University of BRISTOL

Bristol Randomised Trials Collaboration

Long title: A clinical effectiveness investigation of a multi-faceted intervention (incorporating a prognostic algorithm) to improve management of antibiotics for CHIldren presenting to primary care with acute COugh and respiratory tract infection (CHICO): an efficient cluster RCT informed by a feasibility RCT

Short title: The CHIldren with COugh Cluster Randomised Controlled Trial (The CHICO RCT)

Approvals and IDs	Reference
Protocol version	Version 4.0 (20 April 2020)
IRAS project ID	229389
REC Reference	18/LO/0345
Sponsor	University of Bristol, 2835
ISRCTN	ISRCTN11405239
Funder (NIHR HTA)	16/31/98
HOST	APCRC

This protocol has regard for the HRA guidance

The CHICO RCT is an NIHR HTA funded trial stemming from work conducted in the 'TARGET' NIHR Programme Grant for Applied Research (RP-PG-0608-10018)

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TRIAL SYNOPSIS

Trial Title	A clinical effectiveness investigation of a multi-faceted intervention (incorporating a prognostic algorithm) to improve management of antibiotics for CHIldren presenting to primary care with acute COugh and respiratory tract infection (CHICO): an efficient cluster RCT informed by a feasibility RCT	
Short title	The CHIldren with COugh Cluster Randomised Controlled Trial (The CHICO RCT)	
Trial Design	A clustered two-arm open label RCT of a complex intervention using routine data (i.e. an efficient design)	
Trial Participants	GP practices treating children aged 0-9 years presenting with a cough or upper RTI	
Planned Sample Size	155 practices in each arm of the trial	
Trial Intervention	The intervention consists of a short self-directed learning package for the clinician on the background and use of the intervention, a prognostic algorithm to help predict those children at very low risk of hospital admission (both embedded into the existing practice EMIS software system) and a personalised printout of the consultation for the parents. The algorithm is to be used as a decision aide to underline NICE guidelines on when to prescribe antibiotics.	
Control Care	Usual treatment	
Treatment duration & Follow-up	The intervention is designed to reduce antibiotic prescribing during consultation. We will be monitoring monthly routinely collected dispensing data of amoxicillin and macrolides (main antibiotics given to children with coughs) as well as hospital admission for respiratory related illnesses.	
Planned Trial Period	Practices will be recruited into the trial for a 12-month period. Recruitment of the practices from at least 20 CCGs involved will be staggered with practice recruitment starting in October 2018(including an internal pilot). The last month for data collection will be approximately 12 months after the last practice is randomised	
	Objectives	Outcome Measures
Primary	P1) Whether the intervention reduces the dispensing rate of antibiotics given to children with cough (efficacy)	P1) The rate of dispensed amoxicillin and macrolide items prescribed for children (aged 0-9 years) at each practice over a 12-month period. The denominator will be the median list size, taken from

	P2) No change in hospital admissions for children with cough (non-inferiority)	the 12 individual months of follow up data P2) The rate of hospital admission for RTI amongst children aged 0-9 years using the same denominator as above
Secondary	S1) Whether the CHICO intervention results in no change in the Emergency Department (ED) attendance rates for RTI	S1) ED attendance rates for RTI divided using the same denominator as above
	S2) The costs to the NHS of using the CHICO intervention	S2) A between-arm comparison of mean NHS costs in a cost-consequence analysis
	S3) Whether there is any intervention effect modified by the number of locums used in the practice	S3) Comparison of primary outcome P1 stratified by categorisation of proportion of locums used (interaction)
	S4) Whether there is any intervention effect modified by the clinicians' prior antibiotic prescribing rate	S4) Comparison of primary outcome P1 stratified by categorisation of practice dispensing rates in 12 months prior to recruitment (interaction)
	S5) Whether the effects of the CHICO intervention differ between GP and nurse prescribers	S5) Comparison of primary outcome P1 dichotomised by those practices with GP prescribers only and those with nurse prescribers as well (interaction)
	S6) Whether the effects of the CHICO intervention differ between practices with one or multiple sites	S6) Comparison of primary outcome P1 dichotomised by those practices with one site only and those with multiple (interaction).
	S7) Whether the effects of the CHICO intervention differ within child age groups	S7) Comparison of primary outcome P1 stratified by age (5-year epochs) and analysed separately.
	S8) Whether the use of the CHICO intervention varies between practices and over time	S8) An exploration of both usage over a 12-month period and seasonality and the effects they have on P1.
	S9) Whether the embedded CHICO intervention is acceptable to, and used by, primary care clinicians (GPs and practice nurses) and other practice staff (managers, pharmacists) and CCG staff (medicines managers)	S9) Using qualitative interviews with clinicians to investigate the acceptability and explore the use of the intervention, how it was embedded into practice and whether it was used. The CCG staff interviews will be exploring how well practices embedded the

		intervention into their systems and daily life from their perspective

FUNDING AND SUPPORT IN KIND

Funder(s)	Financial and non-financial support given
NIHR Health Technology Assessment Programme National Institute for Health Research Evaluation, Trials and Studies Coordinating Centre University of Southampton Alpha House Enterprise Road Southampton, SO16 7NS Telephone: 023 8059 5586 Fax: 023 8059 5639 Email: htaoas@southampton.ac.uk	Grant funding
Bristol Randomised Trials Collaboration (BRTC) School of Social and Community Medicine University of Bristol Canynge Hall 39 Whatley Road Bristol, BS8 2PS Telephone: 0117 928 7393 Email: enquiry-brtc@bristol.ac.uk	Methodological expertise
Research and Enterprise Development 3rd Floor, Senate House Tyndall Avenue Bristol, BS8 1TH Tel: 0117 928 8676 Email: red-office@bristol.ac.uk	Sponsorship
Avon Primary Care Research Collaborative South Plaza Bristol BS1 3NX	Host

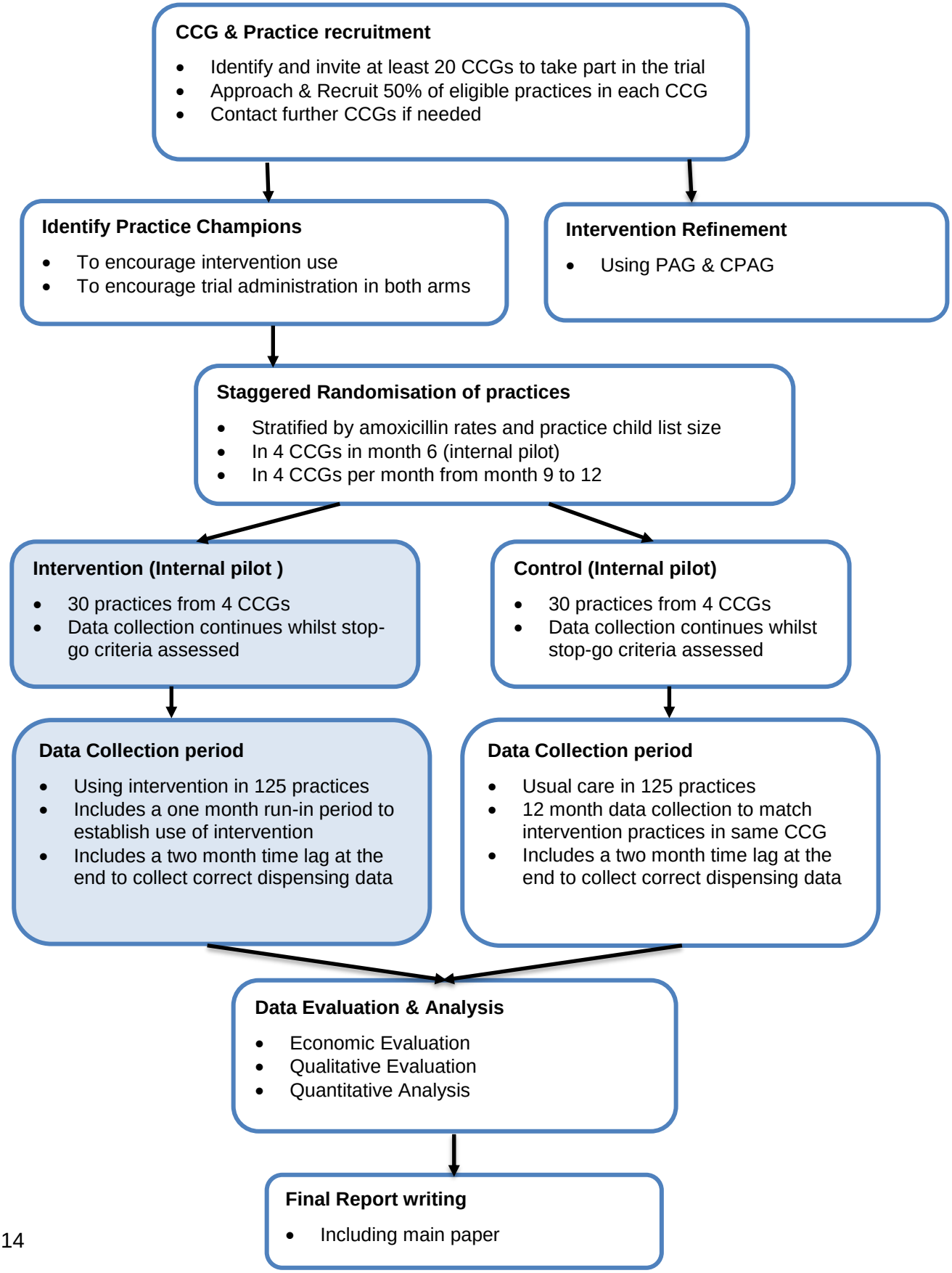
1 Contents

LIST OF ABBREVIATIONS

AE	Adverse Event
AMS	Anti-Microbial Stewardship
AMR	Anti-Microbial Resistance
BRTC	Bristol Randomised Trials Collaboration (UoB Trials Unit)
CCG	Clinical Commissioning Group
CHICO	CHIldren's COugh
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials (Guidelines)
CPAG	Clinician and Pharmacist Advisory Group
CPRD	Clinical Practice Research Datalink
CRF	Case Report Form
CRN	Clinical Research Network
DMC	Data Monitoring Committee
ED	Emergency Department
GCP	Good Clinical Practice
GP	General Practitioner
HTA	Health Technology Assessment
ISRCTN	International Standard Randomised Controlled Trials Number
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NPT	Normalisation Process Theory
PAG	Parent Advisory Group
PI	Principal Investigator
PPI	Patient & Public Involvement
QALY	Quality adjusted life year
QoL	Health-related quality of life
RCT	Randomised Control Trial
REC	Research Ethics Committee
ROC	Receiver Operating Characteristic
RTI	Respiratory Tract Infection
SAE	Serious Adverse Event
SD	Standard Deviation
SOP	Standard Operating Procedure
TARGET	Name given to the programme of research underpinning the CHICO trial – so called since the main aim was to develop an intervention to improve the targeting of antibiotics for children with RTIs
TMG	Trial Management Group
TSC	Trial Steering Committee
TMF	Trial Master File
UoB	University of Bristol

WS	Work Stream

Figure 1: TRIAL FLOW CHART



1 BACKGROUND

Respiratory tract infections (RTIs) in children present a major resource implication for primary health care services internationally for five reasons. First, they are extremely common and costly to service providers, families and employers. [1,2] Second, there is clinical uncertainty in primary care regarding the diagnosis and best management of RTIs, as reflected by the variation in the use of antibiotics in primary care for RTIs between nations, [3] GP practices [4] and clinicians. [5] Third, antibiotic prescribing by primary care clinicians in the UK remains significantly higher than in some of our European neighbours.[6] Fourth, the overuse and misuse of existing antibiotics, combined with the slowing in the development of new antibiotics, is associated with the development and proliferation of antimicrobial resistance between [7] and within [8] nations as well as individuals.[9-11] Finally, the use of antibiotics leads to the subsequent 'medicalisation of illness' in which patients believe they should consult for similar symptoms in the future.[12] A number of key publications have highlighted the need for more research to define the appropriate use of antibiotics and health care resources for RTIs if the public health disaster of ineffective antibiotics for serious infections is to be averted. [13-15] Qualitative work from the NIHR TARGET programme for Applied Research in 2016 identified clinician uncertainty as a major driver of antibiotic prescribing and that improved identification of children at very low risk of future hospitalisation could increase confidence to withhold antibiotics in low risk groups. Clinical prediction rules are designed to reduce clinical uncertainty in an outcome (such as a child's risk of hospitalisation) by assessing the strength of association between the risk of it occurring and baseline characteristics (for example, socio-demographic characteristics or symptoms and signs of illness).

1.1 Findings from the TARGET Programme

The design of the CHICO trial's intervention was borne out of evidence from the TARGET programme's earlier work streams. This has involved data synthesis of qualitative and quantitative evidence [16-19], a qualitative investigation to understand both parents' information needs and influences on clinical decisions surrounding antibiotic prescribing, and quantitative evidence in terms of a large multi-centre, prospective cohort study (over 8,300 children) to derive and internally validate a clinical rule to predict hospitalisation of children with RTIs [20, 21]. This culminated in a feasibility cluster RCT study to measure the acceptability of using symptoms, signs, and demographic characteristics to predict hospital admittance in children presenting to primary care with RTI [22, 23]. Findings across the TARGET programme were synthesised using Greene and Kreuter's Precede-Proceed model [24] which integrates across several behavioural theories into a unified model.

1.1.1 Clinical prediction rule for hospitalisation

The TARGET cohort study aimed to identify signs, symptoms and demographic characteristics that may predict hospitalisation and poor prognosis of a child. In particular, such an algorithm could potentially identify a large group of children at very low risk of hospitalisation and therefore are potentially unlikely to require antibiotics.

In line with expectations, just under 1% of the children were admitted to hospital up to 30 days after their consultation with the primary care clinician. We found seven characteristics independently associated with increased risk of hospitalisation for their acute cough or RTI during the subsequent 30 days, these are described by the STARWAVe mnemonic. Short illness duration

(parent reported ≤3 days), Temperature (parent reported severe in previous 24 hours or ≥ 37.8° on examination), Age of patient (< 2 years), Recession (intercostal or subcostal on examination), Wheeze (on listing to chest with stethoscope), Asthma (currently diagnosed) and Vomiting (parent reported moderate or severe in the 24 hours prior to consultation). The area under the receiver operating characteristic (ROC) curve for the coefficient-based algorithm was 0.82 (95% CI: 0.77 to 0.87).

The prediction rule identifies children at very low, medium and high risk of future hospitalisation with advice given on how the clinician can use this information in conjunction with their own clinical judgement to decide the best course of action for each child. Assigning one point per predictive characteristic, a points-based algorithm was used to quantify absolute probabilities to 3 groups: (i) 'very low' (0.3%, 95% CI 0.2% to 0.4%) scoring 0 or 1 point; (ii) 'normal' (1.5%, 1.0% to 1.9%) scoring 2 or 3 points; and (iii) 'high' (11.8%, 7.3% to 16.2%) scoring ≥ 4 points. The rule can potentially be effective in both reducing the overall prescription of antibiotics by increasing clinician confidence that they are not needed 'just in case' in the very low risk group (just under 70% of children are in this group), as well as better identify those children in need of close monitoring (2% of children are in the high risk group). Children in the medium risk group (29%) have a similar risk of future hospitalisation as all children combined, so management should follow current NICE guidelines [25], which state that clinicians should decide on the use of immediate, delayed or no antibiotics based on their assessment of the child's illness severity.

1.1.2 The interaction within the consultation

Our finding from our qualitative reviews was that clinicians can misinterpret parent's communication about their concerns or ideas regarding their child's illness as pressure for antibiotics and in some cases this led to unnecessary or unwanted antibiotics being prescribed.[26] Clinician communication was focussed on differentiating minor and more serious illnesses, with the message (both implicit and explicit) that viral illness were minor while those that were 'serious' were treated with antibiotics. Clinicians and parents were often talking at cross purposes about the seriousness of the illness; parents emphasising the severity of the symptoms to demonstrate the impact on child health and to justify the consultation; clinicians seeking to justify a no antibiotic treatment decision by minimising the problem.

The findings of our qualitative study suggested that parents want better information on the signs and symptoms of serious RTIs and when to consult, [26] along with more useful advice on home management of symptoms.[27] Parents did not want to know the absolute risk of hospitalisation for their child but they did want advice and information specific to their child.[27] When parents did consult, clinician explanations of diagnosis and treatment recommendations were not well understood by parents, and they remained unclear about how to manage an RTI and when to consult.[26,28,29] Clinicians reported that most often they gave a simple viral diagnosis, communicating that the illness was self-limiting and did not need antibiotic treatment.[30] However, if the child's illness appeared severe to the parent, or the parent was concerned about particular symptoms or impacts which were not addressed by the clinician, the parent reported viewing a simple viral diagnosis as inadequate.[29] Parents concerns encompassed things which fell outside a simple biomedical model for RTIs, including both child health and psychosocial impacts, but reported that clinicians rarely addressed these.[29]

1.1.3 The feasibility study and an 'efficient' design

In the feasibility trial, the intervention group antibiotic prescribing rate at consultation was 25% (compared to 37% in our earlier cohort study), however amongst the control group the overall prescribing rate was even lower at 16%. The paradoxical effects found in the feasibility study were largely explained by a post-randomisation recruitment differential, with possible Hawthorne effects [23]. In the intervention arm there was a significantly higher recruitment rate, difference in clinician-type (proportionally more practice nurses recruiting), the children were significantly younger and importantly the intervention children were more unwell at baseline (significantly higher respiratory rate, significantly higher wheeze prevalence and significantly higher parent and clinician global illness severity scores). Learning from these lessons, we have proposed a more 'efficient' study design that will not only mitigate recruitment differential but will also be resource-efficient, using an intervention designed to be replicable for the NHS. Rather than recruit and consent during consultation or collect individual children's data during consultation and from the practice notes we are proposing a 'lighter touch' efficient design where the primary outcomes (selected antibiotics mainly prescribed for children with acute cough and respiratory tract infection and disease specific hospitalisation rates) are measured using routinely collected data.

1.2 Rationale

Antimicrobial resistance is recognised by the UK government, governments around the world and the World Health Organisation as one of the most pressing public health threats of our time. Around 80% of antibiotics prescribed for human consumption are prescribed in primary care, [31] and it has been estimated that around 50% of antibiotic prescribing in this setting is unnecessary. [32] Approaches to modify antibiotic prescribing in primary care have been developed and evaluated, and prescribing rates in England have declined slightly using figures from 2014-15, [31] although antibiotic prescribing rates in the UK continue to be substantially higher than many other European countries. [9] The UK Five Year AMR Strategy 2013 to 2018 aims to conserve the effectiveness of existing antibiotics through effective antimicrobial stewardship, including reducing the inappropriate use of antibiotics. There is therefore an urgent need for an efficient intervention that can be rolled out at scale that safely addresses many of the key drivers of antibiotic prescribing in children. Recent papers suggest cluster randomized trials aimed at reducing antibiotics may be implemented efficiently in large samples from routine care settings by using primary care electronic health records in the UK. [33-35] We are aware of two ongoing studies, the first investigating the effects of an integrated package of interventions (including delayed prescribing; patient decision aids; communication training; patient information leaflets; and near patient testing with C-reactive protein) [36] and the second (an 'efficient design' study) investigating the effects of a multifaceted intervention consisting of practice antibiotic prescribing feedback, delivery of educational and decision support tools and a webinar to explain and promote the intervention. [37] Both studies focus on the general rather than the paediatric population and have different components compared to our complex intervention. Primary care clinicians [38] and the research community [39] have called for the development of a sound evidence base, currently unavailable, to help them identify children at low and high risk of complications, especially serious complications such as pneumonia, that require hospitalisation. At a minimum it is essential to demonstrate that any change in practice does not increase the number of children with serious complications. A change in practice should improve health outcomes for children whilst

distinguishing children for whom antibiotics are certainly not needed and providing precise information regarding the symptoms denoting poor prognosis for which parents should be vigilant.

2 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

2.1 Aim:

The aim of the CHICO RCT is to reduce antibiotic prescribing amongst children presenting with cough or RTI without increasing hospital admission for this condition.

2.2 Primary objectives

To determine

P1. Whether the CHICO intervention decrease the number of paediatric formulation antibiotic suspension items dispensed for respiratory tract infections to children presenting with acute cough and respiratory tract infection to primary care (efficacy comparison).

P2. Whether the CHICO intervention result in no change in hospital admissions for children with a hospital diagnosis of RTI (non-inferiority comparison).

2.3 Secondary objectives

To determine:

S1. Whether the CHICO intervention results in no change in the ED attendance rates of children with a hospital diagnosis of RTI.

S2. The costs to the NHS of using the CHICO intervention.

S3. Whether any intervention effect is modified by the proportion of locums used.

S4. Whether any intervention effect is modified by the practices' prior antibiotic prescribing rate.

S5. Whether any intervention effect differs between GP and nurse prescribers.

S6. Whether any intervention effect differs between practices with 1 vs 2+ sites.

S7. Whether any intervention effect differs within child age groups.

S8. Whether any intervention effect differs between practices and over time.

S9. Whether the embedded CHICO intervention is acceptable to, and used by, primary care clinicians (GPs and nurses) in consultations with carers and their children and how does this vary between practices.

2.4 Primary outcome measures

These are:

P1. The rate of amoxicillin and macrolide oral suspension antibiotics dispensed by the number of children (aged 0-9 years registered) at each practice over a 12 month period. This is routinely collected data tailored to our needs collected via CCGs

P2. The rate of hospital admission for RTI amongst children aged 0-9 years using the same denominator as above. This data will be collected via the CCGs.

2.5 Secondary outcome measures

S1. ED attendance rates for RTI divided by number of children registered at the practice. This is a secondary outcome already collected from practices by CCGs. Data on out-of-hours is collected by CCGs but presently unreliable so will be investigated as an exploratory analysis.

S2. A between-arm comparison of mean NHS costs in a cost-consequence analysis. This is the health economic outcome.

S3. Comparison of primary outcome P1 stratified by categorisation of proportion of locums used over the twelve months the practice is in the study. This is a potential effect modifier of P1.

S4. Comparison of primary outcome P1 stratified by categorisation of practice dispensing rates taken from the 12 months prior to the data collection from each practice. This is a potential effect modifier of P1.

S5. Comparison of primary outcome P1 dichotomised by those practices with GP prescribers only and those with nurse or other prescribers as well. This will be determined from information collected from practices at baseline. This is a potential effect modifier of P1.

S6. Comparison of primary outcome P1 dichotomised by those practices with one site only and those with multiple sites. This is a potential effect modifier of P1.

S7. Comparison of primary outcome P1 stratified by age (5 year epochs). P1 will be analysed separately for 0-4 year olds and 5-9 year olds.

S8. An exploration into the usage of the intervention, in terms of both usage over a 12 month period and seasonality, and the effects it has on primary outcome P1.

S9. Acceptability of the intervention and variation in use will be determined by qualitative interviews with the clinicians.

2.6 Measurement of clinical outcomes

EMIS or EMIS Health or EMISWeb (formerly known as Egton Medical Information Systems), supplies electronic patient record systems and software used in primary care in England. It is used in more than half the practices in England. Using EMIS we will collect data from the intervention arm on which of the 7 predictors for hospitalisation were chosen to compare against the cohort data from which the algorithm was derived. We will determine if other non-identifiable data can be collected.

2.7 Economic outcome measures

The primary economic outcome measure will be NHS costs. Comprehensive data on quality of life for this young patient group proved to be difficult to collect during the feasibility trial. This reflected both the absence of quality of life instruments designed for young children, and the completeness of data collected from parents on behalf of participating children. We will not measure quality of life of children in this trial.

3 TRIAL DESIGN & STUDY SETTING

3.1 Trial design

The CHICO RCT is an efficient, pragmatic open label, two-arm (intervention vs. usual care) trial, aimed at reducing antibiotic prescribing amongst children presenting with RTI and acute cough with randomisation (clustered at the practice level) using routine antibiotic dispensing and hospitalisation data.

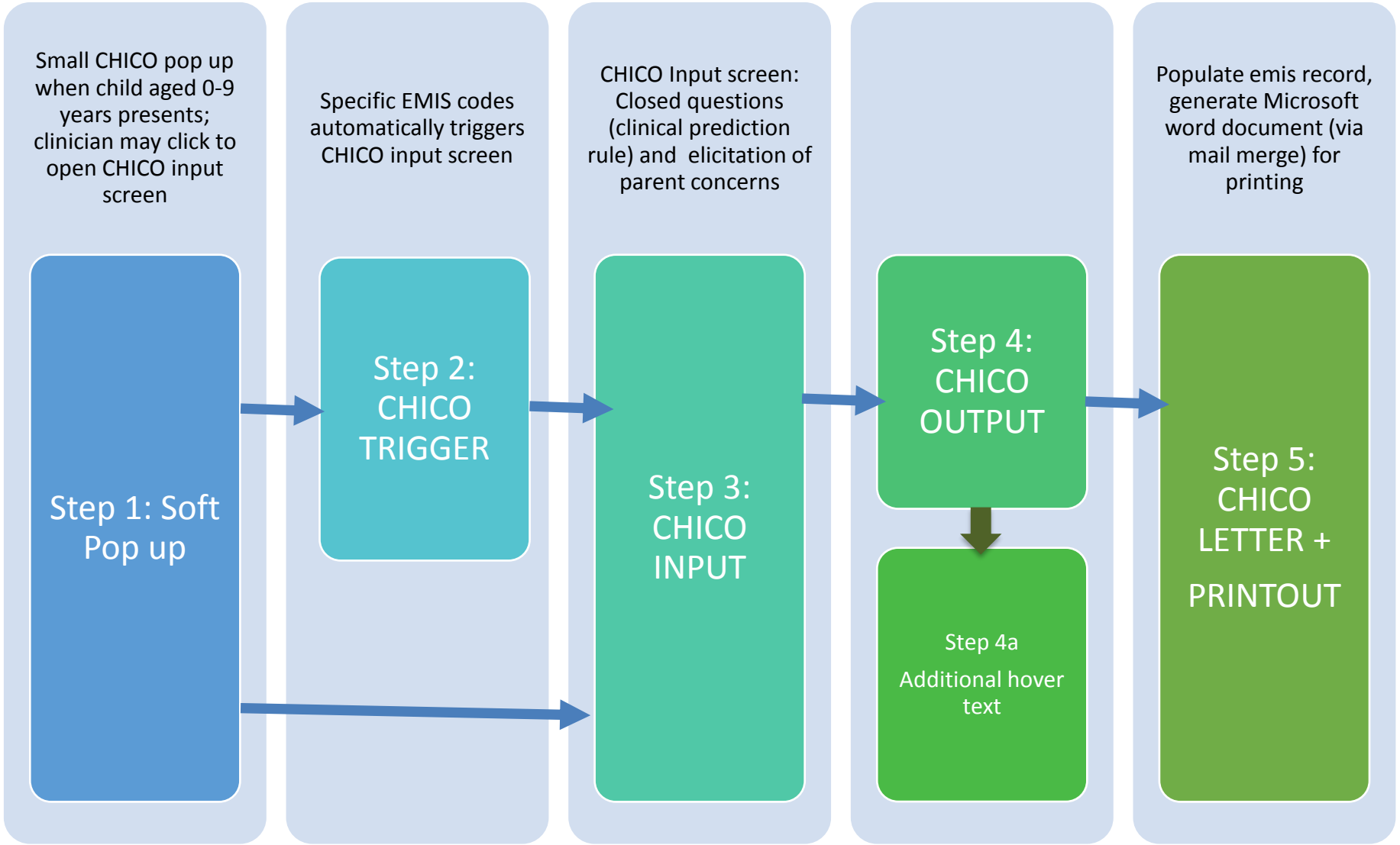
3.2 Trial Intervention

3.2.1 Overview of the intervention

The intervention consists of both a clinician-focused algorithm to predict hospitalisation for children with cough and a carer-focused personalised printout recording decisions made at the consultation and safety netting information. The algorithm is to be used as one tool amongst many the clinicians already have to decide whether the child needs antibiotics. In the training package for clinicians it will be emphasised that the primary purpose of the algorithm is not so much to identify the small proportion of children (2%) at higher risk of hospitalisation (our previous work suggests clinicians already have the skillset for this) but rather the much larger proportion of children (69%) who have a very low risk of hospitalisation.

A flowchart is provided below to outline how the intervention will work in practice, along with further information in subsequent sections.

Flowchart 2: Intervention schematic



3.2.2 CHICO training package

The intervention clinicians will be provided with print and on-line evidence-based information to describe why and how to use the intervention, as well as when to use it.. A practice champion will distribute training materials within the practice, coordinate training of practice prescribing staff, and encourage all clinicians to use the intervention appropriately. The use of the intervention will be monitored.

Patients in control practices will receive usual care and no intervention training will be provided to the practice staff.

3.2.3 Identification of patients

The healthcare professional will receive a pop-up on their screen when a child in the age-range is being consulted. This pop-up will give the option of opening the STARWAVe input page. The text of the pop up will be as follows:

Pop up text: “Child with RTI? CHICO can provide reassurance”

The STARWAVe input page will also open if the healthcare professional inputs an RTI specific EMIS code during the consultation and the patient is within the age range. The EMIS codes which trigger the intervention will be included in the training documentation for clinicians.

3.2.4 CHICO input page

The input page will be displayed prominently in the centre of the EMISweb consultation screen when triggered as above.

This page will capture five components of the STARWAVe algorithm by providing six yes or no checkboxes for the healthcare professional to complete. These components will be:

- Short illness duration (parent/carer reported ≤3 days)
- Raised temperature (parent/carer reported severe in previous 24 hours or ≥ 37.8° on examination)
- Intercostal or subcostal recession on examination
- Wheeze during chest stethoscope examination
- Vomiting (parent/carer reported moderate or severe in the 24 hours prior to consultation)

The sixth and seventh component of the STARWAVe algorithm history of asthma and age of patient, will be calculated from the patient’s medical record held within the EMISweb system.

A question to elicit parental concerns will also be available on template, which can be optionally entered in a provided free text box. This question is:

Question: “Ask parent/carer; what are you most worried about today?”

3.2.5 CHICO Risk Output

When the STARWAVe components have been entered the clinician will save the input page and the output will appear as a small pop up on the screen. This risk output will require no action from the healthcare professional but will inform them of the child’s risk of hospitalisation.

Table 1: CHICO risk outputs

CHICO result	Pop-up text
Low risk group	Very reassuring CHICO score: 0 or 1 CHICO predictors : >99.6% of children will recover from this illness with home care. Consider a no or delayed antibiotic prescribing strategy. CHICO leaflet and letter covers common concerns and safety netting advice.
Average risk group	Reassuring CHICO score: 2 or 3 CHICO predictors: >98% of children will recover from this illness with home care. Consider no or delayed antibiotic prescribing strategy. CHICO leaflet and letter covers common concerns and safety netting advice.
Elevated risk group	Safety netting needed: 4+ CHICO predictors: This is more than average, but >87% of children will still recover from this illness with home care. Highlight SAFETY NETTING advice in CHICO leaflet.

3.2.6 Personalised letter and Information given to parents

When the Intervention input page has been saved the clinician will have the option to print a personalised letter for the parent/carer. This letter will capture the following information:

1) Patient's name and age
2) Pre-specified brief description of the function of the consultation
3) Parent/carer's concerns; manually typed in by the healthcare professional
4) Healthcare professional's advice regarding raised parent's concerns
5) Name of Healthcare professional

This personalised letter should be provided to the parent/carer alongside the "Caring for children with cough" safety netting leaflet providing further information regarding common parent/carer concerns.

3.3 Study setting

The CHICO RCT will recruit GP practices from Clinical Commissioning Groups (CCGs) from demographically diverse regions across England. Recruitment of practices will be via CCGs and Clinical Research Networks (CRNs) using established channels of communication.

3.4 CCGs

3.5 The CCGs are already committed to national AMR strategies and an initial approach to several CCGs about collaboration in this study has been enthusiastically welcomed. Before the trial begins we will advertise for expression of interest from

CCGs and utilising CCGs who have a high number of research active practices using the EMIS system. We will use a member of the CCG medicines management team already in place as the primary contact for each CCG because they already have practice relationships and communication channels and activity. These individuals will help recruit practices within each CCG. The study team may also liaise the Business Informatics team who will provide primary outcome data for the participating practices.GP Practices

We will encourage at each intervention practice, a GP, nurse, pharmacist, practice manager or practice data manager to take on the role of practice champion to help monitor the use of the intervention. These champions will help set up the intervention and run monthly queries via EMIS that will be monitored centrally by the CHICO study team in Bristol. All practices will be collecting data over a 12-month period, to include any seasonal fluctuations in data collection. Our qualitative work suggests clinicians are more likely to use the intervention if we provide print and on-line evidence-based information to describe why and how to use the tool dug consultation. We are focusing on those practices using the EMIS system but may also consider embedding our intervention in different practice systems.

4 ELIGIBILITY CRITERIA

4.1 GP Practice inclusion criteria

GP practices in England using the EMIS medical record management computer software to house the intervention (53% of English practices use this system).

4.2 GP Practice exclusion criteria

Practices will be asked directly whether they are participating in any antimicrobial stewardship activities during our study period and these will be recorded. If these activities involve concurrent intervention studies where there is potential to confound or modify the effects of our intervention, these practices will be excluded. Practices will also be excluded if they are aware that they are either merging with another practice or their CCG is merging with another within the 12-month follow up period.

4.3 Subject population

We will be collecting anonymised data on individuals and this will be gathered using current NHS routine systems. We will not be seeking individual participation or individual parent/child consent, to minimise risks of post-randomisation differential recruitment and Hawthorne effects. The search criteria are data on antibiotic dispensing (liquid amoxicillin and macrolides) collected monthly by pharmacies for children aged 0-4 years and 5-9 years.

4.4 Inclusion criteria

Children aged 0-9 years during the data collection period registered at practices using the EMIS system.

4.5 Exclusion criteria

Children aged 10-14 were considered for inclusion but at this age an increasing number are given antibiotics in tablet form and given the much lower consultation rate in older children we decided to exclude this group from the study population. Practices in which research into antibiotic prescribing or dispensing is being conducted and could directly interfere with our measurements will be excluded.

5 TRIAL PROCEDURES

5.1 Data Collection

In this efficient design the data is mainly being collected from the practices and CCGs rather than patients and clinicians. The different types of data being collected are shown in Table 2.

Table 2:. **Data collection**

	Type	Objective	Content (relation to outcomes)	Who from
5.2	Expression of Interest Data:	Recruitment of CCGs	Proportion of eligible practices in each CCG & consent to take part	From at least 20 CCGs
		Recruitment of Practices	Consent to take part	310 Practices
5.3	Baseline Data:	Stratification of Practices	Proportion of children aged 0-9 and dispensing rates in 2017 (also used to answer secondary outcomes S4 and S6)	ePACT2 (routine data)
		Practice Characteristics	Brief questionnaire about staff composition, patient characteristics, triage systems and prescribing (to answer secondary outcomes S3 and S5)	All practices in the study
5.5	Monthly data:	From Practices	Use of intervention. Sent by practice champions via EMIS query. (to encourage use and answer secondary outcome S1)	Intervention practices
		From ePACT2 (routine data) and CCGs	Routinely collected data from each practice on antibiotic dispensing, hospitalisation and ED attendance (to answer primary outcomes P1 and P2 and secondary outcomes S1 and S7)	ePACT2 and CCGs
5.7	Follow-up data:	Practice profile over last 12 months	Similar to the baseline questionnaire asking about changes since baseline (to further help answer S3 and S5)	All practices in the study
5.8	Fidelity data:	Quality of the intervention delivered	Using both the monthly data from practices described above and qualitative interviews	Intervention practices
5.9	Health Economic Data:	Cost consequence analysis	Costs of the intervention, ED attendance and admissions (this is described above and will be used to answer S2)	CCGs and Intervention practices
5.11	Qualitative data:	Use of intervention and acceptability	semi-structured interviews to explore views and experiences (to answer S8)	Practice & CCG staff

5.2 Expression of Interest

5.2.1 Recruitment of CCGs

There are over 200 CCGs in England and between 10-80 practices per CCG. Some CCGs are currently merging and we may treat these as one CCG depending on the management infrastructure. We will focus on those CCGs that primarily have practices using the EMIS system and aim to recruit on average around 15 practices per CCG, or fewer practices from more CCGs if necessary. One of our co-investigators (EB) is a national project lead for healthcare acquired infections and antimicrobial resistance at NHS England and will co-ordinated expressions of interest from CCGs prior to the start of the trial. The CCGs will provide data for stratification purposes (see below) and then provide monthly routine data related to our primary outcome.

5.2.2 Recruitment of GP practices

Eligible practices will be contacted via the CCGs to take part in the trial. When GP practices are invited to participate, they will be advised on the general principles of the trial, namely that the research will investigate methods to optimise the management of childhood RTI as well agree to provide a practice champion as our primary contact and willingness of a member of staff to take part in qualitative interviews. In the intervention arm we will seek agreement for them to install our intervention on EMIS and the practice champion to monitor its use and send us monthly updates.

5.3 Baseline Data

5.3.1 Stratification data

The CCGs will provide data on the proportion of children (aged 0-9) registered at each consenting practice as well as dispensing rates of amoxicillin and macrolides for 0-9 year olds in 2017 so we can use this for stratification purposes.

5.3.2 Baseline questionnaire

All GP practices that express an interest in the study will be asked to complete a baseline questionnaire prior to randomisation to allow capture of practice characteristics.

Baseline data will include:

I. Data about the practice staff composition (GP partners/salaried/sessional nurse practitioners and practice nurses and locums used in the last 12 months) and any other available characteristics (such as postcode).

II. Data about the patients registered at the practice (the number, age, ethnicity and gender of the patients).

III. Data about triage system used to handle children presenting with a cough or respiratory tract infection and any variation in management.

IV. Data about which clinician-types prescribe antibiotics to children aged 0-9 years.

5.4 The randomisation scheme

GP practices will be randomised on a 1:1 basis by the independent Bristol Randomised Trials Collaboration (BRTC) unit. All children registered at a GP practise randomised to the intervention arm will follow current standard management along with the additional intervention tool and all children registered at a GP practise randomised to the “Usual care” Comparator arm will receive

current standard management. Randomisation will be at the practice level. It will be stratified by CCG and then minimised for list size of children (HIGH/LOW) and the dispensing rate over the previous 12 months, (HIGH/LOW), relative to other practices within their CCG.

5.5 Routinely collected data

5.5.1 Monthly data from the intervention practices

This will be sent to the research team via the practice champions using pre-installed EMIS queries. This will be used for monitoring (and encouraging the use of) the invention and for analytical purposes. The data will include, how often the intervention is being used and for how long (i.e. duration of consultation if possible).

5.5.2 Routine monthly data from CCGs split by practice

This will be collected from CCGs each month and include the number of dispensed amoxicillin suspensions and macrolides given to children aged 0-9 years per practice, the number of hospitalisations for respiratory tract infections and the number of ED attendances.

5.6 Blinding

As this is a cluster randomised controlled trial and due to the nature of the intervention delivery, it will not be possible to blind the practices to their allocation of either control or intervention group

5.7 Follow up data collection

A brief follow-up questionnaire will be sent to practices in the intervention and control arm after 12 months (similar to the baseline questionnaire) asking about staffing levels and management of RTI amongst children as well as use of intervention for those in the intervention arm.

5.8 Fidelity of the Intervention

The fidelity measures will focus on intervention exposure and the quality of the intervention delivered (using the process interviews as part of the qualitative investigation). Ideally we would like a code automatically added when the STARWAVe template is opened and then when it is used by a clinician so we can electronically search for this data although initial exploration suggests there may be issues with this coding. We will look at ways around this problem in the first few months of the trial when we are refining the intervention.

5.9 Economic Evaluation Data Collection

Given the light-touch design of the trial, the economic evaluation will be limited to a between-arm comparison of mean NHS costs in a cost-consequence analysis. NHS costs will be calculated from the costs of the intervention itself, prescriptions of amoxicillin and macrolides per the co-primary outcome, ED attendances and hospital admissions. Ideally, these cost data would be related to the quality of life of children in the trial, but the CHICO feasibility trial confirmed the difficulty of obtaining comprehensive, useable quality of life data in this young patient population. To address our secondary aims (S2) a focus on costs will clarify whether and by how much NHS costs might change in the event of a widespread deployment of the algorithm into routine clinical practice

5.10 Trial Arms

5.10.1 The intervention arm

5.10.1.1 Installing the intervention

Practices randomised to the intervention will be sent instructions including screen shots on how to install the intervention application on the EMIS system. Email support will be offered via the Practice champion to help implement this and encourage appropriate use of the tool. Requests to access a practice EMIS system remotely to assist installation, subject to appropriate data security clearance, will be investigated, alternatively a visit to the practice.

5.10.1.2 Components of the intervention

A web-based interface allows for a single intervention to be delivered in an application that comprises five components:

1. Information provision. For each clinician we will provide the rationale for the intervention as a practical tool. This will include print and online evidence-based information to describe why and how to use the tool during consultation. Qualitative work from TARGET suggests some clinicians were just as interested in what was both what was and what was not predictive as much as those clinical symptoms and signs that were. Thus we will include in the learning package the detailed findings from the TARGET Programme including the best evidence regarding symptom duration and the context of antibiotic over-prescribing. We will also provide a description of the children meeting the criteria for intervention use (e.g. acute (≤28 days) cough (main presenting symptom) with suspected underlying RTI with or without known asthma, so long as the symptoms were considered due to infection and not a non-infective asthma exacerbation) and how to use the personalised printout during consultation. For each practice we will provide instructions on how to embed the tool and offer support, both over the phone and face to face if needed from the study team and practice champion.

2. Encouraging use of the tool. CCG endorsement was identified by clinicians as a key incentive to using the tool. Intervention CCGs will be asked to support the study at both CCG level and to endorse the use of the intervention within practices using local engagement processes and AMS activities. Working with the AMS teams already established amongst practices and CCG pharmacists we will select CCG AMS leads to promote the use of the intervention at practice level. They will support a network of enlisted practice champions (GP, Nurse, practice manager or pharmacist) who will help embed the intervention, encourage use of the tool and monitor its use (see point 5). EMIS-based prompts (triggers) will also be used to identify eligible children. This will include subtle prompts if the child is aged 0-9 and more noticeable prompts if an RTI-related code is put into the system during consultation. The relevance and consistency of how the system is used could potentially be varied across practices; this will be monitored by the practice champions and discussed to increase a more uniform approach.

3. Within-consultation interactive tool. This is embedded within the primary care information system. Clinicians in the intervention arm will be asked to complete an embedded form during consultations for children with acute cough and RTI to record presence or absence of particular signs and symptoms. Some of the 7 predictors (age of patient and history of asthma) will already be available for automatic entry. The embedded intervention will produce for clinicians an individualised risk of future hospitalisation and risk group specific treatment recommendations. Thus, clinicians will be presented with both the recommended (not explicit) treatment option

according to the clinical prediction rule (i.e. this child is unlikely to deteriorate and require hospitalisation for their RTI and an antibiotic prescription is not recommended) alongside other possible options (immediate or delayed antibiotic, re-consult). Clinical details that are required to complete the STARWAVe algorithm will be documented in a standardised EMIS proforma and the electronic medical record will then identify whether the consulting patient is at high, medium or very low risk of hospitalisation.

4. Personalised letter for the parents. A short personalised responsive printout will be produced. It will be combined with a printed leaflet developed from our earlier work on the natural course of a typical RTI illness, typical duration of cough, caring for a child with a cough and safety-netting advice about when to re-consult.

5.10.2 5. Monitoring intervention use**. Given the intervention will be embedded in the practice system an internal dashboard system will be used for reporting frequency of use of the intervention by clinicians to practices during intervention period. Practices will be provided with searches (EMIS queries) which practice champions will be requested to run monthly and feed back to the study team. To encourage use of the intervention, the monthly searches should be checked by the study team and relayed back to the practice if the intervention has not been used, as well as the practice champions reminding the clinicians to use the intervention. The Comparator arm**

The comparator arm for CHICO trial will be usual care for this condition. The clinicians from practices randomised to the comparator arm will just be asked to treat children presenting with cough or RTI as they normally would. Baseline data on control practices will be collected but no data are being collected directly from the clinicians or specific contact being made.

5.10.3 Separate scoping exercise

As a separate scoping exercise to inform future dissemination we will contact users or experts in SystemOne (covers 26% of practices) and INPS/Vision (covers 20% of practices) and report on the potential barriers of embedding the intervention in these systems.

5.11 Qualitative Research

Qualitative interviews with clinicians (GPs and practice nurses) and other practice staff (managers, pharmacists) and CCG staff (medicines managers) will explore the use of the intervention, how it was embedded into practice and whether it was used appropriately. The interview topic guide will be informed by Normalisation Process Theory (NPT), [39, 40] which was developed to explain the social processes leading to routine embedding of innovative health technologies or complex interventions in health care.

NPT proposes that implementation of interventions is dependent on the ability of participants to fulfil four criteria which can be understood using the core constructs of NPT which are ‘coherence’ (how people make sense of the intervention), ‘cognitive participation’ (the work people do to develop new practices), ‘collective action’ (the work to operationalise practices), and ‘reflexive monitoring’ (ways in which people appraise how new practices are working).

Clinicians and other key staff from the intervention practices will be invited to participate in semi-structured interviews to explore their views and experiences of the intervention, with particular reference to the core constructs of NPT. Verbal consent will be taken from the practice staff by

one of the qualitative researchers. We may also collect some quantitative data from a sample of GPs on implementing the intervention based on NPT measures. The first set of interviews will be conducted during the internal pilot phase and findings fed back to the TMG to help guide best practice during the rest of the study. A second phase of interviews will be conducted when the clinicians have been using the intervention for several months to investigate the normalisation and sustainability of using the intervention. Interviews are expected to take 30-45 minutes. Clinicians who agree to participate in interviews will be reimbursed financially for their time.

Purposive sampling will be used to include a maximum variation sample including: clinicians and other staff with more or less experience, clinicians with high and low prescribing practices, and from practices serving areas of high and low social-economic deprivation. The sample sizes will be determined by the need to achieve data saturation, such that no new themes are emerging from the data by the end of data collection. [41] Interviews will be analysed in batches, and sampling will continue until no new themes are emerging from the interviews. This is likely to include up to 30 clinicians and 20 other staff involved in implementation.

5.11.1 Identifying and consenting participants

The participant information sheets will be given to CCGs and practices within the intervention arm at recruitment, and each will be asked to identify two or three members of staff who have agreed to be interviewed for the study. Their names and work contact details will be forwarded to the researchers, who will make contact if participants are selected for interview.

Before interview, the researcher will explain what participation involves, including confidentiality, data recording and the right to withdraw. If the staff member agrees to take part in the telephone interview, the researcher will turn on the audio recorder and ask them to provide their verbal informed consent to being audio recorded, to use of anonymised quotes to illustrate findings, to consent for their data to be used in future research, and to confirm they understand their right to withdraw at any time.

Confidentiality of qualitative data will be maintained by anonymising the interview transcript so that individuals or institutions discussed during the interviews cannot be readily identified. Participants will be provided with pseudonyms and these will be linked to their details in a ‘code breaker’ database. The database will be password−protected and stored on a University of Bristol network file-store space which will be archived with the main study data at the end of the trial.

5.12 Methods to protect against other sources of bias

a) Ensuring standardisation of intervention (performance bias)

The clinicians will be given on-line information on how to use the intervention. Essentially the intervention is one tool of many that will aid their decision making process as to whether to prescribe antibiotics or not. One of the topics of the qualitative interviews with clinicians will be the variation in use which we may use to help refine the initial information provided if the intervention gets rolled out.

b) Ensuring standardisation of outcome measurement (performance bias)

The primary outcome measure will be dispensing data of amoxicillin and macrolides for 0-9 year olds at each primary care practice in the trial. These data are routinely collected and sent to CCGs on a monthly basis. The data collected in 2017 will be used to help stratify practices so

we have balanced baseline dispensing between arms. At this stage the data will be compared between practices, so any differences can be identified, and the information collected can be standardised.

c) Loss to follow up (attrition bias)

As we are not recruiting individual patients to the trial we are unlikely to have loss to follow-up. We are not expecting practices to pull out once they have consented to take part. Identification and comparison of patients hospitalised will be made using the same search strategy for RTI related conditions.

d) Other sources of bias (detection bias)

Although this is not a blinded trial only the junior statistician, trial manager and DMC will be privy to the quantitative data split by arm until the final analysis.

5.13 Withdrawal criteria

Patients cannot be withdrawn from the trial as they are not being recruited. Clinicians in the intervention arm can refuse to use the intervention but this is an issue of fidelity rather than withdrawal as the primary outcome data will still be collected and analysed on an intention to treat basis.

5.14 Post-trial care

This is not applicable for this trial.

6 SAFETY

Serious and other adverse events will be recorded and reported in accordance with Good Clinical Practice guidelines and the Sponsor's Research Related Adverse Event Reporting Policy.

6.1 Definitions

Definitions of terms are shown in Table 3.

Table 3. Definitions of terms

Term	Definition
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that meets one or more of the following criteria: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation* • results in persistent or significant disability/incapacity • consists of a congenital anomaly 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.
*Definition of hospitalisation is an unplanned overnight stay. Note however that the patient must be formally admitted – waiting in outpatients or ED would not count as hospitalisation (even though this can sometimes be overnight). Prolongation of an existing hospitalisation qualifies as a SAE. Planned hospital stays would not be counted as SAEs, nor would stays in hospital for "social reasons" (e.g. respite care, the fact that there is no-one at home to care for the patient). Also, if patients had a day-case operation, this would not qualify as hospitalisation. However, if a planned operation was brought forward because of worsening symptoms, this would be considered as an SAE.	

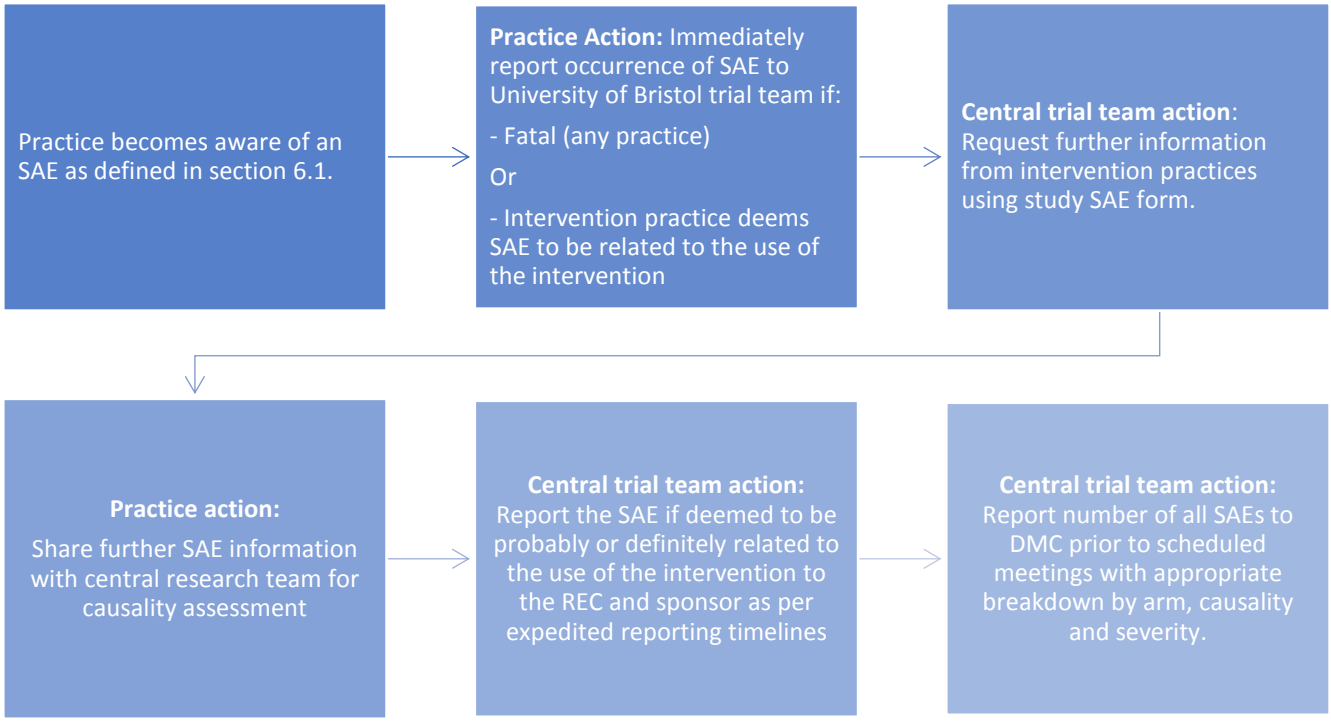
6.2 Operational definitions for (S)AEs

This trial is a low risk study (risks to participants are no higher than that of standard medical care) so SAEs will only be reported if they are fatal or serious AND potentially related to trial participation i.e. they result from advice provided by the intervention algorithm.

As one of the outcomes for the trial is hospitalisation, we do expect some participants to be admitted to hospital (due to a deterioration of their underlying illness for example). Hospitalisation due to RTI is an expected SAE and will **not** be subject to expedited reporting. Expected SAEs include but are not limited to pneumonia, empyema, deteriorating bronchiolitis.

6.3 Recording and reporting of SAEs

6.3.1 SAE Reporting Flowchart



6.3.2 Hospitalisation due to RTI

As set out in section 6.2, hospitalisation due to RTI is an expected outcome in a subset of the sample population, these **will not be subject to expedited reporting**.

The total rate of these expected SAEs will be collected as part of the study data set (Primary outcome 2) and reported by arm to the DMC prior to scheduled meetings. The DMC will raise any safety concerns to the CI, trial team and TSC for further action.

6.3.3 SAEs related to use of the intervention

If the GP practice champion or attending clinician suspects that an SAE resulted from use of the intervention it should be reported to the central research team immediately.

The causality of the event will be assessed by the practice clinician and a delegated clinician working within the central research team, If the event is deemed to be probably or definitely related to the intervention the SAE will be reported to the REC and sponsor according to the expedited timescales outlined in section 6.3.5. In instances where the practice clinician and central clinicians assessment of causality differs the practice clinician's assessment will take precedence.

6.3.4 Fatal SAEs

All practices should inform the central research team immediately of any fatal SAEs in children that had presented with RTI at a practice consultation, and were 0-9years old at the time of consultation. This applies to any deaths occurring within 90 days of the consultation. Practices will report the occurrence of a fatal SAE only at this time.

The central research team will immediately follow up reports of fatal SAEs in the intervention arm for further details. If the event is deemed to be related to the intervention the SAE will be reported to the REC and sponsor according to the expedited timescales outlined in section 6.3.5.

There will be no further details collected of fatalities in the usual care arm as these cannot be caused by use of the intervention and therefore will not be subject to expedited reporting. Fatalities are being reported in the usual care arm to provide context to the DMC for mortality rates during the trial.

The mortality rates will be reported by arm to the DMC prior to scheduled meetings. The DMC will raise any safety concerns to the CI, trial team and TSC for further actions to be discussed

6.3.5 Mandatory reporting information and timelines

Any SAEs that require expedited reporting must be documented on UHBristol's SAE reporting forms and faxed or emailed securely to the central research team and sponsor (or delegate) within 24 hours of the centre staff becoming aware.

For each reportable SAE the following information will be collected

- Full details in medical terms and case description;
- Event duration (start and end dates, if applicable);
- Action taken;
- Outcome;
- Seriousness criteria;
- Causality (i.e. relatedness to trial/intervention), in the opinion of the GP practice champion;

No pseudonymised or patient identifiable data should be captured on the SAE forms.

Each SAE must be reported separately and not combined on one SAE form. Any change of condition or other follow-up information relating to a previously reported SAE should documented on the appropriate SAE follow up form and faxed or emailed securely to the central research team and Sponsor (or delegate) as soon as it is available. Events will be followed up until the event has resolved or a final outcome has been reached.

Expedited reporting timelines

In the event of a fatal or life threatening and related SAE the CHICO trial team will report details to the REC and sponsor within **7 days** of the event being assessed as related to the intervention.

In the event of a non-fatal or non-life threatening and related SAE the central research team will report details to the REC and sponsor within **15 days** of the event being assessed as related to the intervention.

6.3.6 SAE Monitoring

Monitoring for SAEs will take place for the duration of the data collection phase and a further 90 days after this period to allow for the collection of information about any fatalities up to 90 days after consultation.

All practices will be prompted by the CHICO trial team every three months during their participation in the trial to remind practices to report any SAEs as above.

7 STATISTICS AND DATA ANALYSIS

7.1 Sample size calculation

Both sample size calculations assume 90% power and a conservative two-sided alpha of 0.025 to take account of the two co-primary outcomes. Both sample sizes also assume an intra-cluster correlation coefficient of 0.03 (suggested in discussion with Professor Sandra Eldridge, expert in cluster randomised trials and complex designs), an estimated coefficient of variation of 0.65 (to take account of differences in cluster size) and an assumption of 750 children aged 0-9 years registered per practice (based on Bristol & Bath CCG data). For the overall sample size we will need to recruit 310 practices, 155 practices for the intervention and 155 as controls.

7.2 Antibiotic Dispensing Efficacy

The first primary outcome will be child antibiotic dispensing rate. This will be the number of amoxicillin and macrolide oral suspension prescriptions dispensed over a 12 month period per practice divided by the number of children aged 0-9 years in that practice. From our cohort study of 8300 children presenting with acute cough and RTI between 2010 and 2012, 37.2% were given delayed or immediate antibiotics. Annual data from the RCGP in 2011 also suggest 36750 (36.8%) prescriptions per 100,000 children presenting with cough aged 0-14 years were given for Amoxicillin and Macrolides. More recent data from Bristol CCG in 2016 suggest that of 7295 children recorded in their notes as having cough, 2431 received a prescription for amoxicillin suspension (33 prescriptions per 100 children in that year). Assuming a dispensing rate of 33 prescriptions per 100 presentations a reduction to at least 29 prescriptions per 100 presentations will have an impact in reducing antimicrobial resistance, especially as the larger denominator of all children aged 0-9 years in the practice will tend to mute any effect. These assumptions suggest 3317 children would be needed per arm and this would need inflating by a factor of 23.47 for the clustering and a further 1.35 for variability in cluster size. Assuming 750 children at each practice we would need 140 practices per arm of the trial.

7.3 Equivalence in hospitalisation rates

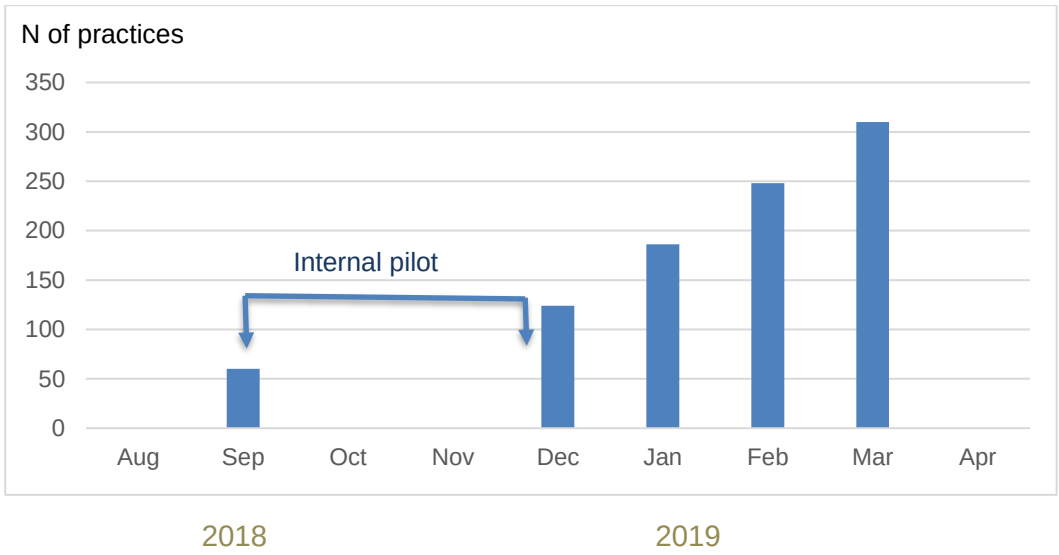
From our cohort study of 8300 children presenting with acute cough and RTI between 2010 and 2012, 0.9% were admitted to hospital for their RTI over the 30 day period. Assuming a hospitalisation rate of 1% amongst 0-9 year olds and defining equivalence as being within 1% of this estimate we would need 3666 children per arm which after inflation. This suggests 155 practices would be needed per arm of the trial. Should recruitment and data retrieval from practices prove reasonably straightforward, we will seek approval to recruit further practices whilst keeping within the funding awarded, so that we would be powered to exclude a smaller increase in hospitalisation rate.

Given each CCG has between 10 to 70 practices, we will choose those CCGs that have practices predominantly using the EMIS system expecting around 50% to participate in the trial. We will approach 20 CCGs in the first instance (more if needed) to achieve these numbers using a staggered approach to achieve the desired levels of participation

7.4 Planned recruitment rate

Recruitment will be staggered. We will approach 4 CCGs at a time (20 in total) to provide on average of around 15-16 practices per CCG, further CCGs will be approached if necessary. Data collection will begin in September 2018 at 60 practices which will be used as an internal pilot. Subsequently we will approach at least 4 more CCGs per month and start data collection in each month from December 2018 until we have randomised 310 practices. (Figure 2)

Figure 3: Recruitment rate of practices to the CHICO RCT



Data will be collected from each practice for a 12-month period. There are over 200 CCGs in England, we are initially approaching 20 of these for the study but will approach more if recruitment is proving difficult.

7.5 Internal pilot

An internal pilot phase lasting 3 months and using 4 CCGs will help establish best practice for recruiting and communicating with practices before widening to the remaining CCGs

The internal pilot is primarily designed to verify that recruitment is possible, and we will make a decision about feasibility after the first three months of the data collection phase. The internal pilot will be conducted in the first 3 months of the data collection phase (from September to November 2018). This will involve 60 practices, 4 CCGs and relevant outcome data from the first month of data collection (given the one to two month time lag to capture routine amoxicillin data for the required time period).

7.5.1 Objectives of the internal pilot trial

Since the intervention will be embedded within electronic records systems we will be able to monitor adherence (and the practice champion feeding back intervention adherence will be part of the intervention). We will implement protocols which automatically code clinician's actions when the within consultation trigger is initiated. This will enable us to monitor adherence; how often the trigger appears, and how clinicians respond to the trigger identifying rates of use. The acceptability of the intervention will be explored further in qualitative interviews. We will conduct clinician interviews during the pilot phase to investigate acceptability. We will purposefully select

clinicians and champions from practices with differing intervention use rates, to understand processes underlying observed adherence rates.

7.5.2 Internal Pilot Areas of Assessment

This will include:

i) The number of eligible practices within the 20 CCGs already approached and whether at this stage we need to approach further CCGs to increase the number of practices in the study.

ii) The recruitment rate of eligible practices within the 4 CCGs in the pilot phase, again as an indicator of whether we need to approach further CCGs

iii) The recruitment of practice champions, a focus on their role and how we maximise strategies to encourage use of the intervention.

iv) The efficiency of embedding the intervention in practice systems and resolution of any barriers or delays.

v) The number of times the intervention is used between practices and over time.

vi) The timeliness of the primary outcome data and consistency of format between CCGs.

vii) The timeliness of the secondary outcome data and consistency of format between CCGs.

7.5.2.1 Stop/Go assessment

A steering committee meeting will be arranged at the end of the internal pilot phase to discuss these findings using traffic light criteria (see Table 4) to address whether specific issues that arise mean that we can continue with the trial as planned (green), we need to implement remedies and assess (amber) or consider a further pilot or stopping the trial (red). There will be 4 stop/go criteria. Our progression criteria at the pilot stage are based on:

i) The percentage of practices recruited against the initial practice target of 60.

ii) The percentage of GP practices with a named practice champion

iii) The percentage of intervention GPs/nurses using the intervention at least once. (The pilot will be conducted during the summer and data collected over a one month period so we expect half of the clinicians in any one practice to have seen at least one eligible patient – this is the denominator we will use)

iv) The percentage of antibiotic dispensing data we can obtain for each practice.

We anticipate that data on hospitalisations will only be available after several months, but routine dispensing data should be available after one month

Table 4. Stop / go criteria for the Internal pilot

Criteria (all must be met, failure of one or more triggers action)	Proposed action
≥80% or 48+ practices recruited ≥80% or 48+ practices naming a champion ≥80% of GPs/nurses using the intervention ≥90% or 54+ practices we can obtain antibiotic dispensing data	Continue as planned
70-79% or 42-47 practices recruited 70-79% or 42-47 practices naming a champion 70-79% of GPs/nurses using the intervention 80-89% or 48-53 practices we can obtain antibiotic dispensing data	TSC and HTA discuss problems with the TMG and implement remedies
<70% or <42 practices recruiting <70% or <42 practices naming a champion <70% of GPs/nurses using the intervention <80% or <48 practices we can obtain antibiotic dispensing data	Discuss plans with TSC and NIHR HTA. Consider further pilot or stopping trial.

A dashboard with red/amber/green thresholds has been agreed to help whether the internal pilot should proceed to the full trial. Achieving all green targets would almost certainly mean proceeding to the full trial; whereas achieving predominantly red targets would almost certainly indicate that a full-scale RCT is not feasible.

7.6 Statistical analysis plan

All analyses and reporting will be in line with CONSORT guidelines and its extension for cluster randomised trials. Primary analyses will be conducted on an intention-to-treat (ITT) basis. A full CHICO statistical analysis plan will be developed and agreed by the Trial Steering Committee prior to undertaking analyses of the main trial. All outcomes will be described and compared with the appropriate descriptive statistics where relevant: mean and standard deviation (SD) for continuous and count outcomes, medians and inter-quartile range if required for skewed data and numbers and percentages for dichotomous and categorical outcomes. The statistical analysis plan will include a health economics analysis plan as a subsection.

7.6.1 Summary of baseline data and flow of participants

Descriptive statistics will be used to summarise characteristics of practices and patients and compare baseline characteristics between groups. Means and standard deviations will be used for continuous and count outcomes or medians and inter-quartile range if required for skewed data. Categorical variables will be summarised using frequencies and proportions. Baseline variables to be explored are those described in section 5.5.

7.6.2 Primary outcome analysis

The co-primary outcomes will be the rate of amoxicillin and macrolide oral suspension antibiotics dispensed by the number of children (aged 0-9 years registered at the start of the designated period) at each practice over a 12-month period along with the number of hospitalisations amongst these children for RTI using the same denominator. Significance will be at the 2.5% level for these two co-primaries (although given we need both conditions to be positive to proceed this is a conservative approach).

Depending on the dispersion of the data we may use linear regression or a random effects Poisson regression (negative binomial regression) model to analyse both of these co-primaries. This has the advantage of incorporating person/years follow up (number of children at a practice multiplied by the length of follow-up for that practice) and examining clustering by practice. For our other co-primary outcome, we have previously shown a hospital admission rate in children with acute cough and RTI is 0.9% (78 children from a cohort of 8394 children presenting). We assume that a difference of no more than 1% between arms of the trial is reasonable to suggest equivalence. The dispensing record of the practices in the 12 months prior to randomisation will be used as a minimisation variable and thus balance the dispensing records at baseline. This will be adjusted for in the primary analysis to resolve any residual difference.

7.6.3 Sensitivity analyses

A per protocol analysis will be utilised if there are non-compliers in the intervention arm, compliance will be defined in the statistical analysis plan prior to analysis.

Small elements to the CHICO intervention were adapted during the pilot phase of the study, such as the generation of an FAQ document, therefore the treatment effect will be assessed without the pilot data to see whether the modifications impacted the effectiveness.

For hospitalisation and A&E data, we are aware that diagnosis codes are sometimes missing. Therefore, we will collect data on the number of “diagnosis missing” hosp/A&Es as well as the total number of hosp/A&Es. Using the proportion of LRTI attendances out of those with a diagnosis we can then deduce what proportion of “diagnosis missing” attendances are likely to be LRTI related and include these in a sensitivity analysis.

For dispensing data, we are also collecting amoxicillin and macrolide items where the age is missing. We will include these as part of the 0-9 total in a sensitivity analysis.

Other baseline characteristics between practices will be examined to ensure randomisation has provided the two pathways with patients that are comparable on equal terms. Any differences in excess of 0.5 SDs or 10% or more will be controlled for in sensitivity analyses to ensure that the imbalance does not affect the overall result. If it does, then both the adjusted and unadjusted results will be quoted in future reports and papers.

The effects of missing data will be explored using sensitivity analyses. We anticipate no more than 10% missing data and anticipate that it will be missing at random. We will follow recommendations by the European Medicines Agency (EMA/CPMP/EWP/1776/99 Rev 1.) and adopt appropriate methods depending on the missing data mechanisms, e.g. Multiple Imputation for Chained Equations for data missing at random (MAR). Other imputation techniques will be explored, and we can also compare complete case analysis versus indicator variable method depending on what is intended. The pattern and extent of missing data will be explored and any changes to the methods described in the analysis plan will be fully justified in the study report and publication. We will collect baseline data from practices before randomisation. A random seed will be pre-specified in the analysis plan. All quantitative data will be analysed using STATA.

7.6.4 Secondary outcome analyses

Secondary outcome analyses include comparing ED attendance (S1) between arms of the trial to help interpret any differences in hospital admission (P2), health economic analyses (S2),

specific subgroup analyses (S3 to S6) of the primary outcomes, exploration of the intervention usage over time and its influence on dispensing rates (S8) and qualitative analyses (S9) all of which are all detailed below. The primary outcomes will analysed for each 5-year epochs to see if the intervention effect differs in the age groups (S7). This will be two separate analyses as this separates patients within practices, rather than separating practice (allowing an interaction).

7.6.5 Subgroup analyses

Subgroup analyses will be carried out for both dispensing rates (P1) and hospital admission rates (P2) Formal tests of interaction between the potential effect modifiers and treatment pathway will be carried out to test whether treatment effect differs between the different sub groups. The potential effect modifiers are proportion of locums used (S3), dispensing rates in 2017 (S4), whether using clinicians other than GPs (S5) and whether the practices have one or multiple sites (S6).

7.6.6 Adjusted analysis

Differences between the arms at baseline will be investigated and anything in excess of 0.5 standard deviations or a difference of 10% or more will be controlled for in a sensitivity analysis of the primary outcome models.

7.6.7 Planned further exploratory analyses

The trajectory of dispensing rates at different practices over the years prior to the RCT will be explored to examine the impact of AMR campaigns over this time period and whether this influences dispensing rates collected for the primary outcome of this trial. Practices will be asked, in a questionnaire, if their practice includes children taking part in a flu vaccination programme. This variable, and its effect on the primary outcomes, may be explored.

7.6.8 Proposed frequency of analyses

The main analysis will be performed when 12 months of data have been collected and cleaned from all randomised practices (between May and October 2020). The Data Monitoring Committee (DMC) will review accumulating data with the help of the study junior statistician at their discretion. The DMC will report to the Trial Steering Committee.

7.6.9 Planned Interim analysis

There are no planned interim statistical analyses for this study.

7.7 Procedure(s) to account for missing or spurious data

The primary analyses will be based on the observed data and a sensitivity analysis will be conducted where missing data are imputed using appropriate methods based on patterns of missingness.

Data will be entered promptly into a study database and data validation and cleaning will be carried out throughout the trial. Where spurious data are observed, values will be checked against paper and/or online records

7.8 Qualitative analysis

Interviews will be transcribed and anonymised. Analysis will begin shortly after data collection starts and will be ongoing and iterative. Analysis will inform further data collection: for instance,

analytic insights from data gathered in earlier interviews will help identify any changes that need to be made to the topic guides during later interviews. Qualitative analysis of the transcripts will follow recognised thematic analysis procedures using NVivo software. Thematic analysis, [42] utilising a data-driven inductive approach, [43] will be used to scrutinise the data in order to identify and analyse patterns and themes of particular salience for participants and across the dataset. [44] Transcripts will be coded, and global themes developed from the codes. Two researchers will code a sample of transcripts independently and compare the coding; any discrepancies will be discussed within the research team and resolved in order to achieve a coding consensus and to ensure robust analysis.

7.9 Health Economic evaluation

The health economic analysis will comprise a between-arm comparison of NHS costs. We do not anticipate a significant between-arm difference to emerge, but the proposed analysis will allow costs in each arm to be quantified, and the respective contribution of different types of cost to be measured. Measured costs will comprise the costs of the intervention itself, dispensed amoxicillin and macrolide medications, ED attendance, and hospital admissions for RTI.

The costs associated with the intervention will be based on non-research related costs associated with software development, integration into EMIS, roll out to practices, and training time in its use. We will value dispensed medication using data from the BNFePACT (Electronic Prescribing Analysis and Cost) system, which will be provided by participating CCGs. We will value GP consultation time using the unit costs published by the Personal Social Services Research Unit. [25] We will value secondary care resource use (ED attendance and admissions) using NHS Reference Costs.

We will explore whether use of the intervention increased mean duration of GP consultations in the intervention arm compared to control arm. It is conceivable that the intervention could extend duration due to the time taken to engage with the algorithm, but it is also plausible that consultations could be shorter if its use brings consultations to an efficient conclusion more quickly than would otherwise be the case.

We will use evidence from two sources to characterise the relationship between consultation length and NHS costs. First, in qualitative interviews, following purposive sampling, we will ask a small number of clinicians to describe the impact that the intervention had on the consultation duration, both in the initial stages of its use and toward the end of follow-up to capture any increased efficiencies in algorithm use that may have occurred over the course of the trial.

Second, for consultations with a relevant respiratory problem coded in the notes for a child of eligible age, we will extract data on consultation duration at intervention and comparator practices. This will be performed for those practices for which these data are accessible by the local CCG, which may be a subset of all included practices. We will work with CCGs to explore ways to obtain data on duration for children aged 0-9 at the time of consultations within the study period, rather than those children aged 0-9 at the time at which the CCG query script is run. Data on consultation duration extract in this way is also likely to be imperfect for a number of reasons, including incomplete coverage of all practices, the distinction between appointment and consultation times, and consultations of unusually long or short duration. The latter issue was encountered in the feasibility trial, and data cleaning rules were used to calculated average consultation duration.

However, it is plausible that any discrepancies between recorded and actual duration will be similar between arms. The data will allow an approximate estimate of difference in consultation duration to be obtained. We will seek to cost any changes in the duration of consultations using nationally representative sources of unit cost data such as the Personal Social Services Research Unit. [45]

8 DATA HANDLING

8.1 Data collection tools and source document identification

Data will not be collected directly from the patients or carers. Data collected in this study is summarised in section 5.1

A brief questionnaire will be sent to each practice to collect data on the characteristics of all practice (intervention and controls) and to report (via the practice champion) the use of the intervention tool (intervention only).

Dispensing data collected routinely every month by CCGs on each practice in the study will be tailored to our needs (amoxicillin and macrolide liquid suspension given to children aged 0-9 years) and entered onto the study database both for the 12 month period each practice will be in the study and the 12 month prior to randomisation (for both stratification purposes and analysis of a secondary outcome). Routinely collected data from the practice, collected via the relevant CCG on hospital admissions for children with respiratory related illnesses will also be collected and entered onto a database along with data on ED attendance.

8.2 Data handling and record keeping

Data will be collected and retained in accordance with the UK Data Protection Act 1998.

8.2.1 Main study data

Only fully anonymised data sets will be sent from the GP practices and CCGs. This will be sent to a secure university e-mail address. Data will be entered onto a purpose designed database and data validation and cleaning will be carried out throughout the trial. Standard operating procedures (SOPs) for database use, data validation and data cleaning will be available and regularly maintained.

Access to the database will be via a secure password-protected with access restricted to university personal qualified by experience and training. Study data transferred electronically between the University of Bristol and the NHS will only be transferred via a secure NHS net network in an encrypted form.

Data are stored in a secured UoB server subject to standard UoB security procedures. The full database is backed up daily. A disaster/recovery plan is in place as part of the SLA we have with IT Services.

8.2.2 Embedded Qualitative study

Participant's names and work contact details, along with the pseudonyms used for interview, will be stored on a secure password protected University network filestore space where access will be limited to the members of the research team involved in the interviews.

Interviews will be digitally audio recorded using University of Bristol approved encrypted digital recorders. Encrypted recordings will be uploaded to the University network filestore space and from there they will be transferred to the University approved transcription company via the secure file uploading feature of their website.

8.3 Access to Data

8.3.1 Source data

For monitoring purposes, the CI will allow monitors from the sponsor (or delegate), persons responsible for the audit, representatives of the REC and of the Regulatory Authorities to have direct access to source data/documents.

8.3.2 Anonymised trial data

The Senior IT Manager (in collaboration with the Chief Investigator) will manage access rights to the data set. Prospective new users must demonstrate compliance with legal, data protection and ethical guidelines before any data are released. We anticipate that fully anonymised trial data will be shared with other researchers to enable international prospective meta-analyses.

8.4 Archiving

This trial will be sponsored by UoB, the data custodian will be the CI or someone nominated from the research team. All anonymised research data will be kept indefinitely in line with RCUK policy on open access. Non-essential study documentation will be deleted at the end of the study. All essential study documentation will be retained in a secure location during the conduct of the study and for 5 years after the end of the study in line with University archiving policy, after which these essential documents will be destroyed.

8.5 Data sharing

Data will not be made available for sharing until after publication of the main results of the study. Thereafter, anonymised individual patient data will be made available for secondary research, conditional on assurance from the secondary researcher that the proposed use of the data is compliant with the MRC Policy on Data Preservation and Sharing regarding scientific quality, ethical requirements and value for money. A minimum requirement with respect to scientific quality will be a publicly available pre-specified protocol describing the purpose, methods and analysis of the secondary research, e.g. a protocol for a Cochrane systematic review.

9 TRIAL MANAGEMENT

The trial is supported by the Bristol Randomised Trials Collaboration (BRTC) unit. The BRTC is a UK Clinical Research Collaboration registered Clinical Trials Unit. The trial will conform to the BRTC standard operating procedures. The central research team will prepare all the trial documentation and data collection forms, specify the randomisation scheme, develop and maintain the study database, check data quality as the trial progresses, monitor recruitment and carry out trial analyses in collaboration with the clinical investigators

9.1 Day-to-day management

The trial will be managed by a Trial Management Group (TMG), which will meet face-to-face with optional skype/teleconference linkage. The TMG will be chaired by the Chief Investigator and will include all available members of the named research team (see Co-investigator details) as well as the trial co-ordinator, trial administrator, junior statistician and junior qualitative researcher when available.

An appropriately qualified person by training will be responsible for identifying potential trial practices, randomising practices, collecting trial data and ensuring the trial protocol is adhered to.

9.2 Trial Oversight

Serious dverse events will be documented and reported to the DMC and TSC and in accordance with University of Bristol's Service Level Agreement (SLA) with UH Bristol who manages SAE reporting on behalf of the University. For that reason all SAEs must be recorded and reported to UH Bristol, in accordance with UH Bristol Research Safety Reporting Standard Operating Procedure. UH Bristol will regularly inform the University about SAEs. Expedited reporting takes place where necessary to agree corrective or preventative actions.

9.3 Principal Investigator

This is not a multicentre study so there are no Principal investigators. Each of the 155 intervention practices will have a practice champion who will encourage the use of the intervention and co-ordinate feedback of how much the intervention is used.

9.4 Chief Investigator

The chief investigator will be responsible for:

- Arranging clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk/benefit with the clinicians available in the team.
- Arranging for medical judgement in assigning seriousness, causality and expectedness of SAEs where it has not been possible to obtain local medical assessment with clinicians in the team.
- Arranging with clinicians in the team medical judgement in assigning expectedness.
- Immediate review of all reportable SAEs.
- Ensuring safety reports are prepared in collaboration with appropriate members of the TMG group for the main REC and DMC.

- Reporting safety information to the independent oversight committees identified for the trial (DMC and TSC).
- Expedited reporting of SAEs to the REC within required timelines.
- Central data collection of SAEs.

9.5 Sponsor

The sponsor will be responsible for overall oversight of the trial.

9.6 Trial Steering Committee (TSC)

The Trial Steering Committee has an independent Chair, GP and Clinical Academic Hazel Everitt (Associate Professor at the University of Southampton). The committee includes an independent statistician (Dr Beth Stuart from the University of Southampton), a second Clinician (Professor Gail Hayward from University of Oxford)] and two PPI representatives.. Meetings have been pencilled in every 6 months but the frequency will be decided at the first meeting in March 2018.

At the first TSC meeting, the committee will agree on its terms of reference.

9.7 Data Monitoring Committee (DMC)

The Data Monitoring Committee will consist of three independent members which will be nominated in 2018 prior to any data collection activity according to NIHR research governance guidance..

At the first DMC meeting, the committee will agree on its terms of reference and agree the frequency in which to meet. The DMC will receive and review reports on the data accruing to this trial and make recommendations on the conduct of the trial to the TSC.

10 MONITORING, AUDIT AND INSPECTION

The study will be monitored and audited in accordance with the Sponsor's policy, which is consistent with the UK Policy Framework for Health and Social Care Research. All study related documents will be made available on request for monitoring and audit by the sponsor, the relevant REC and for inspection by other licensing bodies.

All UoB studies that are registered on the Research Governance system will be eligible for monitoring by an independent service provider [an SLA is in place with UH Bristol to provide this].

Compliance with the ICH GCP guidelines for monitoring is often interpreted as requiring intensive site monitoring. However, "the extent and nature of the monitoring should be proportional to the objective, purpose, design, size, complexity, blinding, endpoints and risks of the study." (ICH GCP, section 5.18.3).

Studies sponsored by UH Bristol will have a monitoring plan set up for them by the sponsor after the risk assessment has been completed.

The sponsor would delegate some of the monitoring to the central research team. The following checks would be typical:

- that data collected are consistent with adherence to the study protocol
- that CRFs are only being completed by authorised persons
- that SAE recording and reporting procedures are being followed correctly
- that no key data are missing
- that data are valid
- review of recruitment rates, withdrawals and losses to follow up.

11 ETHICAL AND REGULATORY CONSIDERATIONS

11.1 Research Ethics Committee (REC) review and reports

Ethical and Health Research Authority (HRA) approval will be sought through the HRA for the trial and the qualitative work embedded within the trial. We believe the proposed research does not pose any specific risks to individual participants nor does it raise any untoward ethical issues. Ethics review of the protocol for the trial and other trial related essential documents will be carried out by a UK Research Ethics Committee (REC). Any amendments to these documents, after a favourable opinion from the REC/HRA has been given, will be submitted to the REC/HRA for approval prior to implementation.

All correspondence with the REC will be retained in the Trial Master File (TMF)/Investigator Site File (ISF). An annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. The CI will notify the REC of the end of the study and if the study is ended prematurely (including the reasons for the premature termination). Within one year after the end of the study, the CI will submit a final report with the results, including any publications/abstracts, to the REC.

Study specific training activities will be carried out to ensure that the rights, safety and wellbeing of research participants are protected, and that research data are reliable. Members of the research team will be qualified by education, training or experience.

11.2 Risks and Benefits

As with all trials the main benefit of participating is an altruistic one to improve care for subsequent children requiring these interventions.

As the trial is assessing a clinician-based behavioural intervention and participants are attending for a routine consultation with a clinician the risk of harm to the participant is minimal. It is the choice of the recruiting clinician as to whether the participant is treated or not for their cough. Subsequent hospitalisation after consultation is a known outcome for a small proportion of these patients (around 1%). The intervention itself will be assessed as to whether the components of the intervention could potentially increase hospitalisations by virtue of reducing antibiotic prescribing

11.3 Ethical Issues

We are not recruiting individual patients to this study and the primary outcome data are already collected routinely thus we do not need patient consent. We will consent the individual practices and encourage that all clinicians in the intervention practices use the intervention tool appropriately. The intervention is directed at the clinician primarily to change their prescribing behaviour. Any data collected from individual clinicians will be anonymised. The personalised letter given to the patients will not contain information on risk of hospitalisation, but rather details of the consultation and the usual safe-guarding information

11.4 Risks and benefits for trial participants and society

If the intervention works, the main benefit will be a reduction in antibiotic prescribing amongst one of the largest groups currently using antibiotics despite NICE recommendations not to. The

only risk we anticipate is the potential for increased hospital admission which will be monitored as a primary outcome of this trial.

11.5 Obtaining informed consent from participants

The CHICO RCT falls under the remit of draft guidance [46] for 'simple and efficient trials' due to the nature of the intervention and the low level of risk involved for patients. In such trials, "consent procedures should always be proportionate to the nature of what is proposed, the risk of the research and the ethical issues at stake." As such, we believe the CHICO algorithm RCT design meets the following suggested principles provided by NHS Health Research Authority (HRA) [47] where simplified consent procedures may be used:

1. Following the normal consent process would place a disproportionate burden in terms of time and resources in relation to the perceived risk, as well as exposing the trial to the risks of post-differential recruitment bias.
2. The study involves little deviation from usual care
3. Research risks are no greater than those involved in standard care/not greater than minimal
4. The use of simplified means to obtain consent does not adversely affect the right of welfare of study participants
5. Healthcare professionals have the option of using an intervention other than the one assigned if they believe doing so is important for a particular patient.

The proposed methods for providing information and gaining consent for the CHICO RCT meet those stated as acceptable in an example 'consent scenario' provided in the HRA guidance [52 scenario 346 (pg. 14)]. The illustrative scenario is a cluster randomised trial (GP surgery level) where patients are not asked to provide consent, but rather their consent is 'deemed', unless they opt-out.

There is currently uncertainty around the effectiveness of the CHICO intervention (hence, the need for this research), but patients will not be subjected to any greater risk than, or deviation from, standard care. The intervention is aimed at clinicians and the interaction between clinicians and parents, rather than at patients per se, and as such, it is a mechanism of potentially assisting the clinical decision-making process. We therefore propose consent for participation is gained at the practice level. This approach means that all patients within a consented practice would be included (anonymously), therefore avoiding biases associated with participant selection for inclusion in clinical trials.

Our proposed method of collecting data is already taking place in GP practices registered with research databases such as the Clinical Practice Research Datalink (CPRD) and QResearch. The CHICO RCT is proposing the same methods, and although patients will not be giving individual consent to take part, practices will be asked to notify patients via posters and notices (for example in practice newsletters), that the research is being conducted, in line with their existing participation in routine dataset research. These issues will be discussed with the Patient and Public (PPI) group to establish an understanding of, and best way to present, these methods.

Draft guidance issued by the NHS HRA states that while neither written study information nor participant consent is legally required for a non-drug trial, it is usually considered good practice. As such, the proposed study will ensure that all staff at recruited practices are aware of the trial

and are able to provide patients with verbal information if requested. As well as this, a study poster advertising the GP practices participation in the trial will be displayed in patient waiting rooms. The poster will display a trial web address and contact details of the research team will be provide if a patient wished to find out more about the trial or ask any questions. We cannot offer 'opt-out' as the routine data is collected anyway.

11.6 Retention of data

No personal data will be collected or retained during this study.

11.7 Peer review

The proposal for this trial has been peer-reviewed through the NIHR HTA peer-review process, which includes independent expert and lay reviewers.

11.8 Public and Patient Involvement (PPI)

This intervention has been developed collaboratively with our parent advisory group (PAG) and clinical advisory group (CAG) throughout the TARGET programme. Their comments and suggestions about the format of the intervention and parent/carer materials have informed both the intervention and the design of the earlier feasibility study.

Similar involvement will be sought for the trial. We will seek agreement from a newly formed PAG to meet throughout the study, allowing the investigators to report on progress of the study and discuss issues that arise during the study. PAG members will input into all the materials for parents/carers as they are further developed including any patient-facing tools. We will also form a clinician and pharmacist advisory group (CPAG) to assist with the implementation and any further refining the intervention. They will meet once in person and then contribute by Skype or email to refine GP information and intervention delivery.

11.9 Regulatory Compliance and Research governance

This study will be conducted in accordance with the UK Policy Framework for Health and Social Care Research

Any amendments to the trial documents must be approved by the sponsor prior to submission to the REC.

Before any site can enrol patients into the trial, the CI/PI or designee will obtain confirmation of capacity and capability for each site in-line with HRA processes.

For all amendments the CI/PI or designee will confirm with the Sponsor, the HRA (+/- REC) and sites' R&D departments that permissions are ongoing.

11.10 Protocol compliance

There will be no prospective, planned deviations or waivers to the protocol. Accidental protocol deviations can happen at any time, but they must be adequately documented on the relevant forms and reported to the CI and Sponsor immediately. Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

11.11 Notification of Serious Breaches to GCP and/or the protocol

A “serious breach” is a breach which is likely to effect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial; or
- the scientific value of the trial

The sponsor must be notified immediately of any case where the above definition applies during the trial conduct phase. They will assess the seriousness of any breach as per the appropriate SOP.

11.12 Data protection and patient confidentiality

The University of Bristol (UoB) will be the data custodian. All data held in Bristol will conform to UoB’s Data Security Policy and in Compliance with the Data Protection Act 1998.

No personal data (e.g. name and address, or any data from which a participant might be identified) will be collected in this study. The data collected from EMIS will be anonymised. Data relating to the characteristics of the individual practices (E.g. How many patients registered? Number and types of clinician etc.) will be collected on paper forms.

Data obtained by paper will be entered onto and maintained on an SQL Server database system maintained by UoB Information Services.

Interviews will be recorded on an encrypted digital recorder which will be locked in a secured cabinet at the Department of Population Health Sciences. Recordings will be transferred onto a computer as soon as possible after each interview and stored only in a password protected drive maintained by the UoB. Only the qualitative researchers working on this study will have access to this drive.

Recordings and transcriptions will be named with a study-assigned participant number, centre initials, and the date of recording. There will be no participant identifiers in files, databases, or transcripts, which will only be labelled with study assigned participant numbers. All recordings will be securely transferred to a University of Bristol approved transcription company or transcriber that has signed the required confidentiality agreements. All transcripts will be anonymised upon receipt.

All electronic data files will be saved in a secured computer and to a password protected University of Bristol network space, in accordance with the University of Bristol’s data security policies.

As in line with RCUK policy all anonymised research data will be kept indefinitely for open access. All nonessential data will be wiped upon completion of the study. Essential study documents will be kept for up to 5 years, after which they will be deleted and all copies destroyed in accordance with the UoB’s secure erasure of data policy.

11.13 Financial and other competing interests

The research team must disclose any ownership interests that may be related to products, services, or interventions considered for use in the trial or that may be significantly affected by the trial. Competing interests will be reported in all publications and in the final report.

11.14 Indemnity

Indemnity for patient clinical care is subject to GP practices usual arrangements. The university of Bristol has arranged Public Liability and Professional Negligence insurance in respect of its responsibilities.

11.14.1 Amendments

The Sponsor will determine whether an amendment is substantial or non-substantial. All amendments will be processed through the HRA and where appropriate the REC. If applicable, other specialist review bodies (e.g. CAG) will be notified about substantial amendments in case the amendment affects their opinion of the study. Amendments will also be notified to NHS R&D departments of participating sites to confirm ongoing capacity and capability to deliver the study.

11.15 Access to the final trial dataset

Anonymous research data will be stored securely and kept for future analysis. Members of the TMG will develop a data sharing policy consistent with UoB policy. Data will be kept anonymous on secure access computers, and access will be via written confidentiality and data sharing agreements (DSA) with the CI (or his appointed nominee), supervised by the CI with the involvement of other members of the research team. Post-trial this may involve the Bristol Data Service who will allow access according to our pre-specified criteria. Any request approved will be covered by a written DSA, detailing limitations of use, transfer to 3rd parties, data storage and acknowledgements. The person applying for use of the data will be scrutinized for appropriate eligibility by members of the research team. All requests will require their own separate REC approval prior to data being released. Data will not be released prior to analyses for purposes that might detrimentally affect the trial integrity

12 DISSEMINATION POLICY

A comprehensive plan for disseminating CHICO results will be developed by TMG. The outputs from this research will comply with the CHICO RCT publication policy and internationally accepted guidelines (CONSORT).

It is anticipated that the Protocol will be submitted to *BMJ Open* or *Trials*.

The results of the study will be published in the academic press and all GP practices will be offered a lay summary of the main findings of the study. We will disseminate the findings both at a primary care level via CCGs and national conferences as well as international conferences. Regardless of whether the intervention is effective or not we will provide evidence of the potential benefits or pitfalls of an efficiently designed trial; including the utility of routine data collection; the capacity to collect data through current practice systems and the effectiveness of using practice champions and progress feedback to encourage use of such interventions.

If the intervention is successful in terms of reducing antibiotic prescribing without increasing hospital admission rates and deemed acceptable to clinicians and patients, preparatory work will be made as to the potential for embedding the intervention into practice systems other than EMIS. As part of the trial we will have already conducted a scoping exercise to this end. In the recruitment of practices using EMIS (covers 53% of practices) via CCGs we will also contact practices using the two other main software systems; SystemOne (26% of practices) and INPS/Vision (20% of practices). We will investigate potential barriers of embedding our intervention into these systems and whether we can find a resolution. Ultimately, we want to provide an additional tool for clinicians that gives increased confidence in their own decision making and improves the consultation experience of the carers. The impact will be both at the individual level of improved advice regarding antibiotic use and at the population level in terms of a successful antimicrobial strategy to reduce unnecessary antibiotic use in one of the major user groups.

On completion of the trial a final report will be prepared for the Funder (NHR HTA) and once approved made publicly available on their website. The Funder needs formal notice in advance of all publications and the Funder, Sponsor and CTU need to be acknowledged within the publications.

13 TIMELINE

Ethical and sponsorship approval, staff recruitment and contact with the CCGs will be sought before the study begins. At least the first 6 months (March 2018 to August 2018) will be spent recruiting practices via the CCGs, appointing practice champions, using both the PAG and CPAG to refine the intervention and developing the study tools, database and website. The internal pilot will be conducted in months 7 to 9 from 60 practices in 4 CCGs, at least months 10 to 13 will be used for staggered recruitment of the remaining practices and CCGs. All practices will be involved in the study for a period of 12 months post randomisation.

The study will last for 45 months until November 2021.

14 REVISION HISTORY

The following revisions have been made to the CHICO protocol:

Version and Date	**Revision(s) made:**
V1.0, 29 Jan 2018	N/A
V2.0, 30 Apr 2018	- REC and ISRCTN number added to protocol - Synopsis and Section 2: Corrected S1 measure denominator - Section 3: Updated with intervention details - Section 6: Updated with safety section details following TSC and clinician advice
V3.0, 31 Aug 2018	- Section 3: Intervention details updated following intervention refinement with Clinician and Pharmacist Advisory Group and intervention testing
V4.0, 20 Apr 2020	- Title change for Principal Investigator - Affiliation change for a co-investigator - Start date changed to October 2018, end date removed. - Trial Flow Chart: Removal of months for activities - Trial Synopsis and Section 2: Alterations to some of the wording of the outcomes and addition of outcome (sub group). - Section 3: Clinical Research Networks (CRNs) added for recruitment of practices - Section 4: Additional exclusion criteria for ‘merging’ practices - Section 5: Addition of ePACT2 as a data source - Section 5 (Table 2): Timeline column for data collection removed - Section 5.4: Additional details on randomisation - Section 5.10: Minor changes to help practices install intervention - Section 7.6: Minor alterations to outcomes - Section 8.1: Clarification of baseline data, not 2017 for all - Section 13: Study duration amended to 45 months - Appendix: Trial Gannt chart removed

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