Bristol Trials Centre (BTC)

RAPID-TEST

Rapid respiratory microbiological point-of-care-testing in primary care

Statistical Analysis Plan

Version 1.0 (02/09/2024)

Study Statistician: Mandy Lui

The following people have reviewed the analysis plan and agree the contents			
Name	**Role**	**Approval signature**	**Date**
Chris Metcalfe	Lead Statistician		02/09/2024
Alastair Hay	Chief Investigator		02/09/2024

CONTENTS

ABBREVIATIONS

Abbreviation	Phrase
AMR	Antimicrobial resistance
NICE	National Institute for Health and Care Excellence
POCT^{RM}	Rapid microbiological point-of-care-test
RTI	Respiratory tract infections

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 **RAPID-TEST**.

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

Respiratory tract infections (RTIs) are the most common problem managed by health services internationally.(1) In the United Kingdom, general practitioners and primary care nurses (from here on 'clinicians') treat 50% of RTIs with antibiotics,(2) with 50% of these considered inappropriate,(3) (4) and despite strong evidence that the majority of patients do not benefit.(5) (6) (7) (8) Overprescribing results in unnecessary side effects,(9) depletion of normal flora,(10) encourages patients to seek help for similar future illnesses,(11) and fuels antimicrobial resistance (AMR),(12, 13) regarded as a major threat to global public health. High treatment rates are attributed to clinician uncertainty regarding patients' microbiological diagnosis and clinical prognosis,(14) (15) leading to 'just-in-case' defensive prescribing.(15)

One potential solution, strongly endorsed by Lord Jim O'Neil in 2016,(13) the 2019 United Kingdom government 5-year AMR action plan,(16) and the 2020 Wellcome Trust AMR report,(17) is 'point-of care-testing'. These 'medical tests at the time and place of patient care',(18) are particularly attractive to primary care because laboratory results are not available in time to inform antibiotic prescribing decisions: typically 24 hours for blood and up to 72 hours for microbiological tests.

The C-reactive protein Point-of-Care Test measures the host inflammatory response to infection. They have been shown in randomised controlled trials to reduce antibiotic prescribing for adults with acute lower RTIs by 15%(19) to 22%.(20) However, despite the National Institute for Health and

Care Excellence (NICE) recommending its use in 2015 for patients with 'suspected pneumonia',(21) primary care uptake remains stubbornly low. In a recent editorial(22) we speculate that in addition to the 'who pays?' question, this could be because clinicians are unclear how the test works (an elevated C-reactive protein does not mean the infection is bacterial(23)). We also observe(22) that C-reactive protein effectiveness could be due to the low prevalence of elevated C-reactive protein in primary care (often not reported) favouring 'no-prescribing' decisions in up to 90% of consultations.

Respiratory microbiological point of care tests (POCT^{RM}) are now available and use polymerase chain reaction to detect viruses and bacteria from respiratory tract samples in 45 minutes.(24) POCTs can be considered to uniplex, duplex or multiplex according to the number of microbes being tested. Until recently, most systems were single/ duplex, testing for Influenza A/B and/or Respiratory Syncytial Virus, but the SARS-CoV-2 pandemic accelerated investment in multiplex POCT technology, with the latest equipment able to test for the presence of multiple viruses (including SARS-CoV-2) and bacteria.(25) (26) Importantly, the regulatory requirements for new POCTs are significantly lower than for new drugs: manufacturers have only to demonstrate they replicate standard laboratory testing. But before adoption and equipoise loss, evidence is needed from well-designed, independent clinical trials to show safety, efficacy, and cost-effectiveness.

2. SYNOPSIS OF STUDY DESIGN AND PROCEDURES

This is a summary of the study design as described in the study Protocol (version 3.0, 6th March 2023) to inform this statistical analysis plan. For all other purposes please ask to see the current version of the protocol.

2.1. TRIAL OBJECTIVES AND AIMS

The RAPID-TEST trial aims to evaluate the use of a rapid respiratory microbiological point-of-care-test POCT for suspected respiratory tract infection (RTIs) in primary care.

2.1.1. PRIMARY CLINICAL OBJECTIVES

To investigate whether the use of a rapid POCT can reduce same-day antibiotic prescribing for children and adults presenting to primary care with RTIs where the Study Clinician and /or patient believes antibiotic treatment is, or may be, necessary. This is assessed by whether any antibiotic was prescribed for a RTI at appointment 2 of day 1.

2.1.2. SECONDARY CLINICAL OBJECTIVES

To investigate whether the use of a rapid POCT impacts on patient symptoms and antibiotic and antiviral consumption, as reported in the participant diary. The key secondary measure is derived from the symptom diary: the mean symptom score on days 2 to 4.

To investigate whether the use of a rapid POCT impacts on primary care presentations for RTI, antibiotic and antiviral prescriptions, and hospital admissions for RTI by review of the participants' primary care records.

To investigate whether the use of a rapid POCT impacts on patient beliefs and intentions, including participant confidence in the clinical management of the infection (reported on day 1) and participant intention to consult for similar illnesses in the future (reported at 2 months).

2.1.3. PRIMARY MECHANISTIC OBJECTIVES

To determine whether there are overall (POCT test vs. No POCT test) and differential (virus detected vs. not detected) effects with respect to reducing number of participants for whom the Study Clinician believes antibiotics are necessary (as a mediator of the primary clinical outcome).

2.1.4. SECONDARY MECHANISTIC OBJECTIVES

To describe the effect of POCT results on Study Clinician and participant (or parent/carer if the participant is <16 years) beliefs and intentions with respect to the necessity, and benefits, of prescribing antibiotics for the respiratory infection, and confidence in the value of the POCT to guide the prescribing decision and explore the relationship between Study Clinician and participant beliefs, attitudes and intentions with antibiotic prescribing and consumption.

2.2. TRIAL DESIGN AND SETTING

A multicentre, individually randomised control trial with mixed-methods investigation of microbial, behavioural and antibiotics mechanisms. Participant will be randomised on a 1:1 basis to either invention group (POCT test) or control group (No POCT test). They will undergo follow-up until symptoms resolution or 28 days post-randomisation as well as review of their primary care medical records at 2 months and 6 months.

The trial duration is expected to be 38 months in total, which included 2 waves. The trial is planned to set up approximately 8 general practices (sites) during Wave 1 for Winter 1 period (the internal pilot study) followed by a Summer 1 period. The initial 8 sites will be closed gradually during Summer 1 period while another 8 sites will be opened as Wave 2 (from Summer 1) and continued for Winter 2 and Summer 2. Study general practices will be recruited from those served for routine laboratory testing by one of the following four hospitals: Southmead (North Bristol), the Bristol Royal Infirmary, Royal United Hospitals (Bath) and Weston General (Weston-super-Mare).

2.3. ELIGIBILITY CRITERIA

In brief, participants must be:

i. Aged ≥12 months on the day of presentation to primary care
ii. Presenting to primary care for the first time in this episode, and within 21 days of illness onset, with a Study Clinician suspected acute respiratory infection.
iii. Study Clinician or patient/parent/carer believes antibiotic treatment is, or may be, necessary (either Study Clinician or patient/parent/carer must answer "strongly agree", "agree" or “neither agree nor disagree" to question 1 from the Study Clinician views and question 1 from Participants Views detailed in Appendix 1)

The key exclusion criteria are:

i. Patient known to have cystic fibrosis
ii. Patient requires hospital admission
iii. Previous participation in the current RAPID-TEST trial
iv. Participation in another study of RTI ≤6 weeks prior to randomisation

2.4. DESCRIPTION OF INTERVENTION

Eligible and consented participants will have Appointment One (pre-randomisation) and Appointment Two (post-randomisation) with Study Clinician. After Appointment One, nasal and throat swabs will be taken using swab collection kit. Swab samples from intervention group will then be analysed using the practice’s BioFire® FileArray® Torch 1 system immediately after randomisation. At Appointment Two, the Study Clinician will contact the participant to inform them the allocation, result of POCT test (for intervention group) and to discuss treatment. They will be advised to use POCT result (for intervention group) as a guide to clinical decision making i.e. antibiotic prescribing. Whether or not the participant is prescribed an antibiotic at appointment two is the primary outcome measure.

2.5. RANDOMISATION PROCEDURES

The randomisation sequence will be generated by Sealed Envelope and will be stratified by age (<16 years vs. ≥16 years) and chronic lung disease (present vs. absent). Allocations will be provided online to the Study Clinician via the Sealed Envelope website.

2.6. BLINDING

The participants and the Study Clinicians will not be blinded to the allocation of treatment group. They will be informed the allocation group after randomisation. The BTC trial statistician will be unblinded in-order to report to the Data Monitoring Committee, while the senior statistician will remain blinded. The central trials team will remain blinded, including the chief investigator and trial manager.

2.7. SAMPLE SIZE CALCULATION

Assuming an antibiotic prescribing rate of 60% in the control group, 244 participants per group will allow a true reduction to 45% in the POCT group to be detected with 90% power at 5% significance. A total randomisation target of 514 will allow for 5% attrition. This number will provide at least 90% power to detect the same absolute difference if the antibiotic prescribing rate is found to be higher or lower than 60% in the control group.

If the POCT results in fewer antibiotic prescriptions, we wish to demonstrate non-inferiority of the POCT in terms of not increasing mean symptom severity at days 2 to 4 to a clinically significant extent. Assuming 80% completion of Trial Diaries (as previously achieved in adults and children) we will have data for symptom severity at 2 to 4 days in 206 participants per group. Data on 7,000 adults and children managed without POCT indicates a mean symptom severity at days 2 to 4 of 2.3 (standard deviation 1.5). We know this measure's distribution is positively skewed and have used a calculation that accommodates this (assuming equal skew in both groups, quantified as a coefficient of variation of 0.7). Assuming, in truth, no difference between groups, 206 participants in each group will give 90% power for a one-sided 95% confidence interval to exclude increases in the average symptom score of 20% or more.

2.8. INTERIM ANALYSES

No interim analyses comparing study outcomes between the allocated groups were conducted.

2.9. DATA COLLECTION

Participants in the trial will undergo a face-to-face assessment, two appointments (pre and post-randomisation) and swab collection on Day 1. They are required to complete online or paper trial diaries at baseline (Day 1, pre-randomisation) and then from Day 1 (post-randomisation) until symptom resolution or 28 days post-randomisation, whichever comes first. At 2 months, there will

be follow-up with a questionnaire on participants' beliefs. Data on any primary care consultations and hospital admission for RTIs or antiviral prescribing up to 28 days will be collected from primary care medical records at 2 months, as well as primary consultation for RTIs between Day 29 or up to 6 months will be collected at 6 months. The Supplementary Table at the end of this document shows the summary of the assessment schedule and outcomes measured at each time point.

2.10. OUTCOME MEASURES

All outcome data will be obtained from case report forms, participants' Trial diary and questionnaires of participants' and Clinicians' views.

2.10.1. CLINICAL PRIMARY OUTCOMES

Primary Outcome	**Type**	**Outcome detail**
Antibiotic prescribing	Binary	The primary outcome is whether an antibiotic is prescribed (included delayed prescribing) for a RTI on day 1. Study clinician report on Appointment 2 case report form.

The study clinician will collect the following data onto the **study case report form**: eligibility criteria, consultation format, signs and clinical measurements at presentation, diagnosis, medical history, previous prescription of antibiotic for current episode of RTI, POCT result, details of any prescription at appointment two (= primary outcome).

2.10.2. CLINICAL SECONDARY OUTCOMES

Participant-completed symptom diaries at baseline (day 1, pre-randomisation) and for 28 days afterwards (first post-randomisation completion on day 1 after appointment 2). Ten symptoms were completed by all participants: blocked nose, fever, shortness of breath, phlegm, wheeze, eating or drinking less than normal, disturbed sleep, ear pain and change in voice. Those age 16+ years completed four further symptoms: sore throat, muscle facial or head aching or pain, sweats or chills, and unable to do usual activities e.g. work school childcare etc. Those age under 16 years completed one additional item: child not themselves or more clingy than usual. Each item was responded to using the following seven-point scale:

0 = Normal/not affected
1 = Very little problem
2 = Slight problem
3 = Moderately bad
4 = Bad
5 = Very bad
6 = As bad as it could be

Participants are instructed to stop completing the diary once they have two consecutive days for which all symptoms are rated at zero, or once 28 days have been completed.

For any diary days that have been partially completed, with at least one symptom completed, symptoms left blank will assumed to be scored as zero (i.e. the symptom is completely resolved). Any days with no symptoms rated will be considered as missing data.

In addition participants were asked to record in the daily diaries if they were taking an antibiotic, which one, and how many doses were taken each day.

The following measures were derived from participant-completed symptom diaries:

Diary measures	**Type**	**Outcome detail**
Mean symptom severity on days 2 to 4 **(KEY SECONDARY OUTCOME)**	Continuous	Each day's responses will be converted to a mean score = sum of responses divided by the listed number of symptoms.
Duration of moderately bad (or worse) symptoms	Ordinal	Longest continuous spell (in days) with one or more symptoms rated ≥3, concluding with two days where all symptoms are rated <3.
Number of days to return to usual activities (adult participants ≥16 years only)	Ordinal	For participants with "Unable to do usual activities" rated ≥3 at baseline, the number of consecutive days that item is rated ≥3, followed by two days where it is rated <3. For participants with "Unable to do usual activities" rated as <3 at baseline, their duration will be zero.
Number of days to return to usual activities (child participants <16 years only)	Ordinal	For participants with "Child not themselves / more clingy than usual" rated ≥3 at baseline, the number of consecutive days that item is rated ≥3, followed by two days where it is rated <3. For participants with "Child not themselves / more clingy than usual" rated as <3 at baseline, their duration will be zero.
Overall symptom duration	Ordinal	The number of consecutive days one or more symptoms are rated >0, concluding with two days where all symptoms are rated 0.
New or worsening symptoms	Binary	Over days 2 to 28, the participant sees one or more symptoms increase to a score of ≥3, and is scored ≥3 for at least one of the subsequent two days.
Consumption of antibiotics	Count	Number of days on which antibiotics are consumed on days 1 to 28.
Counsumption of antivirals	Count	Number of days on which antivirals are consumed on days 1 to 28.

Participant views and study clinician views were collected using the following eight questions at the indicated time points (P: participant, C: clinician). Given wording was for clinicians, with the same questions asked of participants but with wording adapted. The response options were as follows:

1 Strongly disagree
2 Disagree
3 Neither agree or disagree
4 Agree
5 Strongly agree

		First contact	Appt 1	End appt 1	Allocation & test result	End appt 2	2 mths
[1]	I believe an antibiotic is needed to treat the patient's illness	P	C	P	C	P	
[2]	I believe the patient's illness will improve faster	P	C	P	C	P	
[3]	I believe the patient's illness will be less severe if I prescribe an antibiotic	P	C	P	C	P	
[4]	The point-of-care test would help in making the right decision about whether the patient needs antibiotics		C	P			
[5]	The point-of-care test would have helped / has helped in making the right decision about whether the patient needs antibiotics				C	P	
[6]	I am confident that the patient will believe they are getting the right treatment		C	P	C		
[7]	If a patient has a similar infection in future I am likely to prescribe them antibiotics				C		P
[8]	If a patient has a similar illness in future I would like to use the point-of-care test				C		P

Participants' **primary care medical records** will be reviewed at 2 and after 6 months to capture information on prescribing, consultations and hospital admissions.

Medical records review	**Type**	**Outcome detail**
Antibiotic prescriptions after appointment two	Binary	One or more antibiotic prescriptions after appointment two and within 28 days
Antiviral prescriptions after appointment two	Binary	One or more antiviral prescriptions after appointment two and within 28 days
Number of respiratory infection consultations	Count	The number of respiratory infection consultations within 28 days and after 28 days but within 6 months.
Hospital admissions for respiratory infections	Binary	One or more hospital admissions for a respiratory infection within 28 days, from medical records review.

3. GENERAL ANALYSIS CONSIDERATIONS

3.1. ANALYSIS POPULATIONS

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

Per Protocol Analysis set: All participants in the full analysis set who adhere to the protocol according to the following measures will be included in the per protocol analysis set. This dataset will be utilised in a sensitivity analysis for the primary outcome, and will be the basis for analysis of potential mechanisms. The following measures of protocol adherence will be presented:

- The participant provided a useable swab
- The Study Clinician obtained a valid POCT result for an intervention group participant
- The participant did not attend, or was not contactable by phone, for the second appointment (such participants will not have a date and time recorded for the second appointment).

3.2. ADVERSE EVENTS

The number of participants experiencing 0, 1, 2, or 3+ of the following events will be tabulated by allocated group: adverse events possibly, probably or definitely related to the intervention or trial procedures, all serious adverse events, serious adverse events possibly, probably or definitely related to the intervention or trial procedures, all suspected and unexpected serious adverse reactions (**Supplementary Table 7**, see Section 5). Further descriptive details will be given of any events in the latter two categories.

Note the potential overlap between adverse events, and the measure taken from the participant completed diaries “new and worsening symptoms”.

4. STATISTICAL ANALYSES

4.1. STATISTICAL SOFTWARE

The latest version of STATA, supported by the University of Bristol, will be used for all statistical analyses specified in this plan.

4.2. RECRUITMENT AND RETENTION

A CONSORT flowchart will give details of participant recruitment and flow through the study (**Figure 1**, see Section 5). Summary statistics for baseline measures, presented by allocated group, will characterise the study sample (**Table 1**, see Section 5). Supplementary material will give details of recruiting site (**Supplementary Table 1**), and the initial consultation (**Supplementary Table 2**). Details of formal full study withdrawals are presented in **Supplementary Table 8** (see Section 5).

4.3. ANALYSIS OF THE PRIMARY OUTCOME

Analysis of the primary outcome will be conducted on complete data, using the intention to treat principle and appropriate regression model. Model assumptions will be checked and alternative approaches considered if there is concern that estimates may be biased.

The primary outcome, prescription of an antibiotic at appointment 2 on day 1, will be compared between the two allocated groups, POCT versus no POCT, using a logistic regression model with covariates distinguishing the two allocated groups, the two age groups (< 16 years old versus ≥ 16 years old), and chronic lung disease status (present versus absent). The odds ratio, 95% confidence interval and p-value will be presented (**Table 2**, see Section 5).

4.4. SUBGROUP ANALYSES FOR PRIMARY OUTCOME

Three pre-specified subgroup analyses will be conducted for the primary outcome (**Table 2**, see section 5):

Age <16 years versus 16+ years. We hypothesize that, due to less information about symptoms being provided by children, the information from the POCT^{RM} will reduce antibiotic prescriptions to a greater extent in children.

Presence or absence of chronic lung disease. We hypothesize that general practitioners will tend to "play it safe" and prescribe an antibiotic to those with chronic lung disease, and there will be less of an impact of the POCT^{RM} on antibiotic prescribing in that group.

Disagreement (or not) between the general practitioner and the patient in whether an antibiotic is needed. We hypothesize there will be a greater impact of the POCT^{RM} in reducing antibiotic prescribing when the patient believes an antibiotic is needed (agree or strongly agree with this statement) but the general practitioner strongly disagrees or disagrees that an antibiotic is needed,

or is uncertain. In this situation, evidence from the POCTRM that the RTI may have a viral cause may reduce the likelihood of the general practitioner being persuaded to prescribe an antibiotic.

If there is evidence of superiority for the POCT^{RM} group compared to the control group on the key secondary outcome of symptom severity over days 2 to 4, the above subgroup analyses will also be conducted for that measure (and presented in a separate supplementary table).

4.5. ANALYSIS OF THE KEY SECONDARY OUTCOME

The key secondary outcome, participant reported mean symptom severity on days 2 to 4, will be compared between the two allocated groups, POCT versus no POCT, using a mixed linear regression model with covariates distinguishing the allocated groups, the two age groups (< 16 years old versus ≥ 16 years old) and chronic lung disease status (present versus absent), and a random effect at the participant level to accommodate the correlation between the three repeated responses per participant. Keeping the symptom scores separate as three repeated measures, rather than taking an average symptom score over the three days, provides greater transparency in the accommodation of patients who have reported symptoms on only one or two of the three days.

For comparability with previous studies in this area, the estimator will be the difference between the allocated groups in the average symptom score over days 2, 3 and 4. The coefficient of the covariate distinguishing the allocated groups, described in the previous paragraph, will provide this estimator. The distribution of residuals will be checked, and if markedly non-normal, the use of bias-corrected and accelerated bootstrap confidence intervals will be considered.

If a one-sided 95% confidence interval excludes increases of 20% or greater in the mean symptom score reported by the group allocated to POCT, then the POCT group will be considered non-inferior. A two-sided 95% confidence interval and p-value will also be presented to allow comparison with other studies, and inference about superiority of the POCT group in the event that non-inferiority is demonstrated (**Table 3**, see Section 5).

4.6. SENSITIVITY ANALYSES

The following sensitivity analyses will be performed:

1. For the primary outcome only, an analysis based on the per protocol analysis set.
2. For the primary outcome and key secondary outcome, the analysis will be repeated with additional covariates to (i) distinguish the recruiting practices, and (ii) to include any baseline variables observed to be imbalanced (>10 percentage points difference for binary measures, >0.5 standard deviations difference between means for continuous measures).
3. For the key secondary outcome only, to investigate the potential effect of data being missing not at random, the analysis will be repeated (i) excluding participants at two practices with <60% completion rates of diary data for days 2 to 4, and (ii) imputing missing ratings with the individual's baseline assessment for the POCT^{RM} group, and a score of zero for the comparison group. The resulting intervention effect estimate only will be presented in the text, as an indication of the extent to which missing data may be affecting the ITT estimate.

See **Table 2** and **Table 3**, Section 5.

4.7. ANALYSIS OF THE SECONDARY OUTCOMES

The primary outcome analysis will be adapted to the secondary clinical outcomes by the choice of a suitable regression model. Effect sizes, 95% confidence intervals, and p-values will be presented (**Table 3** and **Table 4**, see Section 5).

4.8. MECHANISTIC ANALYSIS

The POCT^{RM} result is a key potential mechanism on the causal pathway between availability of the POCT^{RM}, the clinician's belief that an antibiotic is necessary and the decision to prescribe an antibiotic. We will conduct an mechanistic analysis on the per protocol sample. An interaction term will capture any difference in the effect of the test result on prescribing between the two randomly allocated groups who do and do not have the test result available to inform the clinical decision. In the logistic regression model:

Log odds(antibiotic prescribed) = [Group] + [Virus detected versus not detected] + [Interaction]

"Virus detected versus not detected" will be as determined by the practice POCT^{RM} machine in the intervention group (i.e. the result that will inform the general practitioner's decision making), and as detected by the central study POCT^{RM} machine in the comparison group. Note that any finding including detection of an atypical bacteria will be coded as "virus not detected" as better reflecting the likely influence of this result on decision making.

The null hypothesis for the interaction term is that the 'virus detected/not detected' result has the same effect on prescribing in the POCT^{RM} (have the virus detected/not detected result to inform their prescribing decision) and comparison groups (do not have the result to inform their prescribing decision). The interaction term in the analysis model separates the effect of the POCT result from study clinicians' underlying ability to appropriately diagnose the need for an antibiotic without the POCT^{RM} result. Whilst the POCT result is revealed to study clinicians and intervention group participants post-randomisation, the proportions of viral and bacterial infections will have been balanced by the randomisation, such that an interaction test from the standard regression model will give evidence of the causal role of the POCT^{RM} test result (**Table 2**, see Section 5).

Clinician and participant views, pre-randomisation, will be tabulated by allocated group for the full analysis set (**Supplementary Table 3a, 3b; Supplementary Table 4a**, see Section 5). Clinician views, post-randomisation, will be tabulated by allocated group for the per protocol set, and the null hypothesis of no difference in the population in views between the two groups will be tested using an ordered logistic regression model (**Supplementary Table 4b**, see Section 5). Participant views, post-randomisation, will be tabulated by allocated group for the full analysis set, and the null hypothesis of no difference in the population in views between the two groups will be tested using an ordered logistic regression model (**Supplementary Table 3c, 3d**, see Section 5).

The result of the POCTRM test for each participant in the intervention group will be presented, with the probability of a prescription of antibiotic or of a antiviral for each observed result (**Supplementary Table 5**, see Section 5).

The change in response to the question "I believe an antibiotic is needed to treat the patient's illness" for clinicians in the per protocol set is tabulated for the three groups, POCT^{RM} virus detected, POCT^{RM} no virus detected, no POCT^{RM} group (**Supplementary Table 6**, see Section 5).

The aim of the primary results paper is to present information on the nature and magnitude of the effect of the POCT^{RM} on clinical outcomes, and upon potential mechanisms for that impact on outcomes. These results will guide the scope and approach to a causal analysis of potential mechanisms for any clinical benefit of POCT^{RM}, to be reported in a separate paper.

5. PRIMARY RESULTS PAPER FIGURES AND TABLES

Figure 1. CONSORT flowchart

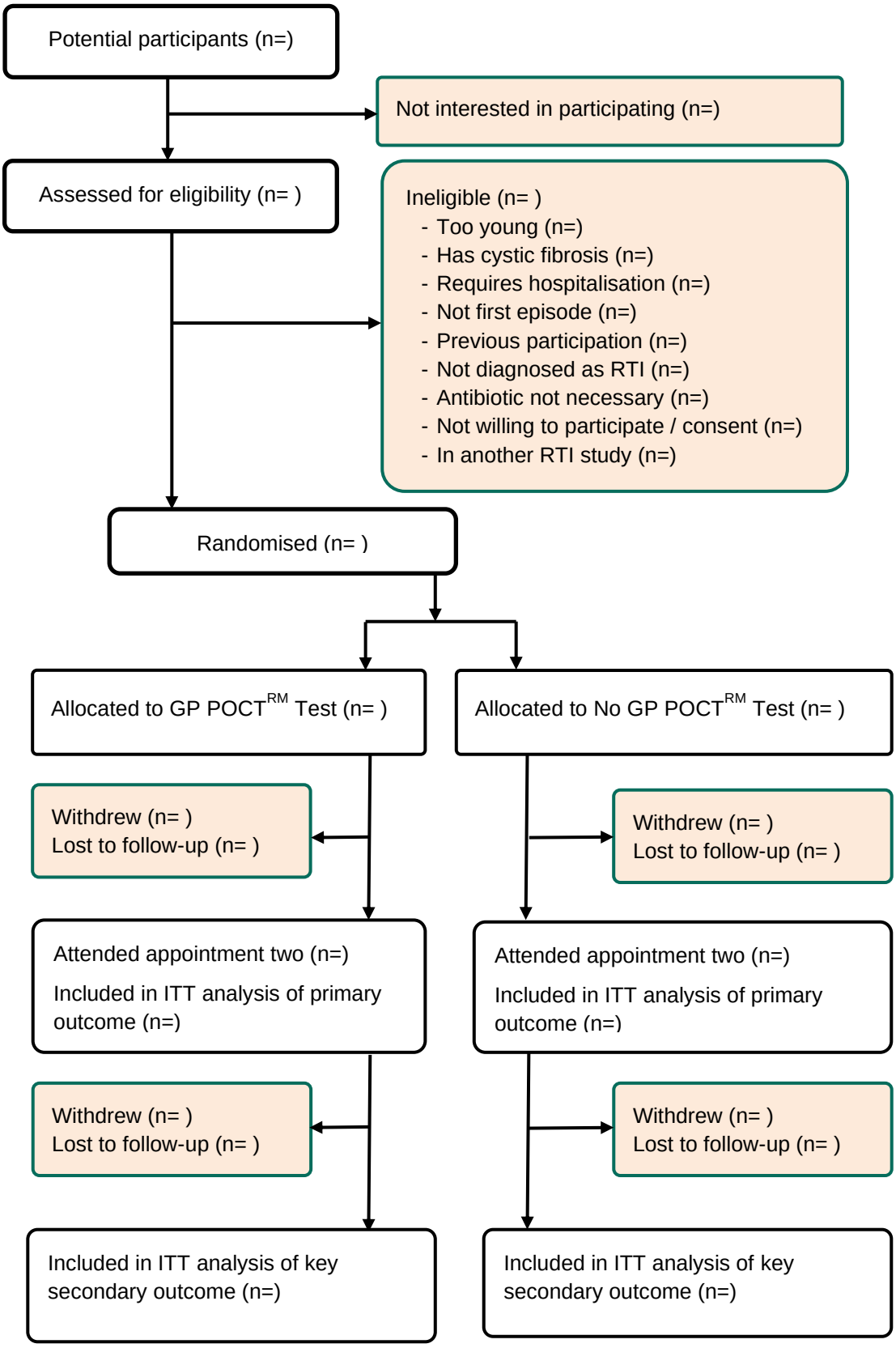

Table 1. Baseline participant characteristics

	Intervention (n=XX)		**Control (n=XX)**	
	N*	***Mean (SD) / n (%)***	**N***	***Mean (SD) / n (%)***
Demographics				
Number of males (%)	XX	XX (XX%)	XX	XX (XX%)
Mean age in years (SD)	XX	XX (XX)	XX	XX (XX)
Number age ≥16 years (%)	XX	XX (XX%)	XX	XX (XX%)
Number white ethnic group (%)	XX	XX (XX%)	XX	XX (XX%)
Medical history				
Chronic lung disease present	XX	XX (XX%)	XX	XX (XX%)
Has consulted for RTI in past 12 months	XX	XX (XX%)	XX	XX (XX%)
Antibiotic treatment received in the past 12 months	XX	XX (XX%)	XX	XX (XX%)
Any positive COVID tests in the past 3 months?	XX	XX (XX%)	XX	XX (XX%)
Any previous antibiotic/ antiviral treatment for the patient's current illness?	XX	XX (XX%)	XX	XX (XX%)
Clinical measures				
Number with oxygen saturation < 94% (%)	XX	XX (XX%)	XX	XX (XX%)
Number with temperature > 38°C (%)	XX	XX (XX%)	XX	XX (XX%)
Number with abnormal pulse in beats per minute (%)	XX	XX (XX%)	XX	XX (XX%)
Number with abnormal respiratory rate in breaths per minute (%)	XX	XX (XX%)	XX	XX (XX%)
Signs present, where assessed				
Pallor	XX	XX (XX%)	XX	XX (XX%)
Inter/subcostal recession	XX	XX (XX%)	XX	XX (XX%)
Cervical glands	XX	XX (XX%)	XX	XX (XX%)
Inflamed pharynx or tonsils	XX	XX (XX%)	XX	XX (XX%)
Pus on tonsils	XX	XX (XX%)	XX	XX (XX%)
Wheeze	XX	XX (XX%)	XX	XX (XX%)
Crackles or crepitations	XX	XX (XX%)	XX	XX (XX%)
Bronchial breathing	XX	XX (XX%)	XX	XX (XX%)
Erythema of ear drum with dullness, cloudiness or bulging, consistent with acute otitis media	XX	XX (XX%)	XX	XX (XX%)

[a]Number of participants providing data for this measure

Table 1 continued.

	Intervention (n=XX)		Control (n=XX)	
	N[a]	***Mean (SD)* / n (%)**	**N[a]**	***Mean (SD)* / n (%)**
Clinician's diagnosis				
Acute otitis media	XX	XX (XX%)	XX	XX (XX%)
Common cold		XX (XX%)		XX (XX%)
Acute sinusitis		XX (XX%)		XX (XX%)
Acute pharyngitis or tonsilitis		XX (XX%)		XX (XX%)
Sore throat		XX (XX%)		XX (XX%)
Acute laryngitis		XX (XX%)		XX (XX%)
Acute cough		XX (XX%)		XX (XX%)
Acute bronchitis		XX (XX%)		XX (XX%)
Chest infection		XX (XX%)		XX (XX%)
Acute lower respiratory tract infection		XX (XX%)		XX (XX%)
Infective exacerbation of chronic lung disease		XX (XX%)		XX (XX%)
Influenza		XX (XX%)		XX (XX%)
Covid-19		XX (XX%)		XX (XX%)
Other		XX (XX%)		XX (XX%)
Clinician's overall assessment				
My gut feeling is 'Something is wrong'	XX	XX (XX%)	XX	XX (XX%)
How unwell do you consider the participant to be: mean (SD) rating on scale 0: well to 10: very unwell	XX	*XX.X (XX.X)*	XX	*XX.X (XX.X)*

[a]Number of participants providing data for this measure

Table 2. Antibiotic prescribing at appointment 2 on day of presentation (primary outcome).

	Intervention n/N(%)	**Control N(%)**	**Odds Ratio[a] (95% Conf. Interval)**	**P value**
Primary analysis				
All antibiotic prescriptions	XX/XXX (XX%)	XX/XXX (XX%)	XX.XX (XX.XX, XX.XX)	0.XXX
Immediate antibiotic prescriptions	XX/XXX (XX%)	XX/XXX (XX%)		
Delayed antibiotic prescriptions	XX/XXX (XX%)	XX/XXX (XX%)		
Sensitivity analyses				
Adjusting for practice identifier			XX.XX (XX.XX, XX.XX)	0.XXX
Adjusting for baseline imbalance			XX.XX (XX.XX, XX.XX)	0.XXX
Per protocol population	XX/XXX (XX%)	XX/XXX (XX%)	XX.XX (XX.XX, XX.XX)	0.XXX
Pre-specified subgroup analyses				
Age at baseline				0.XXX[b]
Child (age <16 years)	XX/XXX (XX%)	XX/XXX (XX%)	XX.XX (XX.XX, XX.XX)	
Adult (age 16+ years)	XX/XXX (XX%)	XX/XXX (XX%)	XX.XX (XX.XX, XX.XX)	
Chronic lung disease at baseline				0.XXX[b]
Yes	XX/XXX (XX%)	XX/XXX (XX%)	XX.XX (XX.XX, XX.XX)	
No	XX/XXX (XX%)	XX/XXX (XX%)	XX.XX (XX.XX, XX.XX)	
Participant – Doctor disagreement at baseline[c]				0.XXX[b]
Yes	XX/XXX (XX%)	XX/XXX (XX%)	XX.XX (XX.XX, XX.XX)	
No	XX/XXX (XX%)	XX/XXX (XX%)	XX.XX (XX.XX, XX.XX)	
Causal mechanistic analysis – per protocol population				
Virus detected on POCT[RM] (comparison group result from laboratory)				0.XXX[b]
Yes	XX (XX%)	XX (XX%)	XX.XX (XX.XX, XX.XX)	
No	XX (XX%)	XX (XX%)	XX.XX (XX.XX, XX.XX)	

a. Odds ratio and confidence interval, from a logistic regression model, adjusting for participant age and chronic lung disease status

b. p-value for interaction term, testing the null hypothesis of equal odds ratios in the population between the two subgroups

c. Participant believes antibiotics are needed to treat the RTI, doctor does not believe or is unsure that antibiotics are needed

Table 3 Symptom measures

Key secondary analysis	**Intervention Mean(SD), n**	**Control Mean(SD), n**	**Difference in means[a] (95% confidence interval)**	**P value**
Mean symptom severity (days 2 – 4)			XX.XX (XX.XX, XX.XX)[b]	0.XXX
Day 2	X.X (X.X), X	X.X (X.X), X		
Day 3	X.X (X.X), X	X.X (X.X), X		
Day 4	X.X (X.X), X	X.X (X.X), X		
Sensitivity analysis				
Adjusting for practice identifier			XX.XX (XX.XX, XX.XX)	0.XXX
Adjusting for baseline imbalance			XX.XX (XX.XX, XX.XX)	0.XXX
Exclude participants at practices with low completion			XX.XX (XX.XX, XX.XX)	0.XXX
Other symptom measures	**Mean (SD), n**	**Mean (SD), n**	**Difference in means[c] (95% confidence interval)**	**P value**
Duration of moderately bad, or worse, symptoms	X.X (X.X), X	X.X (X.X), X	XX.XX (XX.XX, XX.XX)	0.XXX
Time to return to usual activities (adults 16+ years)	X.X (X.X), X	X.X (X.X), X	XX.XX (XX.XX, XX.XX)	0.XXX
Time to return to usual activities (children <16 years)	X.X (X.X), X	X.X (X.X), X	XX.XX (XX.XX, XX.XX)	0.XXX
Overall symptom duration	X.X (X.X), X	X.X (X.X), X	XX.XX (XX.XX, XX.XX)	0.XXX
	n/N (%)	**n/N (%)**	**Odds ratio[a] (95% confidence interval)**	**P value**
Participant experiences worsening symptoms	XX/XXX (XX%)	XX/XXX (XX%)	XX.XX (XX.XX, XX.XX)	0.XXX

a. All estimates adjusted for participant age and chronic lung disease status

b. One-sided 95% confidence interval, for establishing non-inferiority, presented in the text

c. Bias-corrected and accelerated bootstrap confidence intervals, non-parametric p-value

Table 4. Further healthcare contacts post-randomisation

		Intervention N (%)	Control N (%)	Odds ratio* (95% confidence interval)	P value*
Number (%) of patients hospitalised for RTI one or more times between appointment two and day 28		XX (XX%)	XX (XX%)	XX.XX (XX.XX, XX.XX)	0.XXX
Number (%) of patients consulting for RTI one or more times between appointment two and day 28		XX (XX%)	XX (XX%)	XX.XX (XX.XX, XX.XX)	0.XXX
Number (%) of RTI consultations per patient between 29 days and 6 months	0	XX (XX%)	XX (XX%)	XX.XX (XX.XX, XX.XX)	0.XXX
	1	XX (XX%)	XX (XX%)		
	2+	XX (XX%)	XX (XX%)		
Number (%) of patients prescribed one or more antibiotics between appointment two and day 28		XX (XX%)	XX (XX%)	XX.XX (XX.XX, XX.XX)	0.XXX
Number (%) of patients prescribed one or more antivirals between recruitment and appointment two		XX (XX%)	XX (XX%)	XX.XX (XX.XX, XX.XX)	0.XXX
Number (%) of patients prescribed one or more antivirals between appointment two and day 28		XX (XX%)	XX (XX%)	XX.XX (XX.XX, XX.XX)	0.XXX
Number (%) of patients consuming any antibiotics from day 1 to 28 (participant report)		XX (XX%)	XX (XX%)	XX.XX (XX.XX, XX.XX)	0.XXX
Number (%) of patients consuming any antivirals from day 1 to 28 (participant report)		XX (XX%)	XX (XX%)	XX.XX (XX.XX, XX.XX)	0.XXX

*adjusting for participant age and chronic lung disease status

Supplementary Table 1. Recruitment by practice

	Intervention (n=XX)	**Control (n=XX)**
	n (%)	**n (%)**
Sites		
A	XX (XX%)	XX (XX%)
B	XX (XX%)	XX (XX%)
C	XX (XX%)	XX (XX%)
D	XX (XX%)	XX (XX%)
E	XX (XX%)	XX (XX%)
F	XX (XX%)	XX (XX%)
G	XX (XX%)	XX (XX%)
H	XX (XX%)	XX (XX%)
I	XX (XX%)	XX (XX%)
J	XX (XX%)	XX (XX%)
K	XX (XX%)	XX (XX%)
L	XX (XX%)	XX (XX%)
M	XX (XX%)	XX (XX%)
N	XX (XX%)	XX (XX%)
O	XX (XX%)	XX (XX%)
P	XX (XX%)	XX (XX%)

Supplementary Table 2. Details of the first consultation and swabbing

	Intervention (n=XX)		Control (n=XX)	
	N*	**n (%)**	**N***	**n (%)**
Consultation/assessment type				
Face to face	XX	XX (XX%)	XX	XX (XX%)
Phone		XX (XX%)		XX (XX%)
Videoconference		XX (XX%)		XX (XX%)
Swab taken				
Throat and nasal	XX	XX (XX%)	XX	XX (XX%)
Nasal sample only		XX (XX%)		XX (XX%)
Throat sample only		XX (XX%)		XX (XX%)
Swab taken by				
Study Champion	XX	XX (XX%)	XX	XX (XX%)
Study Clinician		XX (XX%)		XX (XX%)
Participant		XX (XX%)		XX (XX%)
Parent or carer		XX (XX%)		XX (XX%)

Supplementary Table 3a. Participant views pre-appointment

Participants		**Intervention N (%)**	**Control N (%)**
I believe an antibiotic is needed to treat my (my child's) illness	Strongly agree	XX (XX%)	XX (XX%)
	Agree	XX (XX%)	XX (XX%)
	Neither agree nor disagree	XX (XX%)	XX (XX%)
	Disagree	XX (XX%)	XX (XX%)
	Strongly disagree	XX (XX%)	XX (XX%)
I believe my (my child's) illness will get better faster if I take an antibiotic	Strongly agree	XX (XX%)	XX (XX%)
	Agree	XX (XX%)	XX (XX%)
	Neither agree nor disagree	XX (XX%)	XX (XX%)
	Disagree	XX (XX%)	XX (XX%)
	Strongly disagree	XX (XX%)	XX (XX%)
I believe my (my child's) illness will be less severe if I am given an antibiotic	Strongly agree	XX (XX%)	XX (XX%)
	Agree	XX (XX%)	XX (XX%)
	Neither agree nor disagree	XX (XX%)	XX (XX%)
	Disagree	XX (XX%)	XX (XX%)
	Strongly disagree	XX (XX%)	XX (XX%)

Supplementary Table 3b. Participant views after first appointment (pre-randomisation)

		Intervention N (%)	**Control N (%)**
I believe an antibiotic is needed to treat my (my child's) illness	Strongly agree	XX (XX%)	XX (XX%)
	Agree	XX (XX%)	XX (XX%)
	Neither agree nor disagree	XX (XX%)	XX (XX%)
	Disagree	XX (XX%)	XX (XX%)
	Strongly disagree	XX (XX%)	XX (XX%)
I believe my (my child's) illness will get better faster if I take an antibiotic	Strongly agree	XX (XX%)	XX (XX%)
	Agree	XX (XX%)	XX (XX%)
	Neither agree nor disagree	XX (XX%)	XX (XX%)
	Disagree	XX (XX%)	XX (XX%)
	Strongly disagree	XX (XX%)	XX (XX%)
I believe my (my child's) illness will be less severe if I am given an antibiotic	Strongly agree	XX (XX%)	XX (XX%)
	Agree	XX (XX%)	XX (XX%)
	Neither agree nor disagree	XX (XX%)	XX (XX%)
	Disagree	XX (XX%)	XX (XX%)
	Strongly disagree	XX (XX%)	XX (XX%)
A point-of-care test would help in making the right decision about whether I need (my child needs) antibiotics	Strongly agree	XX (XX%)	XX (XX%)
	Agree	XX (XX%)	XX (XX%)
	Neither agree nor disagree	XX (XX%)	XX (XX%)
	Disagree	XX (XX%)	XX (XX%)
	Strongly disagree	XX (XX%)	XX (XX%)
I am confident that I (my child) will get the right treatment	Strongly agree	XX (XX%)	XX (XX%)
	Agree	XX (XX%)	XX (XX%)
	Neither agree nor disagree	XX (XX%)	XX (XX%)
	Disagree	XX (XX%)	XX (XX%)
	Strongly disagree	XX (XX%)	XX (XX%)

Supplementary Table 3c. Participant views after randomisation and, in the intervention group, learning the POCT result.

		Intervention N (%)	Control N (%)	p value[a]
I believe an antibiotic is needed to treat my (my child's) illness	Strongly agree	XX (XX%)	XX (XX%)	0.XXX
	Agree	XX (XX%)	XX (XX%)	
	Neither agree nor disagree	XX (XX%)	XX (XX%)	
	Disagree	XX (XX%)	XX (XX%)	
	Strongly disagree	XX (XX%)	XX (XX%)	
I believe my (my child's) illness will get better faster if I take an antibiotic	Strongly agree	XX (XX%)	XX (XX%)	0.XXX
	Agree	XX (XX%)	XX (XX%)	
	Neither agree nor disagree	XX (XX%)	XX (XX%)	
	Disagree	XX (XX%)	XX (XX%)	
	Strongly disagree	XX (XX%)	XX (XX%)	
I believe my (my child's) illness will be less severe if I am given an antibiotic	Strongly agree	XX (XX%)	XX (XX%)	0.XXX
	Agree	XX (XX%)	XX (XX%)	
	Neither agree nor disagree	XX (XX%)	XX (XX%)	
	Disagree	XX (XX%)	XX (XX%)	
	Strongly disagree	XX (XX%)	XX (XX%)	
I am confident that I (my child) will get the right treatment	Strongly agree	XX (XX%)	XX (XX%)	0.XXX
	Agree	XX (XX%)	XX (XX%)	
	Neither agree nor disagree	XX (XX%)	XX (XX%)	
	Disagree	XX (XX%)	XX (XX%)	
	Strongly disagree	XX (XX%)	XX (XX%)	

[a]Ordinal logistic regression model, adjusting for baseline participants' views, age and chronic lung disease status

Supplementary Table 3d. Participant questionnaire at two months.

If I have (my child has) an infection in future that is like the one I had when I joined this trial then I …		Intervention N (%)	Control N (%)	P value[a]
… will see my doctor to check if antibiotics are needed .	Strongly agree	XX (XX%)	XX (XX%)	0.XXX
	Agree	XX (XX%)	XX (XX%)	
	Neither agree nor disagree	XX (XX%)	XX (XX%)	
	Disagree	XX (XX%)	XX (XX%)	
	Strongly disagree	XX (XX%)	XX (XX%)	
… would like to have a point-of-care test to check if antibiotics are needed.	Strongly agree	XX (XX%)	XX (XX%)	0.XXX
	Agree	XX (XX%)	XX (XX%)	
	Neither agree nor disagree	XX (XX%)	XX (XX%)	
	Disagree	XX (XX%)	XX (XX%)	
	Strongly disagree	XX (XX%)	XX (XX%)	

[a]Ordinal logistic regression model, adjusting for baseline participants' views, age and chronic lung disease status

Supplementary Table 4a. Clinician views after the first appointment (pre-randomisation)

		Intervention N (%)	**Control N (%)**
I believe an antibiotic is needed to treat the patient's illness	Strongly agree	XX (XX%)	XX (XX%)
	Agree	XX (XX%)	XX (XX%)
	Neither agree nor disagree	XX (XX%)	XX (XX%)
	Disagree	XX (XX%)	XX (XX%)
	Strongly disagree	XX (XX%)	XX (XX%)
I believe the patient's illness will improve faster if I prescribe an antibiotic	Strongly agree	XX (XX%)	XX (XX%)
	Agree	XX (XX%)	XX (XX%)
	Neither agree nor disagree	XX (XX%)	XX (XX%)
	Disagree	XX (XX%)	XX (XX%)
	Strongly disagree	XX (XX%)	XX (XX%)
I believe the patient's illness will be less severe if I prescribe an antibiotic	Strongly agree	XX (XX%)	XX (XX%)
	Agree	XX (XX%)	XX (XX%)
	Neither agree nor disagree	XX (XX%)	XX (XX%)
	Disagree	XX (XX%)	XX (XX%)
	Strongly disagree	XX (XX%)	XX (XX%)
The point-of-care test would help in making the right decision about whether the patient needs antibiotics	Strongly agree	XX (XX%)	XX (XX%)
	Agree	XX (XX%)	XX (XX%)
	Neither agree nor disagree	XX (XX%)	XX (XX%)
	Disagree	XX (XX%)	XX (XX%)
	Strongly disagree	XX (XX%)	XX (XX%)
I am confident that the patient will believe they are getting the right treatment	Strongly agree	XX (XX%)	XX (XX%)
	Agree	XX (XX%)	XX (XX%)
	Neither agree nor disagree	XX (XX%)	XX (XX%)
	Disagree	XX (XX%)	XX (XX%)
	Strongly disagree	XX (XX%)	XX (XX%)

Supplementary Table 4b. Clinician views after randomisation and, in the intervention group, learning the POCT result. Per protocol set.

		Intervention N (%)	Control N (%)	p value[a]
I believe an antibiotic is needed to treat the patient's illness	Strongly agree	XX (XX%)	XX (XX%)	0.XXX
	Agree	XX (XX%)	XX (XX%)	
	Neither agree nor disagree	XX (XX%)	XX (XX%)	
	Disagree	XX (XX%)	XX (XX%)	
	Strongly disagree	XX (XX%)	XX (XX%)	
I believe the patient's illness will improve faster if I prescribe an antibiotic	Strongly agree	XX (XX%)	XX (XX%)	0.XXX
	Agree	XX (XX%)	XX (XX%)	
	Neither agree nor disagree	XX (XX%)	XX (XX%)	
	Disagree	XX (XX%)	XX (XX%)	
	Strongly disagree	XX (XX%)	XX (XX%)	
I believe the patient's illness will be less severe if I prescribe an antibiotic	Strongly agree	XX (XX%)	XX (XX%)	0.XXX
	Agree	XX (XX%)	XX (XX%)	
	Neither agree nor disagree	XX (XX%)	XX (XX%)	
	Disagree	XX (XX%)	XX (XX%)	
	Strongly disagree	XX (XX%)	XX (XX%)	
The point of care test would have / has helped in making the right decision about whether the patient needs antibiotics	Strongly agree	XX (XX%)	XX (XX%)	0.XXX
	Agree	XX (XX%)	XX (XX%)	
	Neither agree nor disagree	XX (XX%)	XX (XX%)	
	Disagree	XX (XX%)	XX (XX%)	
	Strongly disagree	XX (XX%)	XX (XX%)	
I am confident that the patient will believe they are getting the right treatment	Strongly agree	XX (XX%)	XX (XX%)	0.XXX
	Agree	XX (XX%)	XX (XX%)	
	Neither agree nor disagree	XX (XX%)	XX (XX%)	
	Disagree	XX (XX%)	XX (XX%)	
	Strongly disagree	XX (XX%)	XX (XX%)	
If a patient has a similar infection in future I am likely to prescribe them antibiotics	Strongly agree	XX (XX%)	XX (XX%)	0.XXX
	Agree	XX (XX%)	XX (XX%)	
	Neither agree nor disagree	XX (XX%)	XX (XX%)	
	Disagree	XX (XX%)	XX (XX%)	
	Strongly disagree	XX (XX%)	XX (XX%)	
If a patient has a similar illness in future I would like to use the point-of-care test	Strongly agree	XX (XX%)	XX (XX%)	0.XXX
	Agree	XX (XX%)	XX (XX%)	
	Neither agree nor disagree	XX (XX%)	XX (XX%)	
	Disagree	XX (XX%)	XX (XX%)	
	Strongly disagree	XX (XX%)	XX (XX%)	

[a]Ordinal logistic regression model, adjusting for baseline participants' views, age and chronic lung disease status

Supplementary Table 5. POCTRM result for participants allocated to the intervention group, with subsequent prescription of antibiotics and antivirals.

	Number of cases (N=)	**Number prescribed antibiotic at appointment 2**	**Number prescribed antiviral at appointment 2**
	n (% of participants in POCT^{RM} group)	n (% of participants with this POCT^{RM} result)	N (% of participants with this POCT^{RM} result)
No valid result	XX (XX%)	XX (XX%)	XX (XX%)
No microbe detected	XX (XX%)	XX (XX%)	XX (XX%)
Single microbe detected			
Bordetella pertussis	XX (XX%)	XX (XX%)	XX (XX%)
Bordetella parapertussis	XX (XX%)	XX (XX%)	XX (XX%)
Chlamydia pneumoniae	XX (XX%)	XX (XX%)	XX (XX%)
Mycoplasma pneumonia	XX (XX%)	XX (XX%)	XX (XX%)
Influenza A no subtype detected	XX (XX%)	XX (XX%)	XX (XX%)
Influenza A H1	XX (XX%)	XX (XX%)	XX (XX%)
Influenza A H1-2009	XX (XX%)	XX (XX%)	XX (XX%)
Influenza A H3	XX (XX%)	XX (XX%)	XX (XX%)
Influenza B	XX (XX%)	XX (XX%)	XX (XX%)
Adenovirus	XX (XX%)	XX (XX%)	XX (XX%)
Coronaviruses HKU1	XX (XX%)	XX (XX%)	XX (XX%)
Coronaviruses NL63	XX (XX%)	XX (XX%)	XX (XX%)
Coronaviruses 229E	XX (XX%)	XX (XX%)	XX (XX%)
Coronaviruses OC43	XX (XX%)	XX (XX%)	XX (XX%)
Coronaviruses Mers-CoV	XX (XX%)	XX (XX%)	XX (XX%)
Coronaviruses SARS-CoV-2	XX (XX%)	XX (XX%)	XX (XX%)
Human Metapneumovirus	XX (XX%)	XX (XX%)	XX (XX%)
Human Rhinovirus/Enterovirus	XX (XX%)	XX (XX%)	XX (XX%)
Parainfluenza 1	XX (XX%)	XX (XX%)	XX (XX%)
Parainfluenza 2	XX (XX%)	XX (XX%)	XX (XX%)
Parainfluenza 3	XX (XX%)	XX (XX%)	XX (XX%)
Parainfluenza 4	XX (XX%)	XX (XX%)	XX (XX%)
RSV	XX (XX%)	XX (XX%)	XX (XX%)

Supplementary Table 5 continued.

	Number of cases (N=)	**Number prescribed antibiotic at appointment 2**	**Number prescribed antiviral at appointment 2**
	n (% of participants in POCT^{RM} group)	n (% of participants with this POCT^{RM} result)	N (% of participants with this POCT^{RM} result)
Multiple microbes detected			
Combination 1	XX (XX%)	XX (XX%)	XX (XX%)
Combination 2	XX (XX%)	XX (XX%)	XX (XX%)
…	XX (XX%)	XX (XX%)	XX (XX%)

Supplementary Table 6. Change in clinician response to "I believe that an antibiotic is needed is needed to treat the patient's illness" prior to and post-randomisation in the two allocated groups: per protocol set, percentages are of the total number of clinicians, within the allocation / test result group, responding to the question at both time points

		Clinician views after randomisation and, in the intervention group, learning the POCT^{RM} result				
		Strongly agree	**Agree**	**Neither agree nor disagree**	**Disagree**	**Strongly disagree**
POCT^{RM} group, positive result for virus						
Clinician view pre-randomisation	Strongly agree	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
	Agree	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
	Neither agree nor disagree	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
	Disagree	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
	Strongly disagree	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
POCT^{RM} group, negative result for virus						
Clinician view pre-randomisation	Strongly agree	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
	Agree	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
	Neither agree nor disagree	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
	Disagree	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
	Strongly disagree	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
No POCT^{RM} group						
Clinician view pre-randomisation	Strongly agree	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
	Agree	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
	Neither agree nor disagree	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
	Disagree	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
	Strongly disagree	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)

Supplementary Table 7. Number of adverse events per participant

	Intervention (n=XX)	Control (n=XX)
Number of related* adverse events		
0 events	XX (XX%)	XX (XX%)
1 event	XX (XX%)	XX (XX%)
2 events	XX (XX%)	XX (XX%)
3+ events	XX (XX%)	XX (XX%)
Number of Serious Adverse events		
0 events	XX (XX%)	XX (XX%)
1 event	XX (XX%)	XX (XX%)
2 events	XX (XX%)	XX (XX%)
3+ events	XX (XX%)	XX (XX%)
Number of related* serious adverse events		
0 events	XX (XX%)	XX (XX%)
1 event	XX (XX%)	XX (XX%)
2 events	XX (XX%)	XX (XX%)
3+ events	XX (XX%)	XX (XX%)
Number of suspected unexpected serious adverse reactions		
0 events	XX (XX%)	XX (XX%)
1 event	XX (XX%)	XX (XX%)
2 events	XX (XX%)	XX (XX%)
3+ events	XX (XX%)	XX (XX%)

*Possibly, probably or definitely related to the intervention or trial procedures

Supplementary Table 8. List of participants formally withdrawing from all further participation in the study

Reason for withdrawal	**Days after randomisation**
Intervention group	
	XX
	XX
	XX
	XX
Comparison group	
	XX
	XX
	XX
	XX
	XX

REFERENCES

1. Ferkol T, Schraufnagel D. The global burden of respiratory disease. Ann Am Thorac Soc. 2014;11(3):404-6.
2. Dolk FCK, Pouwels KB, Smith DRM, Robotham JV, Smieszek T. Antibiotics in primary care in England: which antibiotics are prescribed and for which conditions? Journal of Antimicrobial Chemotherapy. 2018;73(suppl_2):ii2-ii10.
3. Fleming-Dutra KE, Hersh AL, Shapiro DJ, Bartoces M, Enns EA, File TM, Jr., et al. Prevalence of Inappropriate Antibiotic Prescriptions Among US Ambulatory Care Visits, 2010-2011. JAMA. 2016;315(17):1864-73.
4. Pouwels KB, Dolk FCK, Smith DRM, Robotham JV, Smieszek T. Actual versus 'ideal' antibiotic prescribing for common conditions in English primary care. Journal of Antimicrobial Chemotherapy. 2018;73(suppl_2):19-26.
5. Fahey T, Smucny J, Becker L, Glazier R. Antibiotics for acute bronchitis (Cochrane Review). The Cochrane Library, Issue 1, 2007 [Internet]. 2004.
6. Arroll B. Antibiotics for upper respiratory tract infections: an overview of Cochrane reviews. Respir Med. 2005;99(3):255-61.
7. Glasziou P, Del Mar C, SL S, M H. Antibiotics for acute otitis media in children (Cochrane Review). The Cochrane Library, Issue 4, 2002Oxford: Update Software [Internet]. 2006.
8. Del Mar C, Glasziou P, Spinks A. Antibiotics for sore throat (Cochrane Review). In: *The Cochrane Library.* Cochrane Database of Systematic Reviews [computer file] [Internet]. 2007.
9. Gillies M, Ranakusuma A, Hoffmann T, Thorning S, McGuire T, Glasziou P, et al. Common harms from amoxicillin: a systematic review and meta-analysis of randomized placebo-controlled trials for any indication. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2015;187(1):E21-31.
10. Elvers KT, Wilson VJ, Hammond A, Duncan L, Huntley AL, Hay AD, et al. Antibiotic-induced changes in the human gut microbiota for the most commonly prescribed antibiotics in primary care in the UK: a systematic review. BMJ Open. 2020;10(9):e035677.
11. Little P, Gould C, Williamson I, Warner G, Gantley M, Kinmonth AL. Reattendance and complications in a randomised trial of prescribing strategies for sore throat: the medicalising effect of prescribing antibiotics. British Medical Journal. 1997;315(7104):350-2.
12. Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. BMJ. 2010;340(May18_2):c2096.
13. O'Neil J. Tackling drug-resistant infections globally: final report and recommendations. https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf; 2016 2016.
14. Horwood J, Cabral C, Hay AD, Ingram J. Primary care clinician antibiotic prescribing decisions in consultations for children with RTIs: a qualitative interview study. Br J Gen Pract. 2016;66(644):e207-13.
15. Cabral C, Lucas PJ, Ingram J, Hay AD, Horwood J. "It's safer to ..." parent consulting and clinician antibiotic prescribing decisions for children with respiratory tract infections: An analysis across four qualitative studies. Social Science and Medicine. 2015;136-137:156-64.
16. Care DfHaS. Contained and controlled: the UK's 20-year vision for antimicrobial resistance. London; 2019.
17. Wellcome. The Global Response to AMR: Momentum, success and critical gaps. 2020.
18. Quesada-González D, Merkoçi A. Nanomaterial-based devices for point-of-care diagnostic applications. Chem Soc Rev. 2018;47(13):4697-709.

19. Little P, Stuart B, Francis N, Douglas E, Tonkin-Crine S, Anthierens S, et al. Effects of internet-based training on antibiotic prescribing rates for acute respiratory-tract infections: a multinational, cluster, randomised, factorial, controlled trial. Lancet. 2013;382(9899):1175-82.
20. Cals JWL, Butler CC, Hopstaken RM, Hood K, Dinant GJ. Effect of point of care testing for C reactive protein and training in communication skills on antibiotic use in lower respiratory tract infections: cluster randomised trial. BMJ. 2009;338(may05_1):b1374.
21. NICE. Pneumonia: Diagnosis and Management of Community- and Hospital-Acquired Pneumonia in Adults. London; 2014.
22. Thornton HV, Khalid T, Hay AD. Point-of-care testing for respiratory infections during and after COVID-19. 2020.
23. Minnaard MC, van de Pol AC, de Groot JA, De Wit NJ, Hopstaken RM, van Delft S, et al. The added diagnostic value of five different C-reactive protein point-of-care test devices in detecting pneumonia in primary care: A nested case-control study. Scand J Clin Lab Invest. 2015;75(4):291-5.
24. BioFire. BioFire® Respiratory Panel 2.1 plus. Biomerieux; 2020.
25. Dx G. Respiratory Pathogen Panels 2020 [cited 2020 02/10/2020]. Available from: https://www.genmarkdx.com/int/solutions/panels/eplex-panels/respiratory-pathogen-panel/.
26. QIAGEN. QIAstat-Dx Respiratory SARS-CoV-2 Panel 2020 [Available from: https://qiastat-dx.com/row/wp-content/uploads/sites/3/2020/03/PROM-15948-001_1121481_FLY_QIAstat-Dx-SARS-CoV-2-CE-IVD_0320_ROW.pdf.

SUPPLEMENTARY MATERIALS

Supplementary Table. Schedule of assessment visits and outcome measurements

Timepoint (→)	Pre-randomisation			Step 4: Randomisation (Day 1)	Post-randomisation					
Trial assessments (↓)	**Step 1: Screening (Day 1)**	**Step 2: Appt 1 (Day 1)**	**Step 3: Post-Appt 1 (Day 1)**		**Step 5: Post-randomisation (Day 1)**	**Step 6: Appt 2 (Day 1)**	**Step 7: Post-Appt 2 (Day 1)**	**Day 1 - 28**	**2 Mths**	**6 Mths**
Screening	●									
Participant views	●		●				●		●	
Study Clinician views		●			●					
Eligibility assessment		●								
Demographics and clinical data		●								
Trial Diary		●						●		
Nasal and throat swab taken			●							
Prescribing decision						●				
Medical records review									●	●

The following supplementary analyses, which do not rely on the random allocation, are planned but do not form part of this analysis plan.

a. To explore the relationships between baseline symptoms and signs, POCT result, antibiotic consumption and participant reported: (i) mean symptom severity at days 2 to 4; (ii) duration of moderately bad (or worse) symptoms
b. To assess agreement between POCT results at practices vs. POCT results at the central research laboratory (intervention group only)
c. To assess agreement between POCT results at central research laboratory vs. extended laboratory respiratory virus and bacteria testing
d. To assess the relationship between weekly EQ-5D measures and symptom severity scores