMC Med* 2020;**18**. doi:10.1186/s12916-020-01581-2

33 Dunn G, Maracy M, Tomenson B. Estimating treatment effects from randomized clinical trials with noncompliance and loss to follow-up: The role of instrumental variable methods. Stat. Methods Med. Res. 2005;**14**:369–95. doi:10.1191/0962280205sm403oa

34 Evidence standards framework for digital health technologies | Our programmes | What we do | About | NICE. https://www.nice.org.uk/about/what-we-do/our-programmes/evidence-standards-framework-for-digital-health-technologies (accessed 4 Mar 2019).

35 Craig J. NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE Evidence Standards Framework for Digital Health Technologies Examples of Functional Classifications for Selected Digital Health Technologies. 2019.

36 British National Formulary. 2019.

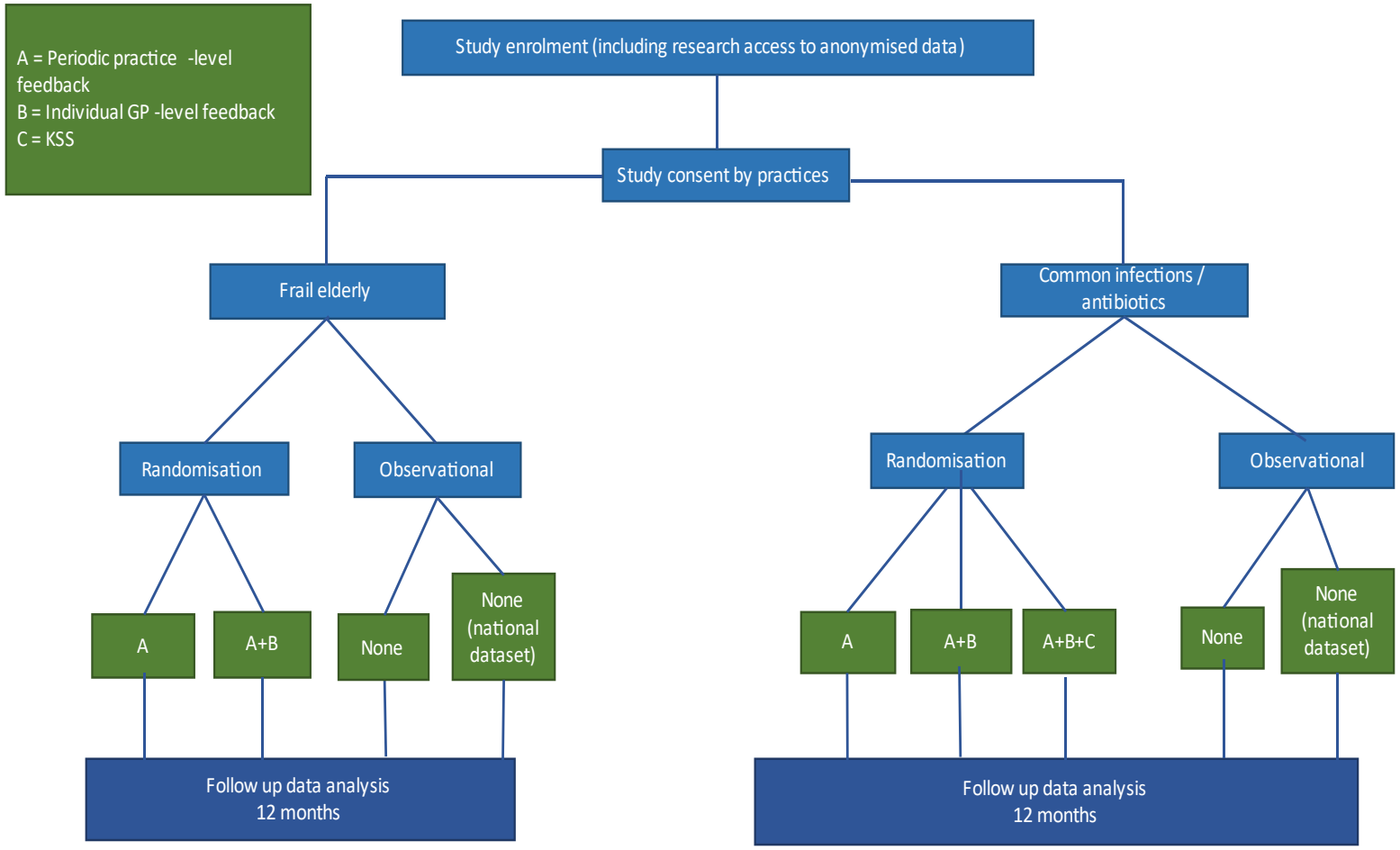
37 Department of Health. NHS Reference Costs 2011/2012. http://www.dh.gov.uk/health/2012/11/2011-12-reference-costs/

38 Curtis L. Unit costs of Health & Social Care 2012. 2012.http://www.pssru.ac.uk/project-pages/unit-costs/2012/

39 Gong CL, Zangwill KM, Hay JW, *et al.* Behavioral Economics Interventions to Improve Outpatient Antibiotic Prescribing for Acute Respiratory Infections: a Cost-Effectiveness Analysis. *J Gen Intern Med* 2019;**34**:846–54. doi:10.1007/s11606-018-4467-x

40 Campbell MK, Piaggio G, Elbourne DR, *et al.* Consort 2010 statement: Extension to cluster randomised trials. *BMJ* 2012;**345**. doi:10.1136/bmj.e5661

Figure 1 Overview of design and intervention in BRIT2



Appendix 1: Summary of dashboards as developed in BRIT project

The BRIT dashboard summarises information on antibiotic prescribing by infection type and where these prescriptions may deviate from the recommended guidelines, overall prescribing rates with comparision to peers, as well as how a practice may prescribe based on a pratients risk of an infection-related complication. On the hompage users have the option to clickthe lage icons or use the menu bar across the top to navigete to each dashbord.

The first group of visulisations (Supplement Figure 1A) show the general practices (GPs) inforation about their antibiotic prescribing by infectious conditions. The first part of the dashboard shows colourful notification boxes with the number of infection-related consultations in a given time period (yellow box), the number of antibiotic prescriptions issued for these consultations (blue box), the number of these prescriptions issed that deviated from the national recommended guidelines (red box) and a nudging notification box (in green) that suggests areas for improvement in their prescribing based on which condition saw more deviating prescriptions. Users reviewing the dashboard, such as prescribing advisor may decide to concentrate their efforts when auditing the practices antibiotic prescribing in a given month by delving deeper into the prescriptions issued for consultations were the system flagged the most inappropriate prescriptions (in this example upper respiratory tract infections; URTI).

Next the user will see a box and whisker plot showing national prescribing rates by infection, i.e. for each practice the percentage of consultations that resulted in an antibiotic prescription by infection type (Supplement Figure 1B). The users of the BRIT dashboard can also see where their practice sits (the black dots overlaid on this plot) compared to the national prescribing rates. Forexample, figure 1 shows the practice has a higher prescribing rate for breast-related infections compared to the national average but have a lover prescribing rate for ear-related infections (otitis externa and otitis media), highlighting which infections warrant further investigation in their practice.

The practice can also see what prescriptions are being prescribed to each infectious condition as a percentage in a sunburst plot, where Supplement Figure 1C shows that when selecting lower respiratiory tract infections (LRTI) over three quarters of the prescriptions their practice prescribed for this condition were fore amoxicillian, followed by doxycycline and clarithromycin as well as other antibiotic less commonly prescribed to these conditionsn in their practice in a given time period.

The practice can also see how their practice is performing in terms of prescribing appropriateness (Figure 1D). The analysis behind these plots assess wheather each antibioitc prescription in agreement (blue) or disagreement (red) with the recommended first- second- or alternative- medicine. For example this plot shows a hypothetical practice were 24% of the consultations for sinusitis resulted in an antibiotic prescription that may have been inappropriate because it deviated form the recommended guidelines. They can also see for each condition what antibiotic type was issued and flagged as potentially inappropriate (figure not shown). If they were to scroll down on the sape dashboard there are snapshots of the most recent antibiotic guidelines , enabiling a quick comparision of the antibiotics they have prescribed deviating from recommendations and

refreshing what antibiotics are currently recommedned appropriate for each condition. Again, this analysis highlights areas for review/improvement specific to each practice that may instigate discussion in a practice manegement meeting ensuring prescribers have refreshed their knowledge on the current prescribing guidelines for a particular infection.

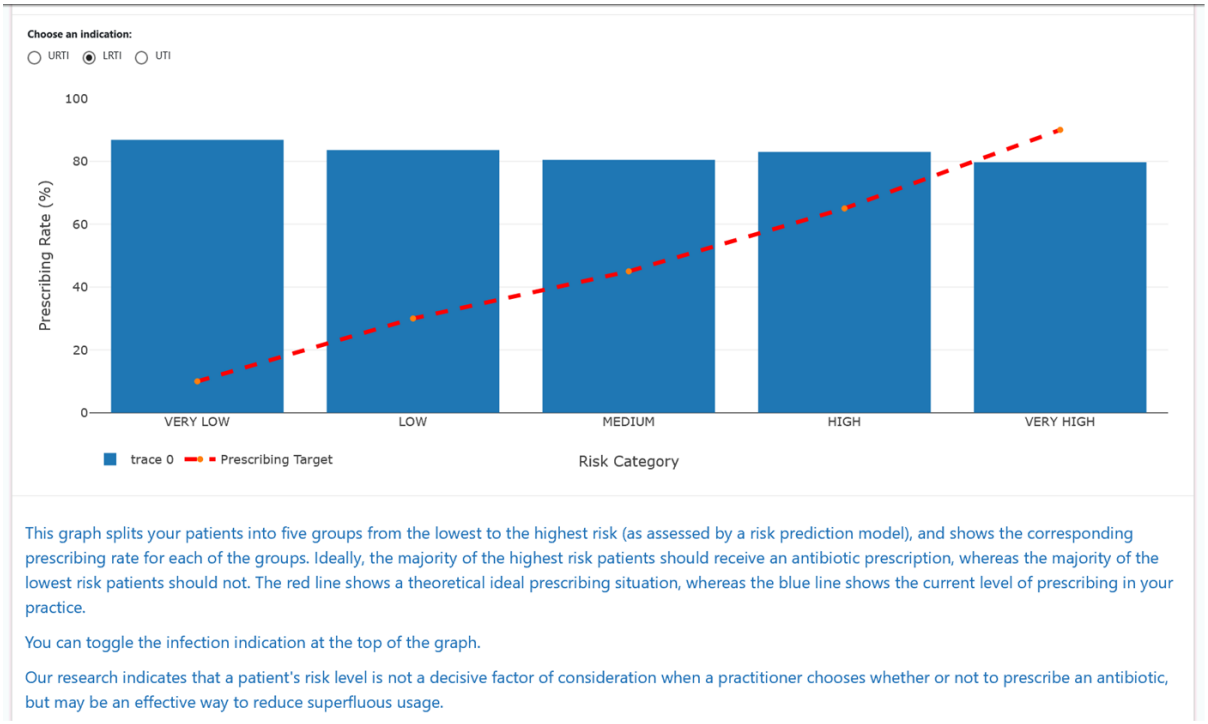
A second topic of analysis is looking at how well a practice prescribed based on a patients predicted risk of a poor outcome (e.g., infectin-related hospitalisation). The analysis is based on a validated risk prediction model using two national datasets . Supplement Figure 2 showa the predicted risk (using the prediction model) for every patient presenting with a particular infection (in this case LRTI) in a given time period (6 months), separated into categories from very low predicted risk to very high predicted risk of complication. For each category the actual prescribing rate is caluculated as a percentage and displayed by the bule bars. Practices prescribing according to patients risk of complication would expect to see the height of the blue bars match the red line here, where very low risk patients received prescriptions on occasion, perhapse due to the severity of their symptom and the very high risk patients are receiving a prescription more often. However, this figure shows a flat line across all risk categories again suggesting prescribing for this infection is not well targeted to high risk patients and there is room for improvement. The dashboard also has a built in a risk prediction calculator, allowing users modify various patient characteristics and see which effects the predicted risk more, again adding a training element to the dashboard that can help to identify ways to further optimise their prescribing.

The final topic of analysis is prescribing benchmarking. The traffic-light visulisation (Supplement Figure 3A) shows STAR-PU adjusted prescriing rates for each practice. This is an age-sex adjusted prescribing rate allowing fair comparison between practices. The yellow dots show bottom 25% of practices with a relatively low prescribing rate, the red dots show the top 25% of high prescribing practices and the green is the middle 50% percent of practices with an average prescribing rate. The black dot then shows where the individual practice sits compared to their peers.

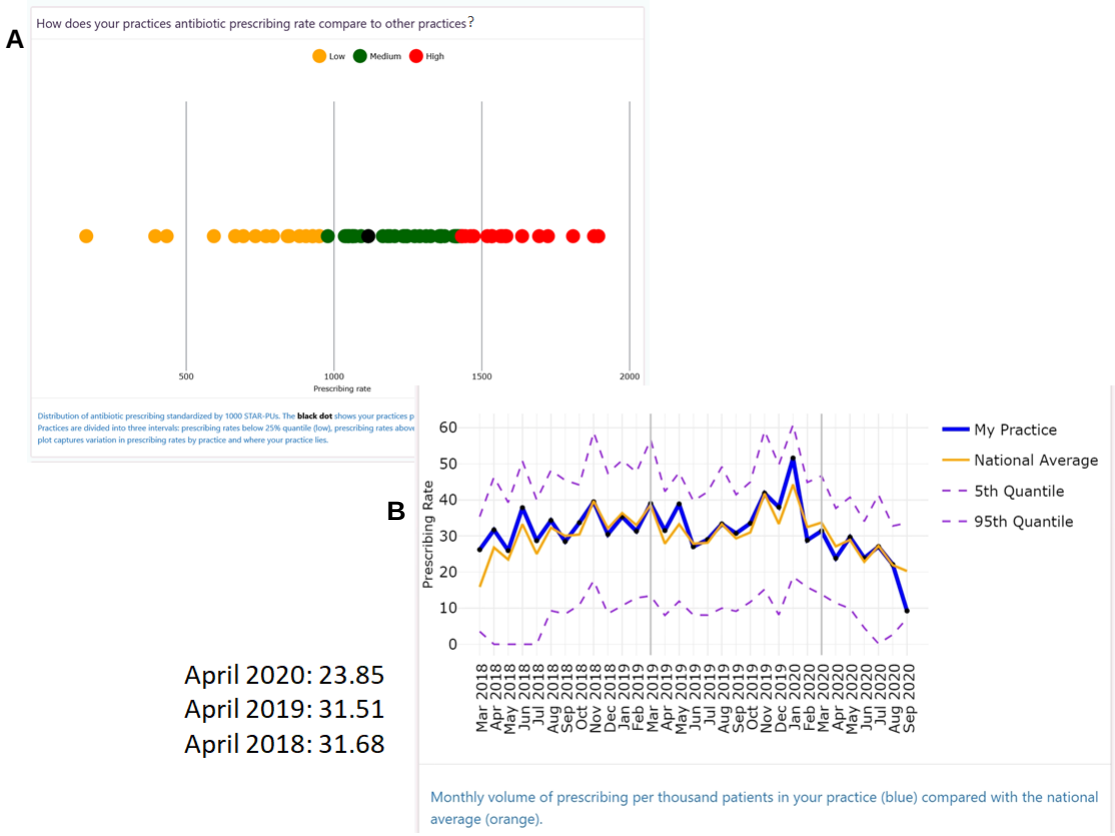
The bottom figure (Supplement Figure 3B) shows the practices prescribing rate over time. This is important compare how a practice is prescribing to their peerd but to also observe any rapid changes to their prescribing rates following an intervention; allowing rapid review and uptake of interventions that work and removal of those that do not. The practice can also use these sort of comparison plots to see seasonality trends as well as changes in prescribing due to an outbreak of a pandemic disease, such as COVID-19. Here we can see the prescribing rate in April 2018 and April 2019 for this demostrative practice was 31.5 units of antibiotics for every 1000 registered patients; however following the outbreak of COVID-19 the prescribing rate in April 2020 has reduced to 23.85 units of antibiotics prescribed per 1000 registered patients.

The data in the dashboard is regularly updated providing practices with frequent incited to their own prescribing and how changes they make can alter and optimise their prescribing. The content of the dahboard visulisations also evolving in an iterative manner based on feedback from users and key stakholders, creating a learning health care system that is evolving with the health care our patner practices provide.

Supplement Figure 1: Antibiotic prescribing stratified by type of infection and where prescriptions deviate from guidelines.



Supplement Figure 2: Antibiotic prescribing by patient risk profile



Supplement Figure 3: Antibiotic prescribing rates