PHarmacy partnership using decision-making tools and near patient testing for Antimicrobial Stewardship for EveryDay practice IN primary care (PHASED IN)

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ABBREVIATIONS

AE	Adverse event
AR	Adverse reaction
AMR	Antimicrobial resistance
AMS	Antimicrobial stewardship
CI	Chief Investigator
CRF	Case Report Form
CRP	C-Reactive Protein
CTU	Clinical Trial Unit
DMP	Data Management Plan
DSMC	Data and Safety Monitoring Committee
GCP	Good Clinical Practice
GP	General Practitioner
LES	Locally Enhanced Service
LRTI	Lower Respiratory Tract Infection
MHRA	Medicines and Healthcare products Regulatory Agency
ISF	Investigator Site File
NRES	National Research Ethics Service
PC-CTU	Primary Care – Clinical Trials Unit
PI	Principal Investigator
POCT	Point of care test
R&D	NHS Trust R&D Department
RADT	Rapid antigen detection test
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TSC	Trial Steering Committee

1. OVERVIEW OF RESEARCH

This study will initially complete the development of an intervention. The intervention is a referral pathway for patients presenting with common acute infections in GP practices to a pharmacy, where initial management of the infection will be undertaken using both decision aids and near patient tests. Following the completion of the intervention development, among 20 GP practices and their linked pharmacies (a GP/pharmacy cluster) 10 clusters will be randomised to intervention and 10 to control to explore the feasibility of using the intervention in everyday practice, and also the acceptability of trial procedures.

2. LAY SUMMARY

Background

One in three people see doctors, nurses, or pharmacists each year with common infections, such as colds, flu, chest, ear, sinus and urine infections. Currently most antibiotics are prescribed in general practices, and half of the people contacting general practices with infections receive antibiotics, but antibiotics mostly don't help. Overuse of antibiotics harms people and causes antibiotic resistance to develop, where antibiotics no longer work well.

This could make modern medicine, such as routine surgery and cancer treatments, difficult or impossible. Early evidence from community pharmacy 'minor illness' schemes, and from piloting of redirection of patients presenting with infections to linked community pharmacies, suggests this is probably both safe and may lower antibiotic use. However, these services are not widely available. Although a new national pharmacy infection management scheme is being negotiated it is going to be limited in scope. There is no high-quality scientific evidence for this type of infection service.

Aim

To finish development and feasibility test a pharmacy package using decision-making tools and POCTs to share the management of acute infections in primary care.

Developing tools to support antibiotic stewardship

We are developing evidence based 'decision-making tools' to standardise care and help identify people who do not need antibiotics, and those who might need them, or need further assessment. The intervention will include these decision-making tools, as well as diagnostic

tests that can be carried out on the spot if needed (such as C-reactive protein) and patient leaflets to support self-care. There will be a training package to help health professionals to use all these tools in patient consultations. We will continue working closely with patients, pharmacists, and other prescribers from general practice (GPs, nurses) to make sure the tools and training are helpful and easy to use.

Testing the feasibility of using the package

10 general practices will continue with management as usual, and 10 will be trained to refer patients presenting with common infections to linked community pharmacies who will use the intervention. We will include practices in a wide range of settings (including high and low income areas, urban and rural, and practices with high ethnic minority populations) and will look at how well the service works, what the implications are for providing the service, and patient and healthcare professional views with a view to any revisions needed prior to a fuller trial of the new service.

PPIE

Public contributors have helped design this study, are members of our study team, and will be involved in study management, delivery, and dissemination. We have also recruited a PPIE reference group with a wider range of people from different backgrounds to help throughout the study.

3. SCIENTIFIC SUMMARY

Background. Half of those contacting general practices with infections receive antibiotics which mostly don't help and drive antibiotic resistance. Early evidence from pharmacy 'minor illness' services suggest they may lower antibiotic use and could help the NHS workload crisis - particularly in the winter. A national pharmacy infection service is being negotiated, but the range of infections covered is limited, and standardised assessment using decision-making tools and targeting of diagnostic tests and antibiotics, as recommended in current national action plans, will not be available. There is currently no randomised evidence of a 'pharmacy first' approach.

Aim.

To finish development and feasibility test a pharmacy package using decision-making tools and POCTs to share the management of acute infections in primary care.

Methods

The intervention will include evidence-based decision-making tools, diagnostic tests (e.g. C-Reactive-Protein) patient leaflets to support self-care, and training packages for both general practices and pharmacists.

Intervention development

We will complete the development and optimisation of the diagnostic tools as follows:
1) Finalise patient and health professionals (pharmacists, doctors, and prescribing nurses) interview analysis to identify key behavioural drivers for using or not using/liking prototype intervention elements (decision-making tools, online training for pharmacists, doctors and nurses, patient-facing support materials).
2) Develop the prototypes iteratively (and for patient facing support materials both hard copy leaflets and digital online to enhance accessibility) using the Person-Based Approach to ensure we maximise facilitators and overcome barriers to the engagement of both patients and clinicians.
3) Test iteratively the acceptability/persuasiveness of materials using in-depth face-to face 'think aloud' interviews and refine the intervention accordingly until no significant new comments arise.

Feasibility trial.

A randomised trial in 20 general practice/community pharmacy clusters (10 intervention, 10 control) in the top two tertiles of antibiotic prescribing will document:
1. Experience of the intervention, acceptability of the intervention and of trial materials based on qualitative interviews
2. Engagement with key behaviours (the use of online training, Use of decision support etc);
3. Recruitment rate of patients and practices
4. Follow-up rates
5. The logistics of this service delivery model (e.g., staff requirements; GP/pharmacy resource use).

6. Clinical safety (complications recorded; adverse events)

A mixed methods process analysis will assess engagement with online training, and explore the range of experiences and contextual influences, and identify any revisions needed to the intervention.

PPIE

Public contributors are part of the study team and have helped design this study. We have also recruited a PPIE I reference group from different backgrounds to help throughout the study.

Anticipated impact.

If the intervention proves feasible and acceptable, we will apply for funding for a definitive trial. We anticipate the intervention could potentially reduce antibiotic use and reduce workload in general practice. Stakeholder panels will meet during the study to identify key needs for adoption of the intervention into routine care should the intervention be shown to be effective. The analysis of the primary and secondary quantitative outcomes will be descriptive (as appropriate means or proportions with 95% confidence intervals) for both baseline and follow-up data. Qualitative interviews will first be analysed using reflexive thematic analysis(41) then explored for how constructed themes may map onto theoretical frameworks.

4. BACKGROUND AND RATIONALE

Acute upper/lower respiratory (URTIs/LRTIs), urinary (UTIs), and skin infections significantly impact everyday life (1, 2). 30% of the population attend general practices annually with RTIs, and 50% 'normally' get antibiotics(3) which have limited effectiveness. 50% of women will suffer UTIs – most getting antibiotics(1). Although consultation rates went down during COVID the antibiotic prescribing rate increased(https://ebmdatalab.net/covid19-prescribing-impact/).

Patients using antibiotics have more antibiotic-resistant organisms subsequently(4) and prolonged infections(1). Outpatient antibiotic prescribing is linearly related to the development of Antimicrobial-resistance (AMR)(5). AMR is a global public-health

threat(6)(CMO-Annual-Report-Vol-2-2011) since much of modern medicine (e.g. complicated infections, cancer care, surgery) relies on antibiotics.

Workload difficulties in primary care are longstanding, with increasing pressures and less funding, hence a key policy driver has been to increase the primary care skill mix (https://www.england.nhs.uk/gp/gpfv/). However, there has been limited progress to date and the workload crisis is worsening (https://www.england.nhs.uk/wp-content/uploads/2016/04/gpfv.pdf). Broadening the workload mix to tackle the management of acute infections, particularly during the winter months, could help alleviate some of the pressure in the system and address antimicrobial stewardship.

REVIEW OF EXISTING EVIDENCE

Antimicrobial stewardship (AMS)

The most recent systematic review (7) documented AMS effectiveness for: Interactive clinic-based participant communication and electronic decision-support, supported by national consensus(8). We propose developing both elements, using as a starting point the research we have previously completed on:

a) **Interactive patient support**. Scalable brief internet-training (30 minutes) for prescribers, including training to support enhanced patient self-care and to reduce antibiotic use for LRTI (adults:(9-12);children:(13, 14)). We are adapting this for pharmacy settings.

b) **Decision-making tools**. Our trial of a diagnostic decision-making tool for sore throat (FeverPAIN)(15) reduced antibiotic use, and improved symptom control. FeverPAIN is endorsed by NICE and was used widely in the recent outbreak of streptococcal infections. Diagnostic or prognostic clinical algorithms are available for several other infections (adult LRTI: 3C(16); children LRTI based on the ARTIC-PC data(17); otitis(18)); UTI(1); sinusitis (Berg/Carenfeldt (19, 20)), but none have been developed with patient and clinician input as decision-making tools, nor adapted for use in pharmacies. We have developed a preliminary app incorporating the above decision-making tools suitable for pharmacy use, and which could potentially be incorporated

into existing pharmacy point-of-care software systems (e.g., PharmOutcomes from Pinnacle under the CPCS [Community Pharmacy Consultation Service] scheme).

Biomarkers/point-of-care-tests (POCTs)

The AHRQ review(7) advocated pro-calcitonin(PCT), but it is poorly validated (21) and impractical (2 tests over separate days). The main POCT contender for LRTI is C-Reactive-Protein (CRP): a systematic review (Verbakel(22)), and our trial in COPD(23) confirm short-term antibiotic reductions. However longer-term follow-up for the two large trials in the review (22) demonstrated little effect(24, 25), largely due to GPs not using the tests. A small uncontrolled 'pharmacy-first' approach for LRTI (including CRP; unpublished personal communication MMa) in the North-East showed a potentially important reduction in antibiotic use (fewer than 5% were prescribed antibiotics) and a similar study in Manchester involving community pharmacy referral for CRP testing, led to only 10% of patients being given an antibiotic(26); almost two-thirds (63%) of patients had very low CRP values and were deemed to have self-limiting illness, yet would likely have been given an antibiotic if the scheme was not in place. A review of CRP POCT use to limit antibiotic overuse found that the regular use of CRP POCTs in Switzerland, Norway and the Netherlands is because testing is reimbursed(27). Since pharmacy management pathways, including Patient Group Directions (PGDs) can be standardized and remunerated, the targeted use of CRP in pharmacies is potentially more sustainable than when used in general practices. Preliminary work also suggests that the targeted use of Streptococcal-Rapid-antigen-tests (widely used in Europe/USA/Scandinavia) could also help pharmacists limit antibiotic prescribing(28) .

Pharmacy management

Preliminary evidence suggests community pharmacies in Scotland managing coughs/sore throat/colds provide similar health-related outcomes and lower costs than GP management(29). A systematic review of such schemes documents low re-consultation and high symptom-resolution rates(30), and a qualitative study (31) identified several positive features, but with structural challenges (the limited range of conditions, training, remuneration/workload, GP advocacy). The CPCS (community-pharmacy-consultation-service) scheme in England (for managing a range of common symptoms including cough, cold, flu, earache, dysuria) documented 1,300 GP practices making referrals (as of 06/12/21) to 3,500 pharmacies: 90% of episodes were completed by the pharmacist, with a minority

referred back. However, the range of illnesses managed is limited and there is no use of either decision-making tools or POCTs as recommended by the National Action Plan (Tackling antimicrobial resistance 2019 to 2024: addendum to the UK's 5-year national action plan - GOV.UK (www.gov.uk), which could be addressed by supporting pharmacists to manage common infections using evidence-based decision-making tools supplemented by diagnostic tests (CRP, RADTs). It is anticipated that a national service to commission community pharmacies in England to manage patients with common infections (both CPCS referrals and 'walk-in' patients) will be implemented starting in 2023, but it is anticipated that not all pharmacies will participate. The proposed range of infections covered is also limited (e.g. Lower Respiratory Tract Infections (LRTI) not included) and the scheme will not propose the use of either decision-making tools nor POCTs.

There is proof of concept that pharmacists can use decision-making tools developed in a general practice. Using the FeverPAIN decision-making tool, which we developed for use in general practice, pharmacists can target the use of POCTs and the subsequent dispensing of antibiotics – and that has proven to be safe and may reduce antibiotic use(28).
There is no good trial evidence for the effectiveness and safety of a pharmacy approach for initial infections management, nor for the proposed expansion of Locally Enhanced Services currently being negotiated by the government.

Work to date: current theoretically informed development work in progress (funded by NIHR School for Primary Care Research (SPCR) and the ANTRUK charity)

Development of the initial version of the decision-making tools for pharmacy use

We are using the Person-Based-Approach [32] to develop the intervention which we provisionally propose will consist of a training package for pharmacists to implement decision-making tools including using POCTs. We have developed the first version of decision tools and have started the iterative work of refining these tools.

The proposal is for a community pharmacist to manage patients between the ages of 1 and 80 who present initially to their general practice. Since patients presenting to general practice are the proposed sample, the algorithms need to be based on prior data from general practice samples (Sore throat, LRTI, UTI, otitis) or where that is not available advice by NICE about management of patients in primary care (e.g., impetigo). In addition to the proposed brief

screening by general practice triage staff for eligibility, once patients present to their pharmacist there will be a further quick screen for higher risk individuals based on a saturation monitor: if high risk (very high pulse for age – NICE guidances moderate risk for sepsis thresholds: 1-2 > 140 bpm, 3-4 > 130 bpm, 5, > 120bpm, 6-7 > 110bpm, 8-11 > 105, >=12, > 100bpm) or saturation <92%, participants will be referred urgently back to the GP or to A+E. Otherwise patients will be managed according to the following algorithms which provide both advice about testing, the supply of antibiotics and brief communication to support patients.

Sore throat. This uses the FeverPAIN algorithm we developed among patients presenting in general practice to target antibiotics to those most likely to have streptococcal infection and is based on five features (Fever, Pus, Attend rapidly (prior history <=3 days), No cough or coryza). Based on preliminary piloting [28] the scheme has been rolled out and is currently widely used by pharmacists in the Welsh test and treat sore throat patient group directions (PGDs). FeverPAIN targets testing (near patient rapid tests) where streptococcus is most likely (FeverPAIN score >= 3 (40% or more likelihood of strep infection)) with antibiotics dispensed where the test is positive. The FeverPAIN threshold for initiating antibiotics will match prevailing guidance (as in the recent invasive group A streptococcal infection outbreak where the threshold was lowered).

LRTI adults. This uses the internally validated algorithm derived from the definitive prospective 3C cohort of 28846 patients study (which uses age, O2 saturation, temperature, history of vascular comorbidity, no coryza, chest pain and severity on a 10 point scale)[16]. 4% of patients with ≥5 features have a 5.7% risk of hospital admission, will have antibiotics dispensed and will be recontacted in 2 days to check progress. The 35% with 3 or 4 features have an intermediate risk of adverse outcome (1 in 50, 2.0%) and are advised to return for a CRP test if the illness progresses (based on score)(and antibiotics will not be dispensed if the CRP is low (<20)). The 61% with ≤2 features have a low (1 in 200, 0.5%) risk and are given advice about management of symptoms and advised to return for a CRP test if the illness progresses (based on re-scoring).

LRTI children. This uses data from the ARTIC-PC study of 800 unwell children (DOI: https://doi.org/10.3399/BJGP.2022.0239) to predict adverse outcome (progression of illness

requiring hospital admission - BJGP paper and HTA Journals Library full report in press). The previously developed algorithm (STARWAVe) in less unwell children [33] was found to have poor predictive value (AUROC 0.66). A new internally validated algorithm of three variables (respiratory rate for age, history of sputum/rattly chest, O2 saturation <95%) performs well (AUROC 0.81) and provides a score based on coefficients of the model. Children scoring 70 or less (89% (600/674)) are classified as low risk (<5%)of progression of illness) – and will be advised that antibiotics are not necessary, and given safety netting advice. Antibiotic will be dispensed for the 11% of children scoring >70.

Otitis media. Based on the IPD of prognosis to predict more prolonged pain and/or fever after 4 days [18] three variables will be used (judged to be very unwell (>7/10 on a 10-point scale); bilateral disease; otorrhoea). Antibiotics can be dispensed for children judged to be very unwell (approximately 10% of the sample). For either of the other variables the advice will be for the participant to return if not starting to improve after three days.

Sinusitis, UTI and Impetigo: the algorithms will be based on NICE and UKHSA guidance, but automated and so easier for pharmacists to use.

In addition to providing guidance on when to test testing and management for each infection, the app output incorporates key brief messages about communication with patients, including advice about self-care and safety netting.

We have developed an initial version of the decision-making tools app for use in pharmacy and have started several rounds of iterative assessment and modification based on patient (16 interviews to date) and pharmacist (18 interviews to date) feedback. Feedback has been very positive to date (see typical quotes documented at the end of the research plan). As part of the development process, we have started working iteratively with our PPIE stakeholder group (3 meetings to date) and patients on patient-facing materials, which can either be shared with the patient in the consultation online or printed out and given to the patient. We have also worked with patients and PPIE to streamline the referral process from GP to pharmacy, including the co-production of a patient triaging leaflet. The current proposal addresses finalising the development and optimisation of the full intervention package and a feasibility trial.

Completing development

All the intervention components are being developed for use on the online LifeGuide platform. The first version of the platform was used successfully in developing the similar GRACE INTRO intervention (9). The platform enables researchers to create, optimise and evaluate interventions iteratively, and at low cost. It has been updated and is being used in the current development process.

The following elements of the intervention package are being developed in parallel:

i) **Decision tools suitable for pharmacy use and the training package for pharmacists.**

The initial versions of the tools have already been developed (see background for description of the decision tools) in LifeGuide software with input from an expert co-design group of public contributors, GPs, Pharmacists, Psychologists and infection researchers. The training package is integrated and uses behaviour change techniques to build motivation, skills and self-confidence to deliver management by the decision tools, outlining the rationale and evidence base, and explaining how to coordinate with GP management (e.g., to provide communication back to the GP and procedures where urgent referral is needed).

We provisionally propose to develop peer group learning as in the GRACE INTRO trial(9), probably through online forums depending on pharmacists' preferences.

We will also arrange for those pharmacists not already trained under the currently available schemes to learn examination skills (for chests, ears, throats) where appropriate, but 9000 pharmacists have already completed the training.

ii) **Training package for GP and nurse prescribers in intervention practices**

This will be important particularly as our initial qualitative work with pharmacists highlighted the 'divide and rule' that not infrequently happens:

some patients who are not given antibiotics by the pharmacist go to the GP or practice nurse prescriber and get antibiotics.

The training package will be essentially the same as for the pharmacists i.e., incorporating the decision tools, and addressing the evidence base, the key rationales, motivation, and barriers to use. The training will emphasise the importance of coordinating management with the pharmacists (in particular, supporting management decisions made by the pharmacist wherever possible) – which will be made possible with brief communication from the pharmacist summarising the pharmacy consultation and the rationale for the decisions made based on the app output.

iii) Training package for triage personnel in the intervention practices

This will be a brief package to enable those who normally triage patients into consultations with their general practitioner or nurse prescriber to instead triage to a pharmacist. It will include brief training in what constitutes an infection if the triage person is a non-clinician, and the simple checklist of exclusion criteria for referral based on the history (e.g., age<1, age>80; chronic lung disease; multiple major comorbidities; rigors; unable to walk etc). A triaging leaflet has been co-produced with public contributors funded by the SPCR (School for Primary Care Research) grant to support communication by triage personnel. Assuming the nationally commissioned LES happens there will be a plan for triage and we will align with that.

For each of the above elements the same iterative development processes are used - intervention planning and then iterative qualitative work with users as the intervention elements are modified by each round of feedback:

a) Intervention planning.

Using our theory-, evidence- and Person-Based Approach to intervention development(34), we use systematic intervention planning to select appropriate theory- and evidence-based behaviour change techniques(35) and practical implementation strategies.

This process involves:

1) Forming an intervention co-design group with key stakeholders (PPIE; prescribers (doctors/nurses/pharmacists) which meets monthly (we have already set the group up).
2) Creating a behavioural analysis table, logic model and guiding principles for important influences on key behaviours (identified from stakeholders, previous studies, the published literature, and relevant theory) and how these will be addressed for each component of the intervention - to focus our group discussions and document reasons for decisions.
3) Theoretical/conceptual Framework. We are drawing on three theoretical frameworks to inform the intervention, process evaluation and implementation planning. The intervention draws on Social-Cognitive Theory(36) to address prescriber/patient motivations and confidence and the Extended-Common-Sense model, which includes the Necessity-Concerns Framework, for patient perceptions of symptoms and treatment (37). Normalisation-Process-Theory (38) provides a framework for implementation planning by enhancing our understanding of factors needed for successful implementation and integration into routine care if appropriate. A logic model outlines the proposed mechanism of action of the intervention (39). The theoretical models are used flexibly in the qualitative process analyses to help understand what worked and how.

b) Qualitative work optimising intervention elements and materials.

The process has already started with our PPIE group and interviews with pharmacists for the pharmacy training package. In total this will involve semi-structured interviews with up to 25-40 patients with RTIs /UTIs /skin infections and 20-30 prescribers (both pharmacists and prescribing doctors and nurses in the intervention practices) (*separate ethics approval*). We will explore views of the proposed intervention elements/materials, including perceptions of the changes in consultations, patient self-management, and clinical assessment in the post-COVID era.

Diversity sampling will ensure a range of views - including prescribing/non-prescribing pharmacists; Experienced/less experienced GP or nurse prescribers;

urban /rural practices; ethnically mixed/socially deprived areas; demographics (gender/age/ethnicity/education); and (for patients) specific syndromes (LRTI,UTI,skin). We will explore contextual facilitators/barriers for engaging with all intervention elements and key behaviours, including patient, practice, and broader socioeconomic/sociocultural factors.

'Think-aloud' methods are used to elicit detailed reactions to draft materials (e.g., patient leaflets; initial paper prototypes of online content), and subsequently to wireframe and beta versions of the online elements of the intervention.
Working with our PPIE and stakeholder co-design group we use our 'Table of Changes' (40) to systematically identify aspects that need to be refined by the development group. Further interviews will be conducted until no important new issues are emerging. Thematic analysis (41, 42) will identify findings with wider relevance to the research community.

The decision tools package for pharmacists has already had considerable input from the co-design group and optimisation through qualitative interviews with 18 pharmacists from a range of community settings and experience, and more interviews are planned using the modest resource remaining from the small SPCR and charity (ANTRUK) grants. As a result, by the time the current grant starts we estimate it will require only 3-4 months to finalise the development work and the remaining work on the training package for triage personnel.

5. AIMS AND OBJECTIVES

AIM: To finish development and feasibility test a pharmacy package using decision-making tools and POCTs to share the management of acute infections in primary care.

OBJECTIVES:

I. To complete co-production of a package of decision-making tools and Point of care tests (POCTs) for managing acute infections, and refine the package

II. To establish parameters and methods in preparation for a full trial.
- To establish methods to maximize recruitment and retention of practices/pharmacy clusters in a range of socio-demographic areas.
- To evaluate the feasibility of cluster randomisation and consent procedures
- To evaluate recruitment of patients
- To evaluate the collection of outcome measures through routine data and individual patient data.

III. To establish the feasibility and acceptability of implementing a pharmacy-first service for patients with common infections using a digital intervention to manage antibiotic dispensing and identify barriers and facilitators to using the service and the intervention.

6. METHODS

Design:

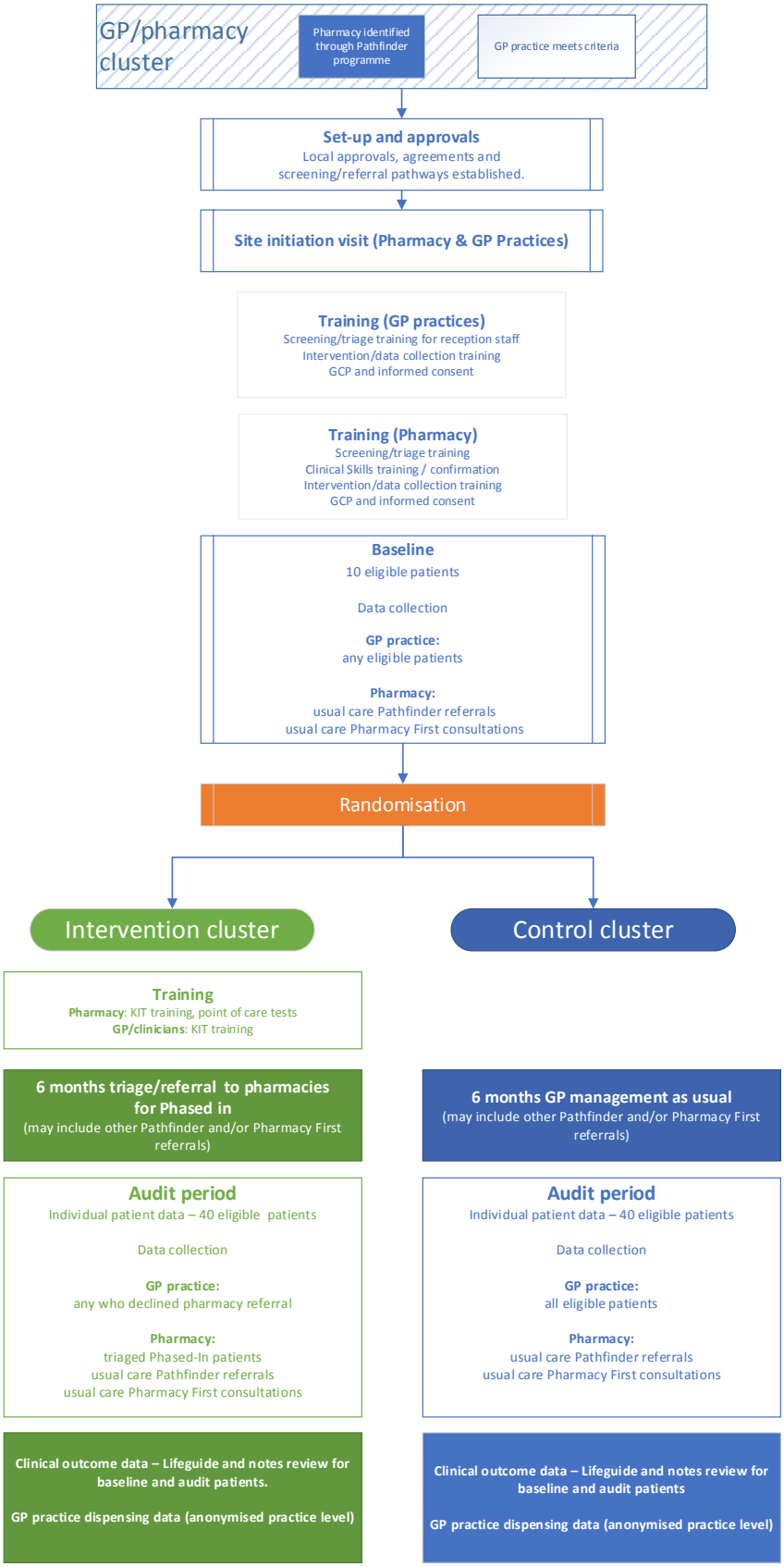
Mixed methods, cluster randomised controlled feasibility trial with process evaluation.
We will also include a sub-study (audit period) which will involve intensive collection of individual patient data for 40 eligible patients in both intervention and control practices at least 1 month after randomisation.

Health Technologies being assessed

GP referral of patients with specified infections to linked pharmacies.

Participants

Study flow chart: practices and pharmacies



PRACTICES:

Inclusion criteria: Primary care practices within England who are in the top two tertiles of antibiotic prescribing nationally for the bundle of antibiotics commonly used for respiratory, urinary, and skin infections (penicillins, macrolides, tetracyclines, cephalosporins, trimethoprim, nitrofurantoin, fluoroquinolones, or topical fucidic acid).

Exclusion criteria: none

PHARMACIES:

Inclusion criteria: Pharmacies participating in the Independent Prescribing 'Pathfinder' Programme, located close to the linked GP practice.

Exclusion criteria: Pharmacies not currently participating in the Pathfinder Programme

PATIENTS

Inclusion criteria: Patients presenting to 'index' general practices with the commonest acute uncomplicated infections:

- UTI (women (16-65 years),
- URTI: (adults 18-79 yrs and children 1-17 yrs): sore throat/otitis-media/sinusitis/influenza.
- LRTI: (adults 18-79 yrs and children 3-17 yrs)
- Skin infections (adults 18-79 yrs and children 1–17 yrs with impetigo and insect bites)

Exclusion criteria:

- Infection not suspected.
- Pregnancy;
- Known immunological deficiencies.
- symptoms of serious illness such as rapid deterioration in conscious level; too unwell to walk;
- age under 1 year or aged under 3 years with LRTI
- over age 75 with 2 or more major co-morbidities;
- age > 80 years;
- those who do not accept referral to the partner pharmacies.
- Recurrent/chronic infection defined as:

- LRTI: 2 or more infections in the last year;
- UTI: 2 or more episodes in the last 6 months or 3 or more in the last 12
- Impetigo: 2 or more episode in the last year
- Chronic sinusitis (symptoms for >= 12 weeks)
- Otitis : more than one infection in the last year in adults (aged > 16) and 3 or more/6 months or 4 or more in 12 months in children

Recruitment and Consent

PRACTICES

Practices will be recruited through the NIHR-CRN who will advertise to local practices who meet our inclusion criteria, ensuring that we have practices in the first 2 tertiles of antibiotic prescribing, at least one in each of urban and rural settings, high and low socio-deprivation, large and small practices, and are located near a pharmacy participating in the Pathfinder programme.

Antibiotic prescribing rates will be determined through Practice level Prescribing Data, available through the NHS Business Services Authority. The NIHR INCLUDE framework will be used to select practices who are diverse in terms of ethnicity, gender, and socio-deprivation.

Selection of practices to be approached will take place with close discussion with the research team. Interested practices will return an expression of interest form directly to the research team.

PHARMACIES

We will identify and approach pharmacy sites participating in the Pathfinder programme through NHS England and local Integrated Care Boards who locally commission the Pathfinder programme.

We will limit pharmacies to those participating in the Pathfinder programme for a number of reasons: pharmacists in the programme are independent prescribers and are already trained in consultation skills and prescribing in a range of common illnesses; appropriate consultation

room facilities are available; GP referral pathways are already established.

We provisionally aim to choose two pharmacies (creating a GP practice/pharmacy 'cluster') to provide sufficient consultation slots for general practice to refer in to. However, there are limited number of pharmacies currently signed up to the Pathfinder programme so we will accept a single pharmacy if they are able to offer sufficient appointments.

Some pharmacies will be participating in the new national 'pharmacy first' scheme and some will not. We propose that both for the feasibility trial and any subsequent full trial randomisation is stratified according to whether the new scheme was being used or not used in each pharmacy cluster, to enable exploration of any differences in the estimates between intervention and control in the two contexts.

PATIENTS

Adults and children aged ≥16 years will be provided with a written participant information sheet and give consent to participate in the study. Parents/carers of children aged 1-15 years will be provided with a written participant information sheet and give consent for their child to participate in the study. Details of participant information sheets and consent forms for each recruitment period are given below:

Time period	**Participant information sheet/consent form version**
Baseline (all patients)	Participant information sheets • Baseline_control audit PIS adult • Baseline_control audit PIS parent-child Consent forms • Baseline_control audit Consent Form adult • Baseline_control audit Consent form parent-child
Main period Intervention group	Participant information sheets • Main period_Intervention_PIS adult • Main period_Intervention_PIS parent-child • Intervention_child 6-10 years PIS • Intervention_child 11-15 years PIS

	Consent forms • Main period_Intervention_consent form adult • Main period_Intervention_Consent form parent-child
Main period: control group	*No patient recruitment in control group (except in audit period)*
Audit period: Intervention group	Participant information sheets • Audit_period_Intervention_PIS adult • Audit_period_Intervention_PIS parent-child • Intervention_child 6-10 years PIS • Intervention_child 11-15 years PIS Consent forms • Audit_period_Intervention_consent form adult • Audit_period_Intervention_Consent form parent-child
Audit period: Control group[1]	Participant information sheets • Baseline_control audit PIS adult • Baseline_control audit PIS parent-child Consent forms • Baseline_control audit Consent Form adult • Baseline_control audit Consent form parent-child

[1] *The same PIS/consent forms will be used during the baseline period (all patients) and the control group audit period.*

Baseline (intervention and control practices):

A total of 10 patients attending at each GP practice (telephone, in-person, 111) will be triaged by trained reception staff for eligibility for Phased-In (see inclusion criteria). Eligible patients (or parents/carers) will be informed about the study (verbally and provided with a paper information sheet, or texted/emailed a link to the PIS hosted on a University website). Initial consent will be recorded in the patient records. Patients will either attend a consultation at the GP practice, or referred to pharmacy (Pathfinder programme or Pharmacy First) through usual care pathways.

- **If patient seen at the GP practice:** Clinicians will check that patients (or parents/carers) have read the information sheet, answer any questions, and

record informed consent for brief clinical information and their medical records to be reviewed as part of the Phased-In study. Consent will be recorded using an online platform (Lifeguide or Qualtrics) and recorded in the patient records. The consultation may be on the same day or on a future date, and patients will likely have 1 – 4 hours (or more) to decide whether to participate.

- Brief demographic information (age, gender, infection) and reason for not taking part will be recorded by the triage staff for those patients who decline participation using a written or electronic audit log.

- **If patient seen at the pharmacy:** Pharmacists will see patients through Pharmacy First or Pathfinders programme and complete the consultation as usual. In addition, pharmacists will ask the patient if they would be willing to participate in the Phased-In study. They will check that patients (or parents/carers) have read the information sheet, answer any questions, and record informed consent for brief clinical information and their medical records to be reviewed as part of the Phased-In study. Consent will be recorded using an online platform (Lifeguide or Qualtrics) for collection of individual patient data (clinical symptoms, examination, diagnosis, and management) and medical notes review. The consultation may be on the same day or on a future date, and patients will likely have 1 – 4 hours (or more) to decide whether to participate.
- Brief demographic information (age, gender, infection) and reason for not taking part will be recorded by the pharmacist for those patients who decline participation using a written or electronic audit log.

Intervention group

6-month study period:

GP practice:

All patients attending at the GP practice during the 6-month study period (telephone, in-person, 111) will be triaged by trained reception staff for eligibility for Phased-In (see inclusion criteria). Eligible patients will be informed about the study (verbally and provided with a paper or online information sheet, or texted/emailed a link to the PIS

hosted on a University website). Initial consent for referral will be recorded in the patient records. Brief demographic information (age, gender, infection) and reason for not taking part will be recorded by the triage staff for those patients who decline participation.

For patients who agree, a referral will be sent directly to the pharmacy via Pharmacy First, other NHS locally commissioned digital pathway, or by NHS email and patients will make an appointment with a pharmacy within the cluster. Pharmacists will check that the patient has read and understood the information sheet, answered any questions, and record informed consent for Phased-In electronically using Lifeguide. This is an acute service for infection management where patients will likely attend for pharmacy consultation in the same day as being triaged so will have 1 – 4 hours to decide whether to participate.

Patients who decline consent at the pharmacy will be directed back to their GP surgery.

Pharmacy walk-in

Walk in patients are not the main target of this intervention since they may have a different spectrum of illness to those presenting directly to general practices. However, patients who present at the pharmacy will have the option to take part in Phased-In. The pharmacist will triage the patient for suitability for Phased in and provide a written participant information sheet. As this is an acute service for infection, it is likely that a consultation will be provided during the same day (maybe immediately). Pharmacists will record consent using an online platform (Lifeguide or Qualtrics). Seeking immediate consent aligns with the new national pharmacy-first service who receive verbal consent for Pharmacy First and collection/sharing of data.

Patients who decline consent will be advised to consult their GP surgery.

Audit period only:

Up to 40 patients at each GP practice during the audit period will be triaged and referred to the pharmacy as described above. Additional consent will be sought for collection of individual patient data (clinical symptoms, examination, diagnosis, and management), medical notes review and optional qualitative interview.

GP practice: Patients who decline referral to the pharmacy and request a GP consultation as usual will be asked if they would consent to their medical records being accessed for the purpose of the trial. Initial consent will be recorded in the patient records. Patients will attend a consultation as usual. Clinicians will check that patients have read the information sheet and record informed consent for brief clinical information, their medical records to be reviewed as part of the phased-in study, and optional consent sought for contact to take part in a qualitative interview. Consent will be recorded using Lifeguide and recorded in the patient records. Brief demographic information (age, gender, infection) and reason for not taking part will be recorded by the triage staff for those patients who decline participation.

Pharmacists:
Clinicians will check that patients have read the information sheet and record informed consent for brief clinical information, medical records to be reviewed as part of the phased-in study, and optional consent sought for contact to take part in a qualitative interview. Consent will be recorded using Lifeguide.

Control group

6-month study period
Patients attending their GP practice will receive usual care/consultation during the 6-month study period. Usual care pathways may include pharmacy management through Pharmacy First and/or the Pathfinder programme.

Audit period only: Up to 40 patients attending at each GP practice (telephone, in-person, 111) will be triaged by trained reception staff for eligibility for Phased-In (see inclusion criteria). Eligible patients will be informed about the study (verbally and provided with a paper or online information sheet). Initial consent will be recorded in the patient records.

Patients will either attend a consultation as usual at the GP practice, or referred to pharmacy (Pathfinder programme or Pharmacy First) through usual care pathways. .

- **If patient seen at the GP practice:** Clinicians will check that patients have read the information sheet and record informed consent for brief clinical information and their medical records to be reviewed as part of the phased-in study. The consultation may be on the same day or on a future date, and patients will likely have 1 – 4 hours (or more) to decide whether to participate. Brief demographic information (age, gender, infection) and reason for not taking part will be recorded by the triage staff for those patients who decline participation.

  If patient seen at the pharmacy: Pharmacists will see patients through Pharmacy First or Pathfinders and complete the consultation as usual. In addition, pharmacists will ask the patient if they would be willing to participate in the Phased-In study. They will check that patients (or parents/carers) have read the information sheet, answer any questions, and record informed consent for brief clinical information and their medical records to be reviewed as part of the Phased-In study. Consent will be recorded using an online platform (Lifeguide or Qualtrics) for collection of individual patient data (clinical symptoms, examination, diagnosis, and management) and medical notes review. The consultation may be on the same day or on a future date, and patients will likely have 1 – 4 hours (or more) to decide whether to participate. Brief demographic information (age, gender, infection) and reason for not taking part will be recorded by the pharmacist for those patients who decline participation using a written or electronic audit log.

Intervention

Intervention group

PRACTICES

Practice training: Triage training:

GP practices will be trained to refer participants using the model of the Community Pharmacy Consultation Service, with triage by GP receptionist or clinical staff before referral to community pharmacy. Patients contacting the practice them by any method (telephone, online, 111) will be triaged (as described above) and referred for pharmacy management. Patients will not be referred where there is doubt as to whether this is an infection, where a home visit is required, or where there are signs of serious illness such as rapid deterioration in conscious level or behaviour.

Practice training: Phased-In decision tool

GPs, practices nurses and other first contact practitioners will receive the use of the decision tools using an integrated online training package in LifeGuide. The training takes approximately 5-10 minutes to complete, and all practice staff who will consult with patients for Phased-In will undergo training prior to the start of the study.

PHARMACIES

We anticipate that each pharmacy will provide four to eight 15-minute slots per day to allow referral from their partner practice as was used in recent piloting of the use of CRP for LRTIs.

Locally Enhanced Service (LES) specifications will be developed and indemnified through the normal arrangement with the Local Pharmaceutical Committee (LPC). Pharmacists will operate under the guidance of the LES:

i. Decision-making tools we have developed from existing algorithms (LRTI(16);Sore throat(45);sinusitis; (19, 20);otitis media (18);UTI (1)) or from NICE guidance (e.g. skin infections)
ii. Patient leaflets to support patient self-care (9, 14) for which we are using as our starting point the nationally available UKHSA TARGET leaflets.

iii. CRP for LRTI (9)
iv. RADTs for sore throats (45)
v. Urine dip tests where the decision-making tools indicate to do so.
vi. Self-throat swabs for COVID (There is currently concern from pharmacists about throat examinations if COVID is prevalent, and if another wave of COVID occurs next winter. If this is suspected self throat swabbing can be used which has been shown to be accurate(50)) in addition to Lateral Flow tests.

Pharmacy training: Phased-In decision tool

Pharmacists will receive training in documenting patient consent and use of the decision tools using an integrated online training package in Lifeguide. The training takes approximately 5-10 mins to complete, and all pharmacists who will consult with patients for Phased-In will undergo training prior to the start of the study.

Pharmacy training: Clinical Skills

Independent prescribing pharmacists will work according to their own Scope of Practice. They are likely to be trained in clinical examination skills under the Independent Prescribing framework. Individual Scope of Practice will be checked by the study team, and additional training will be provided/signposted to ensure that all participating pharmacists scope of practice includes all the conditions triaged as part of the Phased-In study.

Pharmacy training: Point of care tests:

Pharmacists will receive training in use of the rapid tests (CRP, RADT, lateral flow tests etc) to use when appropriate as part of the diagnostic algorithms. Training will be provided by the study team as part of the study initiation visit. Where possible, each test will be from a single manufacturer and specific training will be provided across all sites. If any changes are required during the trial, updated instructions will be provided accordingly.

Intervention: using the decision tool

Pharmacies:

At first presentation in the pharmacy, after consent has been taken, there will be a rapid screen for higher risk individuals based on pulse, and oxygen saturation measurement: if high

risk (very high pulse for age) or saturation <92%, participants will be referred urgently back to the GP or to A+E.

Once the patient is through the first screen (pulse, saturation) the decision tool summarises key features and structures further guidance in providing advice about further referral depending on the clinical presentation.
The decision-making tools stratify management based on the algorithms:

a) High risk: the small minority, requiring a near patient test where appropriate (CRP; RADT) and an immediate antibiotic if the test is positive; and/or referral back to the GP.
b) Intermediate risk: either no antibiotic or active self-monitoring with clear 'safety netting' advice
c) Low risk: no offer of antibiotic but support for self-care and 'safety netting' advice.

If an antibiotic is indicated a supply would be made under a prescription from the Independent prescribing pharmacist. A referral for further assessment by the GP would be made if the history suggested a complication, if the pharmacist was concerned, or the patient requested it.
Audit period only: Pharmacists will contact patients to document what happened after 3 weeks (whether they saw the GP, had antibiotics, went to A+E) – which has been used in previous studies.(28)

GP practices:
During the study, GPs, nurses and other first contact practitioners will use the decision tool in consultations with those patients who were triaged but did not verbally consent to a referral to the pharmacy.
Control group.
Control practices will continue with care as usual.

Sample size calculation

10 intervention practices and pharmacy clusters recruited in different contexts (urban inner city/ urban market town/ rural) and 10 control practices/clusters should provide sufficient variation to explore the key feasibility issues. Assuming that on average at least 20

participants are recruited in both intervention and control practices for the more intensive data collection in the audit weeks antibiotic prescribing can be estimated to within +/- 7% with similar precision for participant recruitment rates

Participants: baseline and audit week

Baseline: 10 patients at each practices will consent to clinical details and notes review (total 200).

Audit period: up to 40 patients at each practice will consent to clinical details, notes review, and (intervention group) pharmacy management and optional interview. (total 800)

Participants: pharmacy referral/management only (intervention group)

We estimate that up to 7,800 patients will be referred for pharmacy management in the intervention group during the study period (15 - 30 per week for 6 months, 10 practices).

Randomisation

Computer-generated 1:1 randomisation of GP/pharmacy clusters stratified by whether the GP/pharmacy cluster includes pharmacies participating in the new nationally proposed Pharmacy-First scheme.

The Pathfinder programme has a limited number of participating pharmacists at present, although this is likely to increase going forward as more pharmacists become independent prescribers. If it is not possible to identify sufficient pharmacies who are part of the Pathfinder programme who are willing to participate, we will adjust randomisation to 2:1 or 3:1 to still permit evaluation of randomisation and data collection from control clusters.

Blocked randomization will be used, with random blocks of 2 and 4. This will be implemented using an Excel file, programmed by our statistician.

Randomisation will be done after baseline data has been collected for 10 patients who would be eligible for the Phased-In intervention. Once this has been confirmed by the practice, the research team will enter the practice details, including whether they are part of the Pharmacy-

First scheme, into the excel file, which will then randomly allocate and display the trial group.

Blinding

The statistician will be blinded to allocation until the analysis has been completed.

Data Collection - Measurements and follow-up

Training records

Triage training and consent training will be recorded by the study team *(intervention/control)* Pharmacy training will be recorded by the study team (consent, clinical, rapid tests) and Lifeguide platform (KIT diagnostic aid) *(intervention only)*

Recruitment/referral data

Staff in intervention practices will document basic details for all patients referred to pharmacists and also brief details for patients not referred and why they were not referred/declined participation. Anonymous data will be collected using electronic audit sheets, which will be transferred to University of Southampton using Safesend at the end of the study period. *(intervention/control)*

Case report forms

During baseline and the audit period, with patient consent, clinicians and pharmacists will complete a case report form collecting the following information: symptoms, examination, diagnosis, management. Data will be collected using the Lifeguide platform (KIT). *(intervention/control)*

Clinical data collected via the decision-making tool

Detailed individual clinical data are needed since routine data will not allow the assessment of the appropriateness of management (the appropriateness of dispensing/supply decisions) in both intervention and control practices, nor whether the spectrum of presentations managed is similar. Thus, for comparison of appropriateness of antibiotic prescribing and possible differences in illness spectrum detailed clinical information is needed, for which individual patient consent is required. The diagnostic aid on Lifeguide will record key baseline clinical

data (symptoms, test results) in pharmacies for patients referred to them *(intervention and control),* and output data from the diagnostic aid used in pharmacies will be stored for all patients and analysed as pseudo anonymised data. *(intervention only)*

Routine data collection.

After 6 months, GP practices will be asked to extract anonymous data from their practice electronic health records. This will include antibiotic prescription data (the same bundle of antibiotic prescription data used in identifying higher prescribing practices), re-consultation, and complications, and also EDI data (age, gender, disability, comorbidity, ethnicity). The anonymised data sets will be transferred to University of Southampton using Safesend *(intervention/control).*

7. OUTCOMES

Feasibility outcomes

1. Recruitment rate of practice/pharmacy clusters/dyads;
2. Retention of both practices and pharmacies
3. Experience of the intervention, acceptability of the intervention and of intervention and trial materials based on qualitative interviews. By the time the full development process has happened we anticipate as in prior studies9 that few changes will be needed. Where the intervention or training is not deemed to be acceptable, assuming changes can be made this will contribute to a table of changes required prior to any subsequent trial
4. Engagement with key behaviours – the use of online training; the use of decision support; (all documented automatically in the online system); and engagement with the in-practice audit (the use of audit tools and documentation of meeting processes will be built into the online system);
5. recruitment rate of patients to more intensive sub-study (documented from the CRFs returned);
6. level of completion of CRFs
7. characteristics of participants in intervention and control practices (to document potential selection bias)
8. follow-up rates for the primary outcome (routine data)
9. follow-up rates for secondary outcomes
10. The logistics of this service delivery model: GP resource use (from routine data) and pharmacy resource use (records in the pharmacy audit and software systems used in pharmacies). The time taken, staff requirements, and resources used to triage and manage infections in both the general practices (including outline data recording of consultation times) and pharmacies (including data from the systems pharmacists will be using to record their management) will be documented. The staffing requirements including time and resource required for training, monitoring and supporting pharmacy staff will be documented both quantitatively and qualitatively (also see process evaluation). Referral rates to and from pharmacies, referrals to pharmacies not made, and referrals from pharmacies to hospitals will be recorded.
11. Clinical safety (complications recorded; adverse events)

Progression criteria which will be used for an application for further funding for a main trial.

- Acceptability: no major issues for the intervention identified in qualitative work (including the process analysis) that cannot easily be addressed for a subsequent trial.
- Completion of training:
    - 80% of pharmacists complete the training: future main trial feasible in current form.
    - 70% of pharmacists complete the training: future main trial feasible with modifications.
    - <60% of pharmacists complete the training: future main trial not feasible without significant modifications.
- Record of management
    - 80% of pharmacy consultations audited have a record of decision-making tool use and outcome: future main trial feasible in current form.
    - 70% of pharmacy consultations audited have a record of decision-making tool use and outcome: future main trial feasible with modifications.
    - <60% of pharmacy consultations audited have a record of decision-making tool use and outcome: future main trial not feasible without significant modifications.

Clinical outcomes collected (in preparation for a future application for funding for a main trial).

- Antibiotic dispensing rates from routinely collected data at a practice level for the key bundle of antibiotics used for the listed conditions (penicillins, macrolides, tetracyclines, cephalosporins, trimethoprim, nitrofurantoin, fluoroquinolones, topical fucidic acid). In control practices this would come from routine data. For intervention practices this would come from routine data supplemented by data on antibiotic supply from PGDs implemented under the new LES we propose for pharmacies. If the new service is used well this data should detect an important signal in the reduction in antibiotic prescribing comparing intervention and control practices.

- Overall antibiotic item prescribing at an individual level using the data captured using the decision-making tools in both intervention pharmacies and also control practices, controlling for illness spectrum. Data collection from control practices will just have the clinical data collection element of the app with no decision-making tools. This data will be important to assess effectiveness in reducing prescribing if the volume of referrals to pharmacies is not sufficient to be detected in the overall practice dispensing or prescribing rates.
- Antibiotic prescribing at an individual level for each condition (LRTI, sore throat etc) using the data captured using the decision-making tools in both intervention pharmacies and also control practices.
- Appropriateness of antibiotic prescribing. The app data from intervention pharmacies and control practices will determine the percentage of consultations where management is appropriate (concordant or discordant with the evidence-based algorithms which for the basis of the management output element of the apps).
- Consultation rates and complication rates (at a practice level from routine data documented in the GP record).

Process evaluation

Aims and objectives of process evaluation

Aim: To assess the feasibility and acceptability of implementing a pharmacy first service for patients with common infections using a digital intervention to manage antibiotic dispensing and identify barriers and facilitators to using the service and the intervention.

Objectives:

- To explore the feasibility of practice receptionists
- identifying eligible patients, explaining the change in care pathway, and triaging them from practices to pharmacies.
- To understand the impact on pharmacists of providing a pharmacy first service, including receiving training, carrying out CRP testing, managing patient appointments, and taking consent.
- To explore the experience of using a digital intervention in pharmacies to support pharmacists in carrying out consultations with patients, deciding management

strategies, and either supporting patients to self-care or dispensing antibiotics where appropriate.

- To explore the use of a digital intervention to support management decisions within practices, including using for patients returning from pharmacy consultations. To understand if the consent process is acceptable and how practices view the intervention.
- To explore trial experiences of control group practice staff for identifying eligible patients, gaining consent in audit week, and using a digital intervention during consultations.
- To understand patient views of the service: change of care pathway; triaging & consent process; pharmacist consultation; management strategies; self-care advice; patient-facing leaflets.

We aim to inform implementation for a full trial, including the exploration of contextual influences (51). Mixed methods will explore how pharmacists, clinicians and patients used the intervention, what influenced their use, and potential mechanisms of change. We will interview a sample of 10-15 health professional participants (community pharmacists, but also referring GPs/nurses/other triage staff) and 10-12 patients from diverse practice/pharmacy contexts, eliciting views/experiences to confirm acceptability/feasibility of the intervention/trial-procedures, or identify optimisation required. If saturation is not achieved, we may recruit more participants. We will explore adherence to all intervention components, and probe areas of uncertainty in our logic model. Qualitative interviews will first be analysed using reflexive thematic analysis(41) then explored for how constructed themes may map onto theoretical frameworks.

Automatic data collection by the digital intervention will assess prescribers' engagement with the online training (e.g. usage patterns, uptake), and clinical data.

Discontinuation / withdrawal of participants from trial

Participants have the right to withdraw from the study at any time. In addition, the investigator may discontinue a participant's treatment or withdraw a participant from the study at any time if the investigator considers it necessary (e.g. the participant experiences an adverse reaction, the patient withdraws consent, or the investigator considers that further

participation in the study would not be appropriate due to the personal circumstances of the participant).

If a participant fully withdraws or is fully withdrawn from the study, no actions will be taken to obtain data other than to monitor adverse events (see section 8. Safety reporting). Consent to proceed with reviewing the medical notes will be specifically confirmed for participants withdrawn from the study.

Definition of end of trial

The end of the trial will be the date of the last medical notes review of the last trial participant.

8. SAFETY REPORTING

All adverse events, for patients participating in the trial, should be reported during 4 weeks from the time of consent. Depending on the nature of the event the reporting procedures below should be followed.

Any questions concerning adverse event reporting should be directed to the Study Team in the first instance. A flowchart will be provided to aid in the reporting procedures.

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. Adverse events will not be collected for this study.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to a trial intervention" means that a causal relationship between a trial intervention and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. All cases judged by either the reporting medically

	qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that led to: a. death, b. serious deterioration in the health of the subject, that resulted in any of the following: a. life-threatening illness or injury, b. permanent impairment of a body structure or a body function, c. hospitalisation or prolongation of patient hospitalisation, d. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, e. chronic disease, c. foetal distress, foetal death or a congenital physical or mental impairment or birth defect. Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to

	be due to the trial interventions, based on the information provided.
Suspected Unexpected Serious Adverse Reactions (SUSAR)	An adverse reaction that is both unexpected (not consistent with the applicable product information) and also meets the definition of a Serious Adverse Reaction. These must be reported to the Sponsor within 24 hours of the study team becoming aware of them. The Sponsor will then work with you to coordinate onward reporting. SUSARs must be reported to the REC within 15 days.

Hospitalisations for elective treatment of a pre-existing condition do not need reporting as Serious Adverse Events (SAEs) in this study.

The antibiotics likely to be used in Phased-In (beta-lactams or macrolides) are licensed medicines whose most common side-effects are mucocutaneous candidosis (thrush), diarrhoea, nausea, vomiting and rash (occurrence >=1/100 to <1/10). If these occur and are non-serious and of mild to moderate severity (based on clinician's assessment) an Adverse Event Report form will not be necessary. We will collect data on events such as severe reactions to the antibiotics such as anaphylaxis, severe allergy requiring steroid administration, emergency hospitalization for chest problems and severe Clostridium (antibiotic related diarrhoea).

Unexpected adverse reactions to antibiotics will be highly unlikely amongst trial participants, as the vast majority of patients will have previously received antibiotics to treat other infections, and any known previous adverse reactions to antibiotics would usually prevent the dispensing of a prescription (i.e., either patient and/or practice are highly likely to be aware of previous reactions). As the study randomisation is at practice level, unblinding procedures will not be necessary.

Definitions

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to

describe intensity of a specific event, which may be of relatively minor medical significance. “Seriousness” is the regulatory definition supplied above.

Severity

Severity is distinct from Seriousness. It describes the extent of an event's effect upon the participant. It does not affect reporting requirements.

Mild: the event has no significant impact upon the participant's daily life.
Moderate: the participant is hampered or distracted in conducting their regular activities, by the event.
Severe: the participant is significantly hampered or unable to continue their usual activities, due to the event.

Causality

Causality is an assessment, conducted by an investigator, of whether an event is related to a research intervention. This should be determined based upon knowledge of the intervention, the timing of the event, the participant's medical history, the effect of treatment or alteration of the intervention, and any other pertinent factors.

An event is either:

- Not Related
- Unlikely Related
- Possibly Related
- Probably Related
- or Definitely Related

An event determined to be in one of the last three categories - possibly, probably, or definitely related - is an Adverse Reaction (AR), or Serious Adverse Reaction (SAR).

Expectedness

All SARs must be reviewed for expectedness. Below is a list of events, related to the intervention, that are expected:

Expected SAE are those events which can be expected to occur in the patient/population or as a result of the routine care/treatment of the patient and do not require expedited reporting to the sponsor or REC.

Exemptions:

- Pre-planned hospitalisation e.g., for pre-existing conditions which have not worsened, elective procedures for a pre-existing condition will not be classed as an SAE unless deemed related to the study.
- Expected SAE/SADE as detailed above, and SAE not directly related to the study as assessed by PI at site do not need to be reported as a SAE.

Events will be assessed and considered unexpected if it does not fall within any of the categories listed above. An event that meets the serious criteria; is Possibly, Probably or Definitely Related to a study intervention; and is unexpected, with regard to that intervention, is a Suspected Unexpected Serious Adverse Reaction (SUSAR). It must be reported as described below.

Reporting Procedures for Serious Adverse Events

Healthcare professionals will report SAEs to the Phased-In study team within 24 hours of becoming aware of the event, either by telephone (initially) or email. If the study team has been informed of the SAE by telephone, a paper copy of the SAE form must be completed and sent to the study team for review within 24 hours.

A medically qualified individual will be responsible for assessing the relatedness of the SAE to the trial procedures. All SAEs will be reported using the SAE form either online or by paper and reporting this to the phased-in study team. The Phased-In Trial Manager will maintain dedicated report lines with answerphone to allow reporting of SAEs. The answerphone will be checked regularly during office hours.

The Chief Investigator (CI) or their designated representative will be responsible for assessing the expectedness of SAEs reported as being related to the trial. Assessment of expectedness will be based on the definitions outlined in this protocol.

The CI or designated PI at each clinical site will supply any supplementary information as requested by the REC or Phased-In study team.

All unexpected SAEs will be reported to the sponsor immediately or within 24 hours of the study team becoming aware of the event.

SUSAR Reporting

All SUSARs will be reported by the CI delegate to the REC and other parties as applicable. For fatal and life-threatening SUSARS, this will be done no later than 15 calendar days after the Sponsor or delegate is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.

Safety Monitoring Committee

The Trial Steering Committee (TSC) will be responsible for reviewing SAEs. The main aims of this review are as follows:

• To ensure the safety of each patient in the trial;
• To pick up any trends, such as increases in unexpected events, and take appropriate action;
• To seek additional advice or information from investigators where required;
• To evaluate the risk of the trial continuing and take appropriate action where necessary;
• To act or advise, through the Chairman or other consultant, on incidents occurring between meetings that require rapid assessment.

Development Safety Update Reports

In addition to the expedited reporting above, the CI will submit once a year throughout the study, or on request, a safety report to the Ethics Committee, Host NHS Trust and Sponsor.

Criteria for the termination of trial

The TSC will review SAEs after each recruitment season. The TSC or Sponsor may advise on whether the trial should be terminated.

9. HEALTH ECONOMICS

We do not propose a formal Economic analysis for the feasibility study, but will undertake some feasibility work to ensure that cost/resource data can be collected in preparation for an application for further funding for a main trial.

10. STATISTICS

Description of Statistical Methods and analysis

The primary analysis will describe the completion of training and record of management to determine whether the feasibility study has met the stop-go criteria. Feasibility outcomes, such as recruitment rates and follow-up rates, will be summarised descriptively. Clinical outcomes, such as antibiotic dispensing/prescribing rates, consultation and complication rates, will also be summarised descriptively by randomised arm.

The Level of Statistical Significance

N/A

Procedure for Accounting for Missing, Unused, and Spurious Data

We will impute missing data using multiple imputation if appropriate.

Inclusion in Analysis

All available data will be used in the descriptive analysis. The number and percentage of missing data will be reported.

11. DATA MANAGEMENT

Personal Data

Participant personal data will be collected and stored securely on a secure server at University of Southampton in compliance with the requirements of the General Data Protection Regulations and the Data Protection Act 2018.

Personal data will be pseudo-anonymised by assigning a participant identifier code (PIC) which will be used to identify the participant during the study. An electronic file linking the PIC to the identifiable patient data will be kept separately in a separate secure place on the University of Southampton server. Only trained research personnel with specific roles assigned will be granted access to the electronic participant data. At the end of the project, all personal data will be permanently deleted.

Research data

Clinical and diagnostic data will be collected by the intervention and stored on secure, firewall protected servers, hosted by the University of Southampton. Only trained research personnel with specific roles within the project will have access to this server. Upon download, usage data will be stored in an encrypted, password protected file, stored on password protected computers.

The results of the study will be written up in reports and publications. Anonymised quotations provided by participants during the interviews may be used to illustrate the findings, but participants will not be identifiable.

The anonymised research data (trial master file, transcripts) will be stored for 10 years after the end of the study in accordance with the procedures agreed by the sponsor. During analysis and write-up (approx. 2 years) it will be stored on a secure server or in a locked filing cabinet at University of Southampton, after which it will be stored off site at an approved storage facility that has been agreed by the sponsor. The data custodian is Professor Paul Little, chief investigator.

At the end of the study anonymous questionnaire data will deposited in a secure data archive which will be made available to researchers at University of Southampton for secondary data analysis.

Audio-recordings of participant interviews

Audio-recordings of participant interviews will be collected using a portable digital recording device or using MS Teams. Following each interview, the audio-recordings will be transferred directly to the University of Southampton server (accessible only by members of the study team and University of Southampton IT Services) and then deleted from the digital device. The audio data will be anonymised and identified by a unique participant ID only. Transcribing will be facilitated through a member of the research team or a University-approved third party, using only the participant ID. Transcribers will sign a confidentiality agreement to keep the data confidential; store the data securely; and delete the data when the transcription has been completed and receipt confirmed. The audio-recordings will be permanently deleted on study publication.

12. QUALITY ASSURANCE PROCEDURES

The study will be conducted in accordance with the current approved protocol, the latest version of ICH GCP, relevant regulations and standard operating procedures. Regular monitoring will be performed according to the latest version of ICH GCP. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, the study team will ensure that the clinical study is conducted, and data are generated, documented and reported in compliance with the protocol, the latest version of GCP and the applicable regulatory requirements.

Healthcare professionals participating in our study will be asked to submit proof that they have completed GCP training, or be required to undertake study specific GCP training (provided by the study team).

The Trial Management Group (TMG) will be responsible for the monitoring of all aspects of the trial's conduct and progress, including recruitment rates, and will ensure that the protocol is adhered to and that appropriate action is taken to safeguard participants and the quality of the trial itself. The TMG will be comprised of individuals responsible for the study's day to day management (e.g. the CI, study manager, statistician, data manager) and will meet regularly.

The Trial Steering Committee (TSC) will provide overall supervision of the trial and ensure that it is being conducted in accordance with the principles of GCP and the relevant regulations. The TSC will review the recruitment rates, accruing study data and assess whether there are any safety issues that should be brought to the REC or Sponsor's attention or any reasons for the study not to continue.

13. SERIOUS BREACHES

A serious breach is defined as "A breach of GCP or the study/trial protocol which is likely to affect to a significant degree:

(a) the safety or physical or mental integrity of the subjects of the study; or

(b) the scientific value of the study.

In the event that a serious breach is suspected, the Sponsor must be contacted within 1 working day. In collaboration with the CI, the serious breach will be reviewed and, if appropriate, the Sponsor will report it to the REC and the NHS host organisation within 7 calendar days.

14. ETHICAL AND REGULATORY CONSIDERATIONS

Declaration of Helsinki

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

ICH Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996 or most up to date version

Approvals

The protocol, informed consent forms and participant information sheets will be submitted to an appropriate Research Ethics Committee (REC), and host institution(s) 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.

Reporting

The CI shall submit once a year throughout the clinical study, or on request, an Annual Progress Report to the REC, host organisation and Sponsor. In addition, an End of Study notification and final report will be submitted to the REC, host organisation and Sponsor.

Participant Confidentiality

The study staff will ensure that the participants' confidentiality is maintained. Other than on the contact information sheet, and consent form, participants will be identified only by a participant ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act (and also the recent GDPR regulations) which requires data to be anonymised as soon as it is practical to do so.

15. PATIENT AND PUBLIC INVOLVEMENT

Two PPIE collaborators are full members of our study team and attend the regular study management meetings. They were involved in the development of the application and supported the proposed intervention elements - especially the use of interactive discussion with patient facing materials. We had additional external PPIE review from: our departmental panel; the SPCR; and our charity collaborator PPIE panel.

Patients are currently being involved as participants in the qualitative work in the development of the intervention and in commenting on the patient facing materials. This includes both the PPIE collaborators at the regular study management meetings, and involves input from two panels (a PPIE panel and a wider stakeholder panel). The PPIE panel consists of 6 individuals to include diversity in age/comorbidity; gender; ethnicity; and SES. The PPIE panel meets monthly initially, and will meet as needed subsequently. PPIE will contribute to design; development; management; interpretation and

dissemination (PPIE will co-lead – see dissemination section). Particularly important is using the insights of PPIE alongside the qualitative work – using methods that this group has developed.(43)

16. FINANCE AND INSURANCE

Funding

This study/project is funded by the NIHR HSDR Programme (project reference NIHR158312). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Insurance

The University of Southampton 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. NHS indemnity operates in respect of the clinical treatment which is provided.

17. PUBLICATION POLICY

The investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by the NIHR SCPR. The publication policy for this Grant will state the lead author(s) and co-authors for each manuscript. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

The funder will have no role in data collection, analysis, data interpretation, report writing or in the decision to submit for publication.

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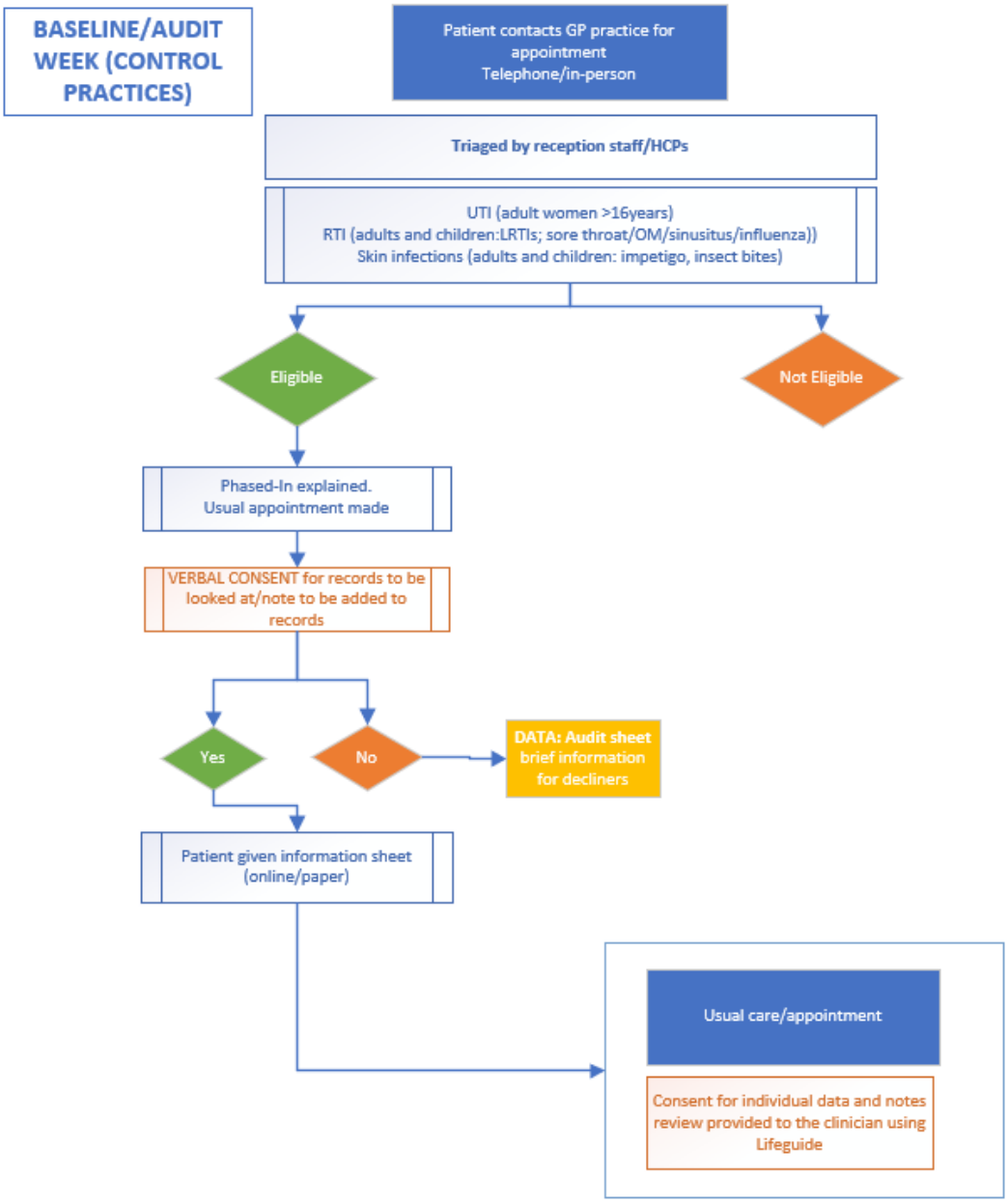
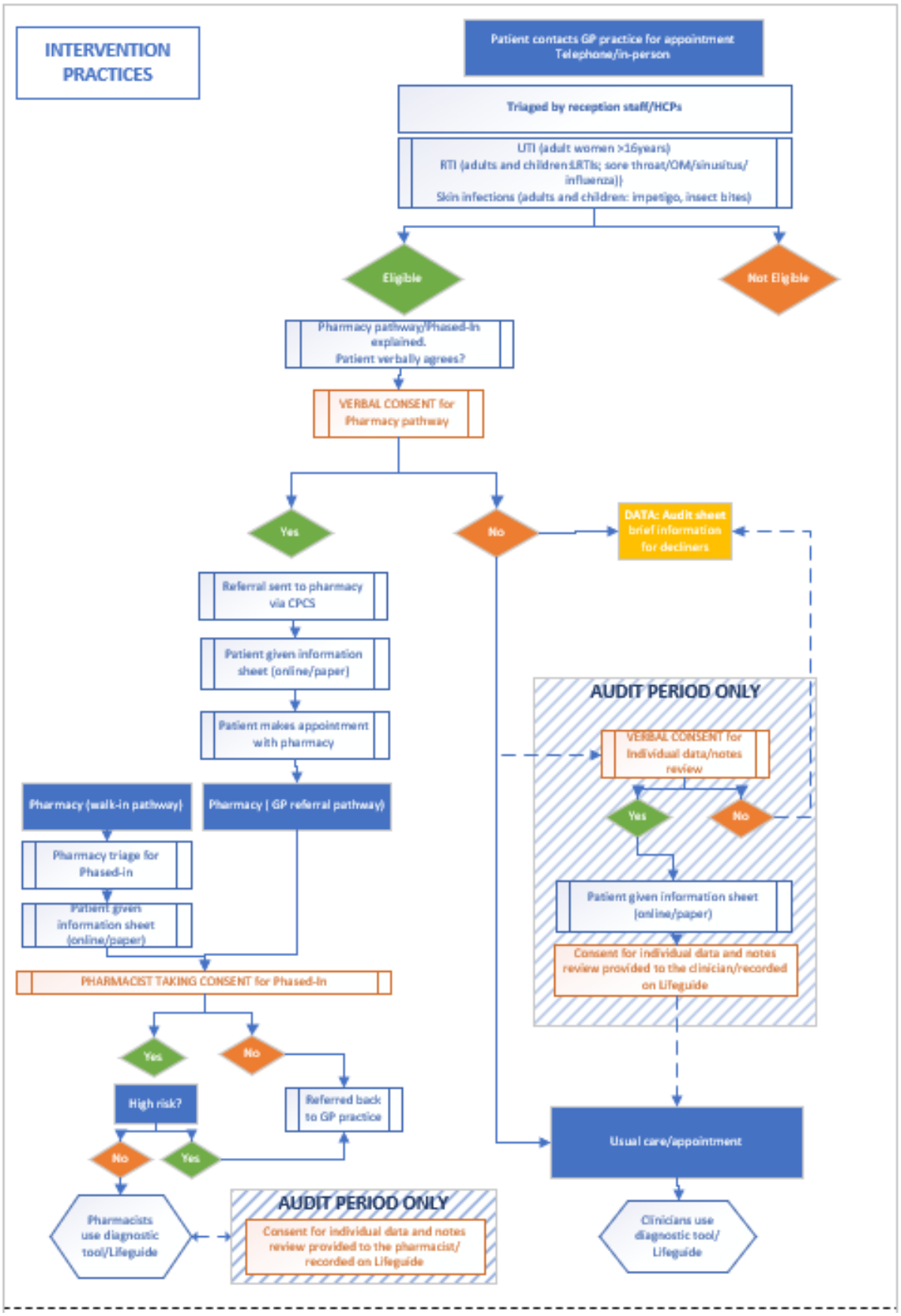
Appendix A: Protocol Change Control

Version	Date	Summary of Changes	Author

APPENDIX B: Patient flow – Baseline and Audit period (control)



APPENDIX C: Patient flow – Intervention practices



APPENDIX D: Diagnostic aid

Fever Pain / Sore Throat

5 items each scoring 1 point: Fever in past 24 hours: Absence of cough/coryza (coryza = nasal discharge): Symptoms for <= 3 days: Purulent tonsils: Severe tonsil inflammation (10-15% patients)

Score	Output
0	**Recommendation: No antibiotic prescription**
1	**Recommendation: No antibiotic prescription**
2	**Recommendation: active self-care and** fast-track review if symptoms have not improved at all in 5
3	**Recommendation: Rapid strep test to guide antibiotic prescribing**
4	**Recommendation: Rapid strep test to guide antibiotic prescribing**
5	**Recommendation: Rapid strep test to guide antibiotic prescribing**

LRTI Adults

7 items score 1 point: Age 65 to 79:: O2 Sats < 95%: Temp > 37.8 degs C: Vascular comorbidity *: No coryza (coryza = nasal discharge): Severity > 5/10: Chest pain

** Vascular co-morbidity: Hypertension, Heart disease, Stroke / TIA, Peripheral vascular Disease, CKD*

Score	Output
0	**Recommendation: No antibiotic prescription**
1	**Recommendation: No antibiotic prescription**
2	**Recommendation: No antibiotic prescription**
3	**Recommendation: No antibiotic prescription**
4	**Recommendation: Active self-care.**
5	**Recommendation: Rapid CRP test to guide antibiotic prescribing**
6	**Recommendation: Rapid CRP test**

7	**Recommendation: Rapid CRP test**

LRTI Children

4 items: Age categories, Respiratory rate, sputum / rattly chest, O2 Sats < 95%.

Scores are allocated to age categories as follows:

Age	**Score**
3- <4 years	25
4- <6 years	23.5
6- <8 years	21
8-11 years	19

A total score is calculated using the formula:

LRTI children score = 46 - age score (table above) + respiratory rate + 14 (if sats < 95%) + 18 (if sputum or rattly chest present)

Example if age = 8, respiratory rate = 35, O2 sats > 95% and sputum present:

Score = 46-19+35+18 = 80.

Score	**Output**
< 70	**Recommendation: No antibiotic prescription**
>=70	**Recommendation: Active self-care.**
>=80	**Recommendation: Immediate antibiotics**

Sinusitis

Output in all cases:

Symptomatic <11 days. Recommendation: No antibiotic prescription. Safety netting.

Symptoms >= 11 days & purulent secretion, recommend nasal steroid. If unsuitable or worseing, CRP test +/- antibiotics

Otitis

3 criteria: Severe infection >=7/10 (based on score 1=mild infection to 10=severely unwell - approx 5% patients): Bilateral Acute Otitis Media: Otorrhoea .

Criteria	**Output**
Severe infection (+/- other criteria)	**Recommendation: Immediate antibiotics**
Otorrhoea (no severe infection, +/- other criteria)	**Recommendation: Active self-care.**
Unilateral otitis, (no otorrhoea or severe infection))	**Recommendation: Active self-care.** Discuss safety-netting and low risk of serious complications.
Bilateral otitis, (no otorrhoea or severe infection))	**Recommendation: Active self-care.**

Impetigo

Output in all cases:

Localised (i.e., affected area no larger than the patients' handprint and can reasonably be treated with topical treatment), **non-bullous** (no blisters), **patient is not systemically unwell, and not at high-risk of developing complications** (i.e. significantly immunocompromised).

Recommendation: hydrogen peroxide 1% cream (2 or 3 times daily for 5 days). If hydrogen peroxide 1% cream is not available or unsuitable (e.g.

should not be used around eyes) offer a short course of a topical antibiotic.

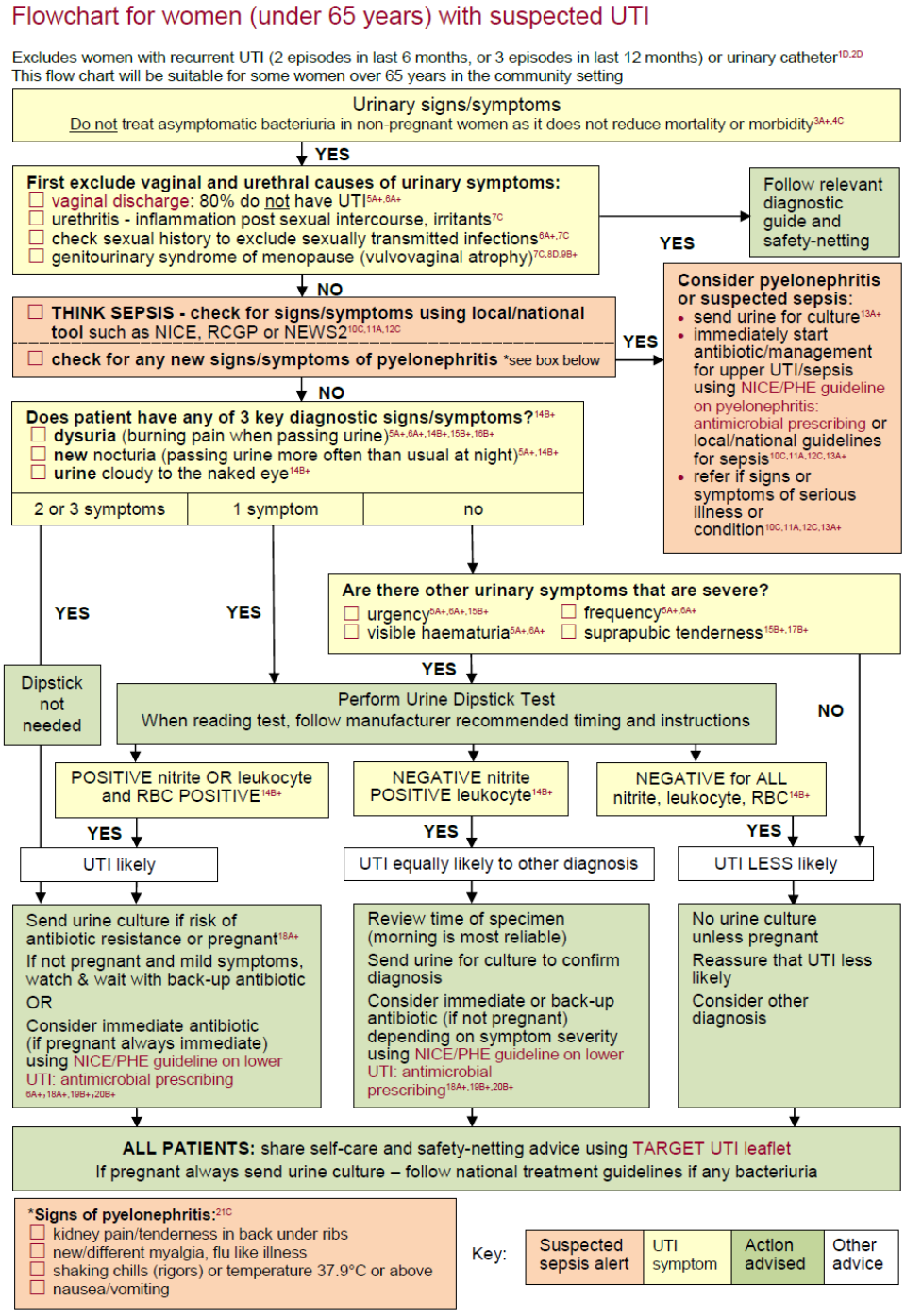
UTI (children > 3 years)

3 criteria: Urine dip +ve for nitrites: Urine dip +ve for leukocytes

Criteria	**Output**
+ve nitrites, +ve leukocytes	**Recommendation: Immediate antibiotics.**
+ve nitrites, -ve leukocytes	**Recommendation: Immediate antibiotics if dipstick on fresh urine sample tests positive**
-ve nitrites, +ve leukocytes	**Recommendation: Only start antibiotics if good clinical evidence of UTI;**
-ve nitrites, -ve leukocytes,	**Recommendation: No antibiotic prescription.**

UTI (women < 65 years)

The diagnosis and advice follows the flowchart below:



Criteria	Output

UTI likely, no severe symptoms, not pregnant	**Recommendation: Active self-care.**
UTI likely, (symptoms severe or patent not will to consider delayed dispensing) or patient pregnant	Recommendation: Immediate antibiotics (if pregnant always immediate).
UTI equally likely as other diagnosis, no severe symptoms, not pregnant	**Recommendation: Active self-care.**
UTI equally likely as other diagnosis, severe symptoms, and or pregnant	**Recommendation: Immediate antibiotics (if pregnant always immediate). UTI as likely as other diagnoses.**
UTI unlikely	**Recommendation: No antibiotic prescription.**
Vaginal discharge present	**Recommendation: No antibiotic prescription. UTI unlikely consider other diagnosis.**