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University of BRISTOL

BRISTOL TRIALS CENTRE

Bristol Trials Centre (BRTC)

CHICO

The **CHI**ldren with **CO**ugh study

Statistical, Health Economic and Qualitative Analysis Plan

Version 1.0 (26/05/2021)

The following people have reviewed the analysis plan and are in agreement with the contents			
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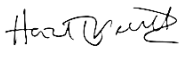
Hazel Everitt	TSC Chair		01/06/21
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ABBREVIATIONS/GLOSSARY

Abbreviation	Phrase
AE	Adverse Event
A&E	Accident and Emergency
Antib	Antibiotics
BRTC	Bristol Randomised Trials Collaboration
CCG	Clinical Commissioning Group
CHICO	Children's cough study
CI	Chief Investigator
CPAG	Clinician and Pharmacist Advisory Group
DMC	Data Monitoring Committee
eCRT	Cluster randomised trial using electronic health records
EMIS	Egton Medical Information Systems (electronic patient record system)
GP	General Practitioner
IMP	Investigational Medicinal Product
NIHR	National Institute for Health Research
PAG	Patient Advisory Group
PPI	Patient and Public Involvement
NHS	National Health Service
QoL	Quality of Life
RCT	Randomised Control Trial
SAE	Serious Adverse Event

AMENDMENT HISTORY

Date	Page	Description of change
02/05/19	6, 12	Additional sub group analysis, number of sites per practice
02/08/19	12, 18	Health economic outcomes/analyses added
08/08/19	11, 19	Qualitative outcomes/analyses added
19/11/19	6	Updated the protocol version (v3.0) and amended typos found by DMC
19/11/19	15	Section 4.2.1 and 4.2.2 were added (suggested by DMC and TMG)
19/11/19	11, 12, 18, 19, 24, 25	Sensitivity analyses amended: multiple imputation removed as considered unnecessary, described process of including 'missing' diagnoses Subgroup analyses amended: Directional hypotheses added, Number of sites added, flu vac added, 5-yr epoch removed (moved to secondary analysis). Secondary outcomes (pg 11) and tables (pg 24) were then altered to reflect these changes.
03/12/19	16	Section 4.2.3 was added (after discussion at a TMG)
13/03/19	All	New version created, incorporating previous comments
23/07/20	6, 13, 16, 20, 25, 26	New sensitivity and subgroup analysis to factor in Covid-19 issues and deprivation. Removal of flu vaccination sub-group analysis due to poor quality/missing data.
25/03/21	17	Based on a sample of 49 practices a suitable level of compliance was agreed.
25/05/21	12, 18, 19, 21	A few sentences added for clarification, as suggested by Beth Stuart (TSC). New "worst-case" sensitivity analysis added.

1. INTRODUCTION AND PURPOSE

This document details the rules proposed and the presentation that will be followed, as closely as possible, when analysing and reporting the main results from **CHICO**.

The purpose of the plan is to:

1. Ensure that the analysis is appropriate for the aims of the trial, reflects good statistical practice, and that interpretation of *a priori* and *post hoc* analyses respectively is appropriate.
2. Explain in detail how the data will be handled and analysed to enable others to perform the actual analysis in the event of sickness or other absence

Additional exploratory or auxiliary analyses of data not specified in the protocol are permitted but fall outside the scope of this analysis plan (although such analyses would be expected to follow Good Statistical Practice).

The analysis strategy will be made available if required by journal editors or referees when the main papers are submitted for publication. Additional analyses suggested by reviewers or editors will, if considered appropriate, be performed in accordance with the Analysis Plan, but if reported the source of such a post-hoc analysis will be declared.

Amendments to the statistical analysis plan will be described and justified in the final report of the trial.

1.1 MOTIVATION

There is clinical uncertainty around the correct diagnosis and management of respiratory tract infections (RTIs) in children. This has led to a large variation in antibiotic prescribing for the condition, fuelling the antimicrobial resistance threat that exists today.

A previous study, called TARGET, identified that it was this uncertainty regarding treatment that was the main driver of antibiotic prescribing. Clinician's felt that if 'low risk' patients could be easily identified it could allow greater confidence in withholding antibiotics. The TARGET study ran both a qualitative and quantitative study on over 8,300 children and used the information to predict hospital admittance in children presenting with RTI.

They used this prediction to generate an algorithm that identified children as low, medium or high risk of future hospitalisation. This provided clinician's with greater confidence in seeking the optimum treatment for their patient. When put into practice, in a feasibility trial, it was the control arm (who were not using the algorithm) that led to a lower antibiotic consumption rate. There were various possible explanations for this; 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. Learning from these lessons a more efficient trial was designed that would mitigate recruitment differential and be resource efficient and use routine data at the practice rather than patient level. This could also remove Hawthorne effects in the control arm.

2. SYNOPSIS OF STUDY DESIGN AND PROCEDURES

This is a summary of the study design as described in the study Protocol (version 3.0, 31st August 2018) with the single purpose of insuring an informed statistical analysis. For all other purposes reference MUST be made to the current version of the protocol.

The aim of the CHICO RCT is to reduce antibiotic dispensing amongst children (aged 0-9) presenting with cough or RTI without increasing hospital admission for this condition. It will be a clustered two-arm open label RCT of a complex intervention using routine data (i.e. an efficient design). As this is a novel trial design there may be additional hypotheses arising from it. Therefore, additional outcome measures are expected but will be highlighted as post-hoc analyses, with justification, in any future reporting.

2.1. TRIAL OBJECTIVES AND AIMS

2.1.1. PRIMARY CLINICAL OBJECTIVES

P1. Whether the CHICO intervention decreases the number of dispensed prescriptions for amoxicillin and macrolide antibiotics in children aged 0-9 (superiority comparison).

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

2.1.2. SECONDARY CLINICAL OBJECTIVES

S1. Whether the CHICO intervention results in no increase in the A&E attendance rates of children with a diagnosis of RTI.

S2. Whether any intervention effect is modified by the number of locums used

S3. Whether any intervention effect is modified by the amoxicillin/macrolide dispensing rate, over the 12 months prior to randomisation.

S4. Whether any intervention effect differs between practices with/without nurse prescribers.

S5. Whether any intervention effect differs between practices with 1 site versus multiple sites

S6. Whether any intervention effect differs within child age groups (0-4, 5-9).

S7. Whether any intervention effect differs in practices followed up during/after the Covid-19 pandemic (from March 2020)

S8. Where any intervention effect differs in areas of high/low deprivation

S9. Whether the intervention usage differs over time and its impact on the primary outcomes.

2.1.3. HEALTH ECONOMIC & QUALITATIVE OBJECTIVES

S10. The costs to the NHS of using the CHICO intervention.

S11. 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 this varies between practices.

2.2. TRIAL DESIGN AND CONFIGURATION

A cluster randomised trial utilising electronic health records (within EMIS), randomising practices to intervention and control according to their current list size and dispensing rates for children aged 0-9. The main outcome of antibiotic dispensing is designed as a superiority outcome while the secondary outcome is designed as a non-inferiority comparison. The cost implications and acceptability of the intervention will be assessed by a health economic and qualitative evaluation.

Two-arm trial:

Intervention: A short self-directed learning package for the clinician consisting of a prognostic algorithm to help predict those children at low, medium and high risk of hospital admission, both embedded into the existing practice EMIS system and a printout of the consultation for the parents.

Control: Clinicians from practices randomised to the comparator arm will just be asked to treat children presenting with cough or RTI as they normally would.

2.3 PILOT STAGE (STOP, GO CRITERIA)

An internal pilot phase lasting 4 months, using 7 CCGs helped establish best practice for recruiting and communicating with practices before widening to the remaining CCGs over the 6-month planned recruitment period (which was later extended).

The internal pilot was primarily designed to verify that recruitment was possible. The internal pilot ran from October 2018 to January 2019. The Stop/Go criteria are listed in the table below:

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.

Overall 49 practices were involved in the pilot phase of the trial and we could obtain 100% antibiotic dispensing data for these practices and a champion was named at each one. We could not be sure what percentage were utilising the intervention but we will be reporting this at the end of the trial.

2.5. ELIGIBILITY CRITERIA

2.5.1. 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).

2.5.2. 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.

2.6. DESCRIPTION OF INTERVENTION

The intervention consists of both a clinician-focused algorithm to predict hospitalisation for children with RTI and a carer-focused printout recording decisions made at the consultation and safety netting information. 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. The algorithm is to be used as one tool amongst many the clinicians already have to decide whether the child needs antibiotics, thus the 70% of children identified at very low risk of hospitalisation is just as important additional knowledge as the 1% identified at higher risk. The clinician will receive soft pop-up prompts when a child in the age-range is coming for consultation with harder prompts if a respiratory related illness is identified. A practice champion will be used to encourage all clinicians to use the intervention appropriately. Patients who attend the practice, despite not being registered there, will not have data on ‘history of asthma’ stored within the practice’s EMIS system. For safety, we will be asking practice champions to discourage use in unregistered patients (actioned in August 2019). The use of the intervention will be monitored. 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.

Patients in control practices will just receive usual care, with no embedded EMIS system.

2.7. RANDOMISATION PROCEDURES

Randomisation of practices is stratified by CCG and minimized by list size (high/low) and dispensing rate (high/low). When a CCG has agreed to take part, all practices using EMIS will be invited to confirm capability and capacity. Once a CCG is on board and ready to randomise some of its practices, the number of children aged 0-9 listed at the practice will be obtained. All list sizes within a CCG will then be split by the median (<median list size vs. ≥median list size) providing "high" and "low" size practices.

Amoxicillin and macrolide prescription items dispensed over the past 12 months for those aged 0-9, per month, will also be obtained, from ePACT2 (with a two-month lag). The total number of prescription items dispensed will be divided by the GP registered list size (of 0-9 yr olds) and this will be utilised in randomisation. The statistician will calculate this for every practice within the CCG and then split the by the median (≥median rate vs. <median rate) providing "high" and "low" dispensing rate practices, relative to other practices within their CCG. The statistician will keep these on file so that they are ready when each practice is recruited. They will not be shared with the trial team to ensure that practices cannot be 'cherry-picked' based on their characteristics and dispensing habits.

Randomisation will be carried out via the BRTC randomisation system. When a practice is eligible and provides consent to participate, the trial team will request the high/low categorisation for that practice from the statistician. These categories will then be used to randomise the practices. Practices within the CCG will be randomised to intervention and control, stratified by CCG and minimised by high/low dispensing and high/low list size. Practices can therefore be randomised, at any time, from any CCG.

2.8. SAMPLE SIZE CALCULATION

Both sample size calculations assume 90% power and a conservative alpha of 0.025, to take account of the two co-primary outcomes.

After discussions with Sandra Eldridge, a leading expert in cluster randomised trials (CRTs), the team chose an intraclass coefficient (ICC) of 0.03, which has been described as the upper confidence interval for ICCs in eCRTs[1] and used in previous antibiotic reduction CRTs[2]. This means that 3% of the total outcome variation can be explained by the variation between CCGs. Bristol and Bath CCG data provided us with an estimate of 750 children aged 0-9 per practice, giving an inflation factor of 1+0.03×(750-1)=23.47. Further to this the coefficient of variation of cluster sizes was estimated to be 0.65, requiring a 35% increase.

Bristol CCG data collected in 2016 revealed that the prescribing rates of amoxicillin were 33 per 100 children (33%). From routine CCG data we should be able to obtain dispensing prevalence

[1] Gulliford, M.C., van Staa, T.P., McDermott L. et al. 2014. Cluster randomized trials utilizing primary care electronic health records: methodologoical issues in design, conduct, and analysis (eCRT study).

[2] Hemming K, Eldridge S, Forbes G et al. 2017. How to design efficient cluster randomised trials. BMJ 2017;358:j3064

(amoxicillin and macrolides divided by the number of 0-9 year old children registered at each practice) as a crude marker for antibiotic prescribing. Based on these assumptions, the sample size required to detect an absolute reduction in dispensing rate of 4% (to 29%) is 280 practices[3].

The rate of hospital admission for RTI amongst children aged 0-9 years was estimated to be 0.9% based on our cohort study. Based on our assumptions the calculated sample size required to test whether hospital admissions are no worse in the intervention arm by more than of 1% is 176 practices. However, the trial team decided to err on the side of caution and consider it as a two sided test; requiring 310 practices[4].

2.9. BLINDING AND BREAKING OF BLIND

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.

The senior statistician will be blinded to the different arms of the trial when overseeing the main analysis, although the junior statistician will have access to this information to be able to report to the Data Monitoring Committee (DMC) and monitor hospitalisations.

2.10. TRIAL COMMITTEES

CHICO has a Trial Steering Committee chaired by, 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.

Reporting to that committee is an Independent Data Monitoring Committee, chaired by Jill Mollison of Oxford University. The DMC will have access to unblinded trial data.

[3] STATA: power twoproportions 0.33 0.29, power(0.9) alpha(0.025) = 3317, (3317×23.47×1.35)/750=140 practices per arm

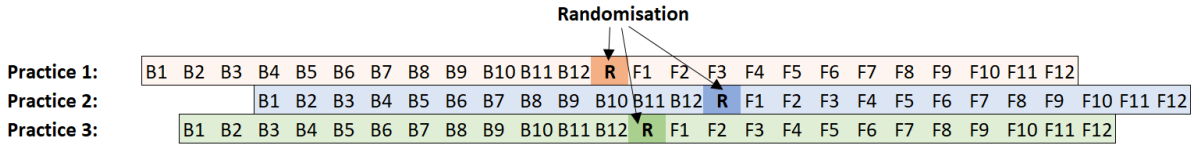
[4] STATA: power twoproportions 0.01 0.02, power(0.9) alpha(0.025) = 3666, (3666×23.47×1.35)/750=155 practices per arm

2.11. INTERIM ANALYSIS

There are no planned interim statistical analyses for this study.

2.12. DATA COLLECTION

A brief questionnaire will be sent to each practice to collect data on the characteristics of all practices prior to randomisation and at the end of the study. The number of dispensed prescription items for amoxicillin and macrolide antibiotics, for children aged 0-9Y, is reported monthly by the NHSBSA ePACT2 system (https://www.nhsbsa.nhs.uk/epact2). The research team will collect this every few months, in order to report to the Data Monitoring Committee. We will collect data for the 12-month period each practice will be in the study (F1-F12) and the 12-month period prior to randomisation (B1-B12). Our 'implementation period' will allow time for the practices to install the intervention and encourage staff to use it. Any data collected during this period will not be used in the analysis. This will normally be during the month of randomisation; however, this may be longer if the practices need more time to get ready.



For the same 24-month period, we will be collecting data on hospitalisations and A&E attendances. Data on hospital admissions for children with respiratory related illnesses, already routinely collected by each CCG, will be entered onto a database along with data on A&E attendance, per practice. List size data, per month and 5-year epoch, will be obtained from the NHS digital website. We will also collect this in the follow up questionnaire, asking practice champions to estimate the true number of children they believe they see in a 12-month period. For each month of follow up, we will be asking intervention practices to run a 'search' to see how many times the intervention was used and by how many individual users.

Only fully anonymised data sets will be sent from the GP practices and CCGs. This will be sent to a secure NHS e-mail address. Data will be entered onto a purpose designed database and data validation and cleaning will be carried out throughout the trial.

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.

2.13. OUTCOME MEASURES

All outcome data will be obtained from routine data or from the CCG. In all analyses we will present regression coefficients/rate ratios, with 95% confidence intervals and p values. If the data does not conform to the assumptions of the following parametric tests, suitable transformations or non-parametric methods will be utilised and justification given.

2.13.1. CLINICAL PRIMARY OUTCOMES

Primary Outcome	Type	Detail
Dispensing rate (1)	Rate	Per practice we will collect the number of dispensed amoxicillin and macrolide prescription items for children aged 0-9 years, divided by the list size of 0-9 year olds in the practice. We will collect this over the 12 months leading up to randomisation as well as the 12-month following implementation of the intervention (or equivalent time frame for controls).
Hospitalisations (2)	Rate	Per practice we will collect the number of hospital admissions for RTI amongst children (aged 0-9 years) at each practice over a 12-month period, divided by the list size of 0-9 year olds in the practice. These will be defined using ICD-10 codes agreed by the TMG prior to recruitment (see appendix 1).

2.13.2. CLINICAL SECONDARY OUTCOMES

Secondary Outcome	Type	Detail
Accident & Emergency attendance	Rate	This will be analysed in the same way as the hospitalisation rate (primary outcome 2).
5-year epoch dispensing rates[a]	Rate	This will be analysed in the same way as the hospitalisation rate (primary outcome 1) but the data will be separated into those aged 0-4 and those aged 5-9.
The use of the CHICO intervention between practices and over time	Not by arm	The proportion of staff using the intervention will be collected per month and this will be explored, alongside the prescribing rates per month to see whether increased usage decreased prescribing rates.
Effect modification: no. of locums	Subgroup interaction	The primary outcome will be analysed again, assessing the moderating effects of other variables: - Practices will be split into those with a high/low proportion of locum staff - The dispensing rates will be split by the median into high and low dispensing rates - The practices will be broken down into those with GPs only vs. those with GPs and nurse prescribers - The practices will be broken down into those with a single site vs. multiple sites. - Practices with follow up periods before Covid-19, compared with those during or after the pandemic. - Practices within areas of high deprivation compared with areas of low deprivation.
Effect modification: past dispensing		
Effect modification: GPs and nurses		
Effect modification: Sites (1 vs 2+)[b]		
Effect modification: Pre/post Covid-19[c]		
Effect modification: Deprivation level[d]		

[a]Originally listed as a sub-group analysis in the protocol but, as we cannot categorise practices into age groups, we will instead look at each age group separately in a secondary analysis, [b]New addition, a large number of practices have more than one site, [c]New addition (2020) to account for the differences in triage and intervention usage caused by the Covid-19 global pandemic. [d]New addition (2020) to account for differences in uptake of the intervention in different areas on deprivation, possibly attributable to Covid-19

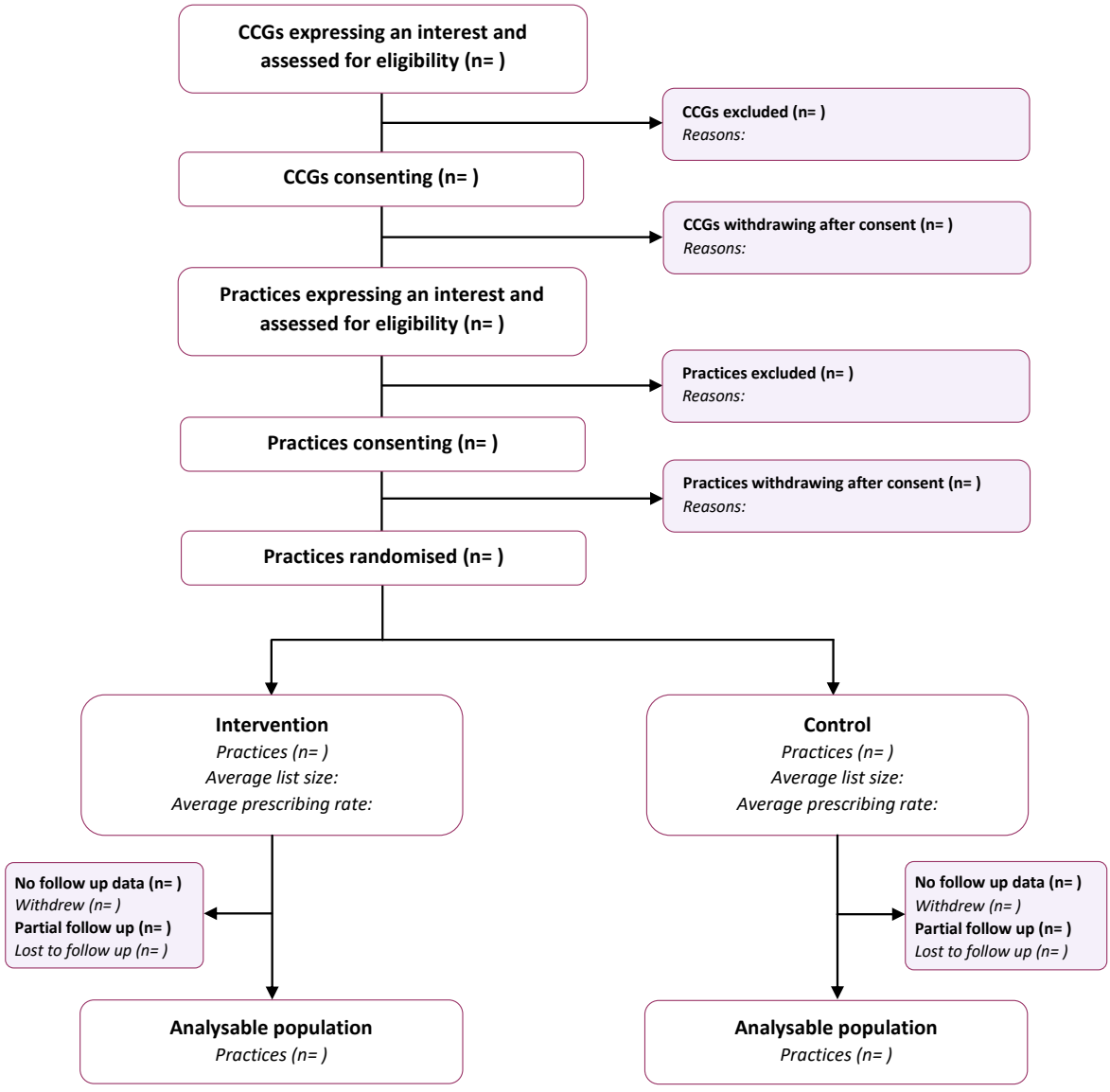
2.13.3. HEALTH ECONOMIC & QUALITATIVE OUTCOMES

Secondary Outcome	**Type**	**Data Analysis**
The costs to the NHS of using the CHICO intervention	Costs expressed in £	The costs, from a primary and secondary care perspective, in each arm will be compared, and the difference assessed using mixed effects linear regression
The acceptability of the CHICO intervention and variation in use.	Semi-structured interviews to explore views and experiences	Thematic analysis.

3. DESCRIPTION OF PARTICIPANT CHARACTERISTICS

3.1. DISPOSITION

A flow of CCGs and practices through the trial will be summarised in a CONSORT diagram that will include the eligibility, reasons for exclusion, numbers randomised, losses to follow up and the numbers analysed.



3.2. BASELINE CHARACTERISTICS

Baseline questionnaires are sent to practices that wish to take part in the trial, with randomisation taking place after the questionnaire has been returned to the study office. Baseline characteristics will be compared between the arms by reporting relevant summary statistics in order to determine whether any potentially influential imbalance occurred, by chance. Characteristics will be reported

as means (SD), medians (IQR) or number (%) depending on the nature of the data and its respective distribution. P-values will not be reported for differences between the two groups at baseline since appropriate randomisation methods will have accounted for this. Therefore, any differences identified would be due to chance such that a significant p-value would in reality be representative of a type 1 error (a rejection of the null hypothesis of no relationship when it is in fact true). Instead, it is better practice to identify differences in the groups at baseline by their standard deviations; if the baseline characteristics of the groups differ by more than half a standard deviation (or half an interquartile range) then the effect of this variable on the outcome will be investigated. For categorical and binary outcomes, a difference of 10% will be considered an imbalance.

CCG baseline characteristics will include:-

- Total number of GP practices within the CCG
- Average list size and dispensing rate (minimisation variables)

Practice baseline characteristics will include:-

- List size and dispensing rate (minimisation variables)
- Distance from the practice to the nearest children's A&E
- Total number of practice GPs
- Total number of practice salaried nurses
- Total number of practice sessional nurses
- Total number of independent pharmacist prescribers
- Total number of locums in the previous 12 months
- Total number of 'other' clinical staff
- Total number of practice GPs (100% FTE)
- Total number of practice salaried nurses (100% FTE)
- Total number of practice sessional nurses (100% FTE)
- Total number of independent pharmacist prescribers (100% FTE)
- Total number of locums in the previous 12 months (100% FTE)
- Total number of 'other' clinical staff (100% FTE)
- Total number of females aged 0-4
- Total number of males aged 0-4
- Total number of females aged 5-9
- Total number of males aged 5-9
- Ethnicity of children aged 0-9
- How are children triaged (e.g. nurse telephone triage)?
- Proportion of paediatric RTIs triaged over the telephone
- Proportion of paediatric RTIs dealt with entirely over the telephone
- Use of the CHICO leaflet
- Participation in pilot winter flu vaccination

Additionally, 12 months post randomisation (follow up), we will also ascertain:-

- Number of sites the practice has
- Whether they've participated in a practice merger (or split) during the trial
- The number of locums
- A revised estimate of the list size (including the number of unregistered children they see)
- Involvement in other trials aiming to reduce antibiotic consumption
- Whether there have been changes to triage and/or intervention usage due to Covid-19 (for those completing follow up after March 2020).

4. GENERAL ANALYSIS CONSIDERATIONS

4.1. ANALYSIS POPULATIONS

Outcomes will be analysed at the practice level.

Full Analysis set: All randomised practices: analyses will be based on the intention to treat principle, analysing practices in the groups to which they were randomised.

Per protocol Analysis set: All practices in the full analysis set who are deemed to have no major protocol violations that could interfere with the objectives of the study. For example, practices that have not adopted the EMIS system well, e.g. if an individual site has removed the intervention from their computer system.

The per protocol set will be utilised in a sensitivity analysis, excluding non-compliers in the intervention. In the unlikely event that control practices have access to the intervention, these will also be removed in this analysis.

4.2. DERIVED VARIABLES

4.2.1. PRIMARY OUTCOME RATES

The rate of amoxicillin/macrolide items dispensed will be calculated as:

$$\frac{\text{Number of amoxicillin and macrolide items dispensed to 0-9 year olds* (during the 12 months)}}{\text{Number of 0-9 year olds registered at the practice (median month list size)}}$$

*Prescriptions to patients with unknown age will be explored in a sensitivity analysis.

The rate of LRTI hospitalisations will be calculated as:

$$\frac{\text{Number of hospital admissions for LRTI in 0-9 year olds}}{\text{Number of 0-9 year olds registered at the practice (median month list size)}}$$

A&E attendances will be analysed in the same way. We will also be capturing the total number of hospitalisations/A&E attendances and those with a missing diagnosis which will be used in a sensitivity analysis (see section 5.5).

4.2.2. COMPLIANCE

In relation to the per protocol analysis above (section 4.1) we will exclude practices that are non-compliant with the intervention. Compliance will be measured as the number of times the intervention was used over 12 months, divided by the list size of 0-9 year olds in the practice. If this is lower than 0.05, then the practice will be considered to be non-compliant and excluded from the per protocol analysis. This value was chosen by the principal investigator, based on a sample of 49

non-identifiable practices. The compliance definition may need to be adjusted at the end of the trial due to the varying levels of compliance brought on by the Covid-19 pandemic. We will undertake a secondary analysis to investigate the rate of antibiotic dispensing among intervention practices with different compliance levels. This should also inform and verify whether our compliance definition holds.

4.2.3 LOW NUMBER SUPPRESSION

Due to contracts between CCGs and NHS digital, various CCGs only provided suppressed data to avoid identifying individuals, e.g. they replaced figures with an asterisk if n<5. As no other data was collected at the patient level, we did not foresee this to be a problem. The team will be requesting 12-month cumulative figures for each practice from these CCGs, to obtain accurate data, that is above the suppression limit. If, in small practices for example, the figure is still n<5 over a 12-month period we will impute a value of 3 for these practices.

4.3. ADVERSE EVENTS

Serious and other adverse events will be recorded and reported in accordance Good Clinical Practice guidelines and the Sponsor's Research Related Adverse Event Reporting Policy. 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 as SAEs if they are fatal or serious AND potentially related to trial participation i.e. they result from advice provided from the intervention algorithm. Hospitalisation and A&E attendances will be monitored in intervention and control practices.

5. STATISTICAL ANALYSES

5.1. STATISTICAL ANALYSIS

The latest version of STATA will be used for all statistical analyses. A pre-specified random seed of 32348 has been chosen to ensure all analyses can be replicated.

5.2. SUMMARY OF THE PRIMARY AND KEY SECONDARY OUTCOMES

All primary and secondary analyses will be conducted on complete data, using the ITT principle and appropriate regression model. Assumptions for each regression will be checked to make sure the correct method of analysis is being used. All tests are for superiority apart from the hospital admissions primary outcome. Mixed models will be used to appropriately distinguish between the *within* CCG (level 1) and *between* CCG (level 2) variation, incorporating the latter as a random effect.

5.3. PRIMARY ANALYSIS

The first primary analysis will explore the dispensing rates by arm, adjusting for baseline dispensing rates and treating the list size as the exposure (minimisation variables). This is a test for superiority therefore emphasis will be on the estimate, 95% confidence interval and p value. This will be analysed using random effects Poisson regression:

```
mepoisson disp arm b_disp, exposure(list_size) || ccg_id
```

The second primary analysis will explore the hospitalisation rates by arm. This is a test for non-inferiority therefore emphasis will be on the estimate and 95% confidence interval, not the p value. The non-inferiority margin was pre-specified as 0.01 ≈ 1%. Therefore, if comparing the intervention arm, to the control, the focus will be on the upper bound of the confidence interval, concluding non-inferiority if this is below 0.01. This will, again, be analysed using random effects Poisson regression:

```
mepoisson hosp arm b_hosp, exposure(list_size) || ccg_id
```

5.4. SECONDARY ANALYSES

The dispensing rate primary analysis will be repeated for 0-4 year olds only and 5-9 year olds only. In the protocol this was incorrectly listed as a sub group analysis but, as these categories lie within practices rather between practices, an interaction test is not possible.

Another secondary analysis will explore the A&E attendance rates by arm. This is a test for superiority therefore emphasis will be on the estimate, 95% confidence interval and p value. This will be analysed using random effects Poisson regression:

```
mepoisson AE arm b_AE, exposure(list_size) || ccg_id
```

The number of times the intervention is used will be measured monthly so we will be able to decipher whether usage varies over time. We will also explore the effect increasing intervention usage has on prescribing patterns, using a plot and test for correlation.

5.5. SENSITIVITY ANALYSES

As described in section 4.1, a per protocol analysis will be utilised if there are non-compliers in the intervention arm (described in section 4.2.2).

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 with and without the pilot data to see whether the modifications impacted the effectiveness. There were unexpected delays in importing the intervention during the Covid-19 pandemic. We plan to account for this in a sensitivity analysis by adding a continuous variable for the number of months of follow up affected by Covid-19 (subject to change, depending on how the pandemic progresses).

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. We will also add all missing diagnoses to the number of LRTI diagnoses as a "worst-case" 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. The primary analyses will also be repeated for each 5-year age group (epoch).

5.6. SUBGROUP ANALYSES

These subgroup analyses will use practice level data to assess whether the intervention is more/less effective in certain practices. Rather than assessing each group individually, an interaction term will be added to the model, followed by a likelihood ratio test.

Subgroup	Cut off	Rationale/hypothesis
Proportion of staff that are locums	Median	The intervention effect may be less apparent in practices with a high proportion of locums as they will not be familiar with the tool.
Past dispensing rates based on a continuous variable for all practices, not defined per CCG	Median	The intervention effect may be less apparent in those who were low prescribers initially.
Practices with nurse prescribers	Yes/No*	The intervention effect may be more apparent in those practices with prescribing nurses.
Number of sites	1 vs. ≥2	The intervention effect may be less apparent in practices with multiple sites as the intervention will be difficult to implement across multiple sites.

Before/after Covid-19	FU before Mar '20 vs. after	Due to the reduction in routine consultations for children with a cough, during the Covid-19 pandemic, there was less intervention usage.
High/low level of deprivation	Median	Areas of higher deprivation may be less likely to comply with the intervention, especially given the additional link between deprivation and Covid-19

** If a large majority of practices have nurse prescribers then we may look at this as a continuous percentage of nurse prescribers, out of all GP and nurse prescribers.*

6. HEALTH ECONOMIC ANALYSES

The health economics analysis will comprise a between-arm comparison of NHS costs. The analysis will identify which resources are used, calculate a unit cost, and then value overall resource use in each arm of the trial by multiplying unit costs for every item by the associated number of units used. Costs will include the costs of the intervention, prescriptions of amoxicillin and macrolides per the co-primary outcome, A+E attendances and hospital admissions. This comparison will be undertaken from the perspective of NHS primary and secondary care. As the follow-up period does not extend beyond one year, discounting of costs will not be applied.

The costs associated with the intervention will be based on non-research related costs including those associated with integration into EMIS, roll-out to practices, and training time in its use. We will value prescriptions 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] and will examine the sensitivity of costs to the impact of algorithm use on consultation duration. Information on consultation duration will be elicited in qualitative interviews from a small sample of clinicians. We will value secondary care resource use (A+E and admissions) using NHS Reference Costs.

We will undertake exploratory analysis to ensure ranges and distributions of variables used in the economic analysis are appropriate. We will also present by-arm descriptive statistics of data, such as means, medians, and frequencies. We will liaise with trial statisticians and the trial project manager in identifying issues with data such as mis-codings, although in practice we expect the volume of any data miscodings to be modest. Data cleaning and imputation will be undertaken prior to unblinding by the economic researcher.

The comparison of between-arm costs will use mixed effect linear regression to account for CCG-level clustering, and will be implemented in Stata in a manner resembling the following specimen code:

```
mixed secondary_care_costs arm || ccg_id
```

If the volume of missing data is material, we will implement a multiple imputation model to predict missing cost data. If possible, the same imputation models will be used for the primary effectiveness analysis and for the economic evaluation. The approach taken to missing data and any imputation will be clearly justified in terms of best practice and the characteristics of the data. The exact specification of an imputation model will depend on the level of missingness of each variable but it will be stratified by arm, and will include available cost measurements and baseline measures. There will be a clear discussion of the equations used in any multiple imputation, in line with best practice recommendations. The software package and software version used for multiple imputation will be reported.

Reporting of all results will adhere to the CHEERS (Consolidated Health Economic Evaluation Reporting Standards) statement.

7. QUALITATIVE ANALYSIS TECHNIQUES

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, utilising a data-driven inductive approach, 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. 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.

8. FINAL REPORT TABLES AND FIGURES (SUBJECT TO CHANGE)

Table 1. CCG and Practice Level Characteristics

		Intervention		Control
	n*	*Mean (SD)* or N (%)	n*	*Mean (SD)* or N (%)
Total number of participants				
Baseline CCG level				
Number of practices per CCG				
...				
Baseline Practice level				
Median list size (IQR)				
Median prescribing rate (IQR)				
Median total patient list size				
Aged 0-4				
Aged 5-9				
Ethnicity of 0-9 year olds (all practices totalled)				
White				
Mixed				
Asian				
Black				
Other				
Not stated				
Data missing				
Median # of General Practitioners				
Median # of salaried nurses				
Median # of sessional nurses				
Median # pharmacist independent prescribers				
Median # of Locums in previous 12 months				
Patient management (not mutually exclusive)				
No triage				
Nurse face-to-face				
GP face-to-face				
Receptionist telephone triage				
Nurse telephone triage				
GP telephone triage				
Other				
Proportion of RTIs consulted over the phone (pre Mar '20)				
None				
Very few				
Some cases				
Most cases				
Always				
Proportion of RTIs consulted over the phone (post Mar '20)				
None				
Very few				
Some cases				
Most cases				
Always				
CHICO leaflet in use at the practice				
Are patients involved in school winter flu vaccination?				

Table 2. Withdrawals

	Intervention N (%)	Control N (%)	P value*
Withdrawals/Lost to follow up			
CCG Withdrawals			
Practice withdrawals			
Reason 1, 2,…			
Loss to follow up			
Practices lost due to merging			

*Chi Square

Table 3. Adverse events, notified by the practice

	Number in the intervention (%)	Number in the control (%)
SAEs		
…		
Deaths		
…		

Table 4. Compliance with the CHICO intervention

	Intervention N(%)/*Mean (SD)*
Compliance	
Practices that reach the definition of compliance (section 4.2.2)	
Proportion of prescribing staff using the intervention:	
- At least one	
- At least once per month	
Proportion of intervention practices which:	
- Unsuccessfully installed the intervention	
- Uninstalled the intervention after installing	

Table 5. Primary, secondary and *sensitivity* outcomes for the CHICO trial

	Intervention Rate	Control Rate	IRR (95% CI)	P values*
CHICO outcomes				
Amoxicillin/macrolide prescriptions*				
Per protocol				
0-4 year olds only				
5-9 year olds only				
Including "age unknown"				
Excluding pilot practices				
Covid-19 month indicator				
Hospital admissions*				
Including % missing diagnoses				
Including all missing diagnoses				
Covid-19 month indicator				
Accident & Emergency attendees*				
Including % missing diagnoses				

Including all missing diagnoses

Covid-19 month indicator

*The denominator for these is the list size of children aged 0-9 (median over 12 months)

Table 6. Subgroup analyses for the CHICO trial

Variable	Intervention *Mean(SD); n*	Control *Mean(SD); n*	Subgroup specific IRR (95% C.I)	Interaction IRR (95% C.I)*	P#
Subgroup analyses					
Proportion of locums					
<Median					
≥Median					
Nurse prescribers					
Yes					
No					
Past dispensing					
<Median					
≥Median					
Practices sites					
1 site					
≥2 sites					
Follow up completed before the Covid-19 pandemic					
Yes					
No					
Level of deprivation					
Low					
High					

*The interaction coefficient, #Taken from a likelihood ratio test comparing models with/without the interaction term included, treating the subgroup of interest as a continuous variable where possible.

Appendix 1

Hospital admissions data dominant diagnosis code to be included in data reporting set

J00	Acute Nasopharyngitis (Common Cold)
J01	Acute sinusitis
J02	Acute pharyngitis
J03	Acute tonsillitis
J04	Acute Laryngitis and tacheitis
J05	Acute obstructive laryngitis croup and epiglottitis
J06	Acute upper respiratory infections of multiple and unspecified sites
J09	Influenza due to identified zoonotic or pandemic influenza virus
J10	Influenza due to identified seasonal influenza virus
J11	Influenza, virus not identified
J12	Viral pneumonia, not elsewhere classified
J13	Pneumonia due to Streptococcus pneumoniae
J14	Pneumonia due to Haemophilus influenzae
J15	Bacterial pneumonia, not elsewhere classified
J16	Pneumonia due to other infectious organisms, not elsewhere classified
J17	Pneumonia in diseases classified elsewhere
J18	Pneumonia, organism unspecified
J20	Acute bronchitis
J21	Acute bronchiolitis
J22	Unspecified acute lower respiratory infection
J36	Peritonsillar Abscess
J39	Other diseases of upper respiratory tract
J40	Bronchitis, not specified as acute or chronic
J47	Bronchiectasis
J85	Abscess of lung and mediastinum
J86	Pyothorax
J960	Acute Respiratory Failure
H65	Nonsuppurative otitis media
H66	Supperative and unspecified otitis media
A37	Whooping Cough
J390	Retropharyngeal And Parapharyngeal Abscess
J391	Other Abscess Of Pharynx
J392	Other Diseases Of Pharynx
A481	Legionnaire's disease
B953	Strep Pneumoniae As Cause Of Dis Classif Other Chapters
A403	Septicaemia Due To Streptococcus Pneumoniae
J45	Asthma
J46	Status Asthmaticus

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