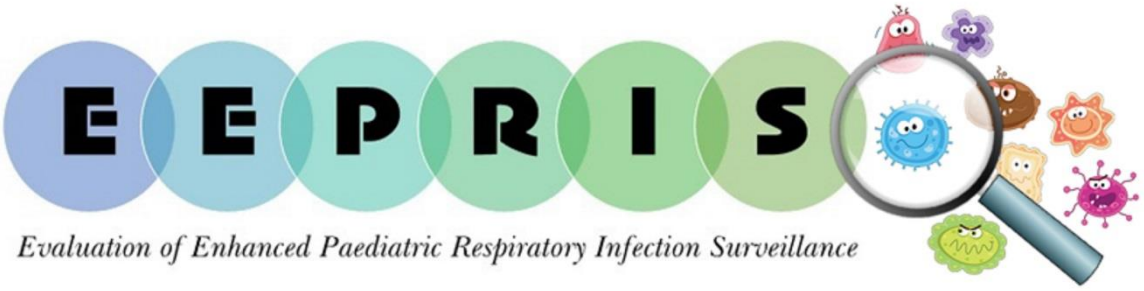


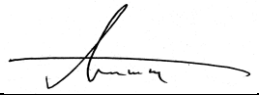
SHORT TITLE:

EEPRIS Study
Evaluation of Enhanced Paediatric Respiratory Infection Surveillance:
Community-based feasibility cohort study

LONG TITLE:
Evaluation of a Bristol-wide enhanced paediatric respiratory tract infection (RTI) microbiology surveillance feasibility cohort study, and nested qualitative study among a prospectively recruited, representative cohort of children with RTI.

Chief investigator:	Professor Alastair Hay
Sponsor:	University of Bristol
Sponsor reference:	2408
Funder:	National Institute for Health Research, Health Protection Research Unit (NIHR HPRU)
Funder reference:	HPRU-2012-10026
REC reference:	15/SW/0264

University of BRISTOL NHS Funded by NIHR Public Health England

This protocol has been authorised by:			
Name	**Role:**	**Signature**	**Date**
Alastair Hay	Chief Investigator		13/08/2015

Chief Investigator:
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EEPRIS Study team:

** Key for planned stage of involvement in study:*
A = inception/design; B = data collection/analysis; C = write up/comment on manuscript

Co-investigators (will have active responsibility for project delivery)

Study Manager:	**Study statistician:**
Ms Emma C. Anderson [A, B, C*] Research Associate, CAPC, SSCM University of Bristol, Canynge Hall, 39 Whatley Road, Bristol BS8 2PS Tel: 0117 33 14573 E-mail: eepris-study@bristol.ac.uk	Dr Suzanne Ingle [A, B, C] Research Associate, SSCM University of Bristol, Canynge Hall, 39 Whatley Road, Bristol BS8 2PS Tel: 0117 92 87262 E-mail: S.Ingle@bristol.ac.uk

Please contact the Study Manager for general queries and supply of study documentation.

Dr Charles Beck, Consultant Epidemiologist, Public Health England (PHE)
Role: Genomics lead and PHE perspective on study methods and results [A, C]; **Study Management Group (SMG) member**

Dr Peter Muir, Consultant Clinical Scientist (Virology), Public Health England
Role: Advice regarding microbiological methods, delivery and interpretation of microbiological data and PHE perspective on methods [A, B, C]; **SMG member**

Dr John Leeming, Principal Clinical Scientist, Department of Cellular and Molecular Medicine; Southmead Hospital, North Bristol Trust
Role: Advice regarding microbiological methods, delivery and interpretation of microbiological data [A, B, C]

Professor Adam Finn, Professor of Paediatrics, School of Cellular and Molecular Medicine, School of Clinical Sciences
Role: Advice on microbiological methods, ensuring consistency with other HPRU studies and advice on clinical microbiological vignette development [A, C,] **SMG member**

Dr Jo Kesten, Research Associate, NIHR CLAHRC West and NIHR HPRU, University of Bristol
Role: Qualitative project co-lead (parents' perspective) [A, B, C]

Ms Emma C. Anderson, Research Associate, SSCM, University of Bristol; Trainee Health Psychologist taking Professional Doctorate qualification, University of the West of England
Role: (in addition to study manager) Qualitative project co-lead (clinicians' perspective) [A, B, C]

SMG members will be expected to attend monthly/bimonthly meetings (face to face or by teleconference) and to take an active role in study management

Collaborators (will provide advice and input as requested by SMG members)

University of Bristol collaborators:

Dr Katy Turner, Research Fellow in infectious disease modelling, SSCM
Role: Advice on modelling implications for community RTI transmission

Dr Christie Cabral, Research Associate, CAPC, SSCM
Role: Qualitative project advisor [A, C]

Dr Jennifer Oliver, Research Co-ordinator, School of Clinical Sciences
Role: Advice on sampling techniques, microbiology, ensuring consistency with other HPRU studies

Professor William Hollingworth, Professor of Health Economics, CPH, SSCM
Role: Health economics advice [A, B, C]

Dr Hannah Thornton, Research Associate, CAPC, SSCM
Role: Advice on sampling techniques, microbiology

Public Health England (PHE) collaborators:

Dr Isabel Oliver, Director of Field Epidemiology for Public Health England
Role: PHE perspective on study methods and results [A, C];

Dr Paul Cleary, Consultant Epidemiologist with an interest in antimicrobial resistance, influenza and respiratory infections
Role: Advice on PHE epidemiological perspective

Dr Richard Puleston, Consultant Epidemiologist with an interest in antimicrobial resistance and pandemic influenza planning
Role: Advice on PHE epidemiological perspective

University of the West of England (UWE) collaborator:

Dr Tim Moss, Associate Professor of Health Psychology, Director of Postgraduate Research, Health and Applied Sciences, University of the West of England
Role: Doctoral supervisor to Emma Anderson for qualitative project (clinician interviews); qualitative research and health psychology advice.

Laboratory work

Will be conducted by staff at the **PHE Virology Laboratory** (led by Dr Peter Muir) at Myrtle Road, Bristol BS2 8EL

NB: This laboratory is due to be relocated to Pathology Sciences, Southmead Hospital during the course of this project.

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1 LIST OF ABBREVIATIONS

Admin DB	Administration Database
A&E	Accident and Emergency
AE	Adverse Event/Adverse Experience
AMR	Antimicrobial Resistance
BCARE	Bristol Centre for Antimicrobial Research and Evaluation
CCG	Clinical Commissioning Group
CHARGE	**C**oloboma of the eye, **H**eart defects, **A**tresia of the choanae, **R**etardation of growth and/or development, **G**enital and/or urinary abnormalities, and **E**ar abnormalities and deafness
CI	Chief Investigator
CLAHRC	Collaboration for Leadership in Applied Health Research and Care
CRF	Case Report Form
CRN	Clinical Research Network
Ct	Cycle threshold
DBS	Disclosure and Barring Service
EMIS	Egton Medical Information Systems
GCP	Good Clinical Practice
GP	General Practitioner
HIT	Health Integration Team
HPRU	Health Protection Research Unit
HRA	Health Research Authority
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
LIMS	Laboratory Information Management System
N	Number (of participants)
NHS	National Health Service
NIHR	National Institute for Health Research
NRES	National Research Ethics Service
OOH	Out of hours
PAG	Parent Advisory Group
PCR	Polymerase chain reaction
PGfAR	Programme Grant for Applied Research
PHE	Public Health England
PI	Principal Investigator
PPI	Patient and Public Involvement
QSR NVivo	Qualitative data analysis computer software produced by QSR International.
R&D	Research and Development
REC	Research Ethics Committee
REDCap	Research Electronic Data Capture
RN	Research Nurse
RTI	Respiratory Tract Infection
RCT	Randomised Controlled Trial
SAE	Serious Adverse Event
SMG	Study Management Group
SSCM	School of Social and Community Medicine
SOP	Standard Operating Procedure
SSC	Service Support Costs
STATA	Syllabic abbreviation of the words statistics and data
STGG	Skim milk, Tryptone, Glucose, and Glycerin
TLDA	Taqman low density array
WIC	Walk In Centre

2 DEFINITIONS

Clinician	General practitioner or prescribing practice nurse
Case Report Form (CRF)	A record of pertinent information and data collected on each participant during the study
Parent	Main carer contact (with legal responsibility) for a child who is participating (or potentially participating) in the study
Respiratory Tract Infection (RTI)	In EEPRIS, we are using the term "respiratory tract infection" to mean the presence of any of the following symptoms above the normal threshold for the child: Runny/blocked nose; earache/ear discharge; sore throat; cough (dry, productive or barking); chest symptoms (wheezing/whistling or breathing faster/shortness of breath) We are aware that this definition refers to symptomatic presentation only (not clinician or laboratory confirmed diagnosis).

3 KEYWORDS

Humans
Infant
Child
Paediatrics
Parents

Primary Health Care
Cohort Studies
Feasibility Studies
Prospective Studies

Microbiology
Saliva
Viruses
Bacteria

Respiratory Tract Infections
Community–Acquired Infections
Community-Acquired Infection - microbiology
Community –Acquired Infection - virology

4 STUDY SUMMARY

Evaluation of a Bristol-wide enhanced paediatric respiratory tract infection (RTI) microbiology surveillance: Feasibility cohort study and nested qualitative study among a prospectively recruited, representative cohort of children with RTI.

Overall aim: To determine the feasibility of enhanced paediatric RTI microbiology surveillance. This will inform the design of a future full scale RTI surveillance study with a nested randomised controlled trial (RCT) to test an online real-time illness symptoms and microbiological information intervention that informs parents and clinicians about circulating infections in the community. EEPRIS will inform the design and development of this online intervention, as well as informing the design of the full scale cohort study. The onward intention is to inform clinician prescribing practices and improve antibiotic stewardship, as well as potentially reducing consultation rates for paediatric RTIs.

Research design: Prospective, feasibility cohort study with data collection over one winter period (November 2015 to May/June 2016), with nested qualitative studies.

Setting: Primary care, recruiting from 12 GP practices within 10 miles of the centre of Bristol

Participants: Approximately 777 immuno-competent children in the community aged >3 months and <15 years, for **300 RTI episodes** over one winter period. Children are to be recruited via postal invitation to parents (estimated 457 parents involved in the study) from GP practice registers.

Study duration: 23 months from February 2015 to December 2016 inclusive.

Study objectives:
The **main objective** is to determine recruitment and retention rates (presented as number of complete sets of data collected on each study RTI compared with the number of children and families enrolled) to inform the design of a full scale cohort study and nested RCT.

The **main secondary objectives** are to:

- Describe the duration of community paediatric RTI symptoms, with a comparison between consulting and non-consulting children.
- Describe the primary and secondary care consultation rates

Further secondary objectives are detailed within this protocol, and include: Assessment of the clinical utility and costs of different community sample types (saliva versus nasal samples; nurse-taken versus parent taken and posted samples); development and acceptability of a parent online data collection platform; feasibility of data collection and preliminary analysis of data regarding likely RCT outcomes; cost projection for a large scale study with RCT.

Qualitative sub-study objectives
Interviews with parents - and with willing and competent assenting children will assess:

- The acceptability of the study components, including the paperwork, swab taking, the website and data collection processes. Willingness to be randomised for future RCT.

Interviews with parents – and separately with clinicians – will also assess:

- Perceptions regarding how the microbiology and real-time illness symptoms data could be used as part of a future online intervention that informs parents and clinicians about circulating microbes and illness profiles in the community.

Duration of participants' active study involvement:
A maximum of 30 weeks (majority significantly less), depending on when (if) a child develops an RTI and whether parents continue in the study (with the same child or other children) after symptom resolution. i.e:

- Minimum: From enrolment in November/ December 2015 (or early 2016) until a child has one episode of illness (cough, cold, sore throat, chest or ear infection) through to recovery.
- Maximum: From enrolment in in winter 2015 (/2016) until data collection ends on 30/04/16.

Data collection:

(i) **Baseline data** (collected online prior to first study RTI)**:** Parent, child and household demographics, optional parent health anxiety/confidence scales.

(ii) **Incident RTIs** (<7 days of symptom onset): Parents are asked to click on an online survey link sent weekly by email (or text) to confirm (simple Y/N response) if each child has developed: *blocked/runny nose, earache/ ear discharge, sore throat, cough or chesty symptoms in the last 7 days over and above what is normal for them*. A 'Y' response elicits a symptoms and recovery survey for the parent to complete online (via smartphone, tablet or computer) retrospectively for all days the child has been ill.

(iii) **Microbiological sampling:** A 'Y' response also prompts the EEPRIS nurse to arrange a home visit while the child is symptomatic. The research nurse performs a clinical examination of the child and collects a set of saliva and nasal swabs from the child which are transported via usual clinical procedures to the laboratory (clinical gold standard). The nurse also asks the parent to take a saliva and nasal swab from the child during the visit and post these to the laboratory.

(iv) **Follow up RTI data:** Parents are asked to continue to complete an online symptoms diary to record: RTI symptoms and severity until illness resolution (two consecutive RTI symptom-free days), and impact of the illness (school/day-care attendance; time off work; symptomatic status of household members, primary care consultation, antibiotic consumption and other medication use). Daily symptoms data is collected for a maximum of 21 days. If symptoms are ongoing beyond 21 days, data collection reverts to a weekly online questionnaire up to a maximum of 8 weeks from the date of first RTI symptom presentation. Following symptom resolution, the parent can choose to opt in or out of continuing to participate in the study with the same child or any other children in the household (i.e. resume receiving weekly emails in case of further RTI development in a child). Reminders for diary completion are via an automated email (or text) every two days. Complementary telephone calls are elicited after a week of missing data.

v) **Asymptomatic sample:** As soon as possible after symptom resolution (and within one month maximum), the parent will collect a saliva and a nasal swab (without a nurse visit) to post to the laboratory.

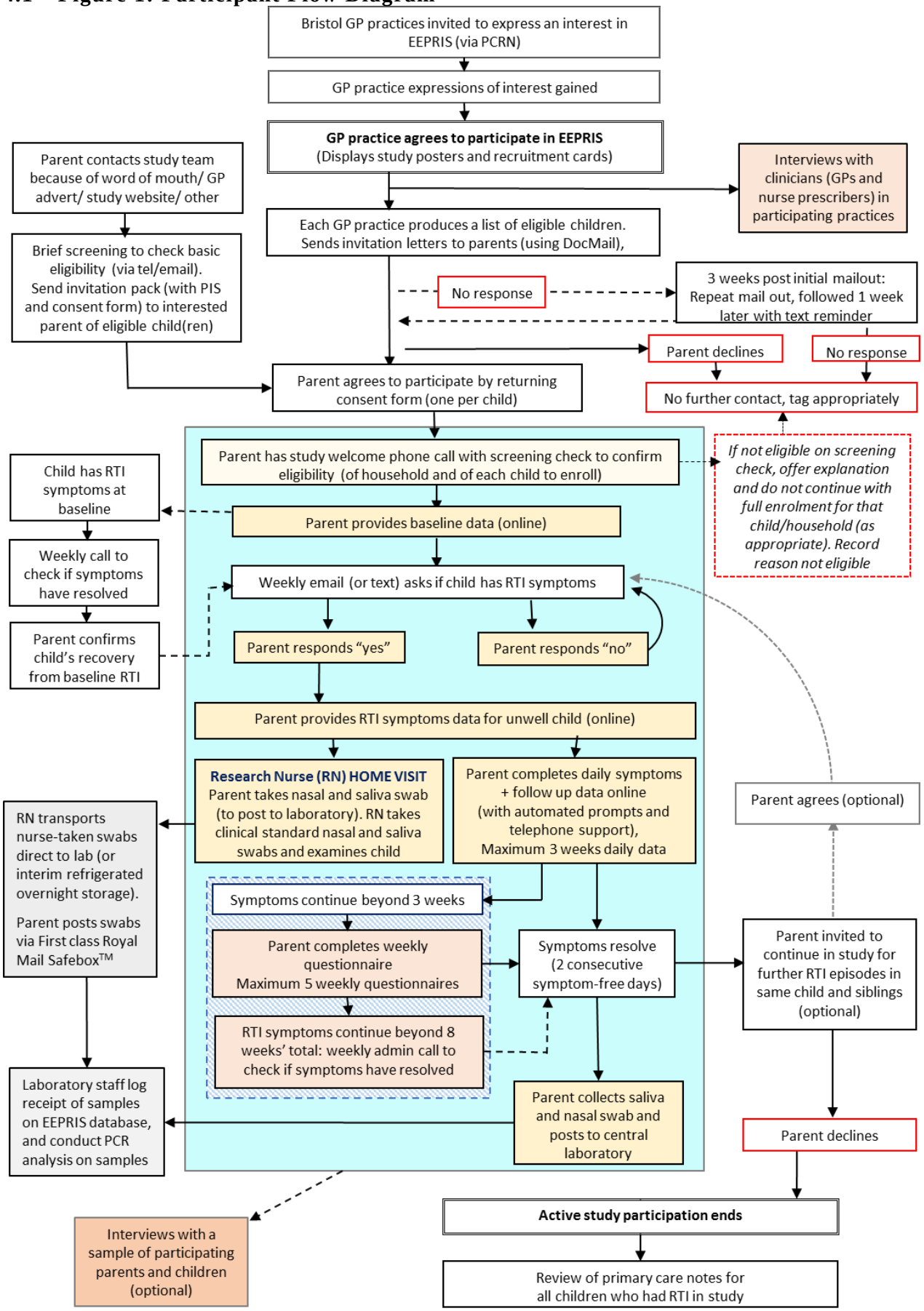
vi) **Follow up primary care notes data:** to record primary care RTI consultations and antibiotic prescribing during the RTI, as well as secondary care referrals or contacts, and diagnostic information relating to RTI (conducted on all children contributing RTI data to the study; collected at the end of the winter 'live' data collection). Child's relevant medical history will be extracted from the child's medical records (collected at end of active participation phase during notes review) to supplement baseline data.

Qualitative sub-studies:

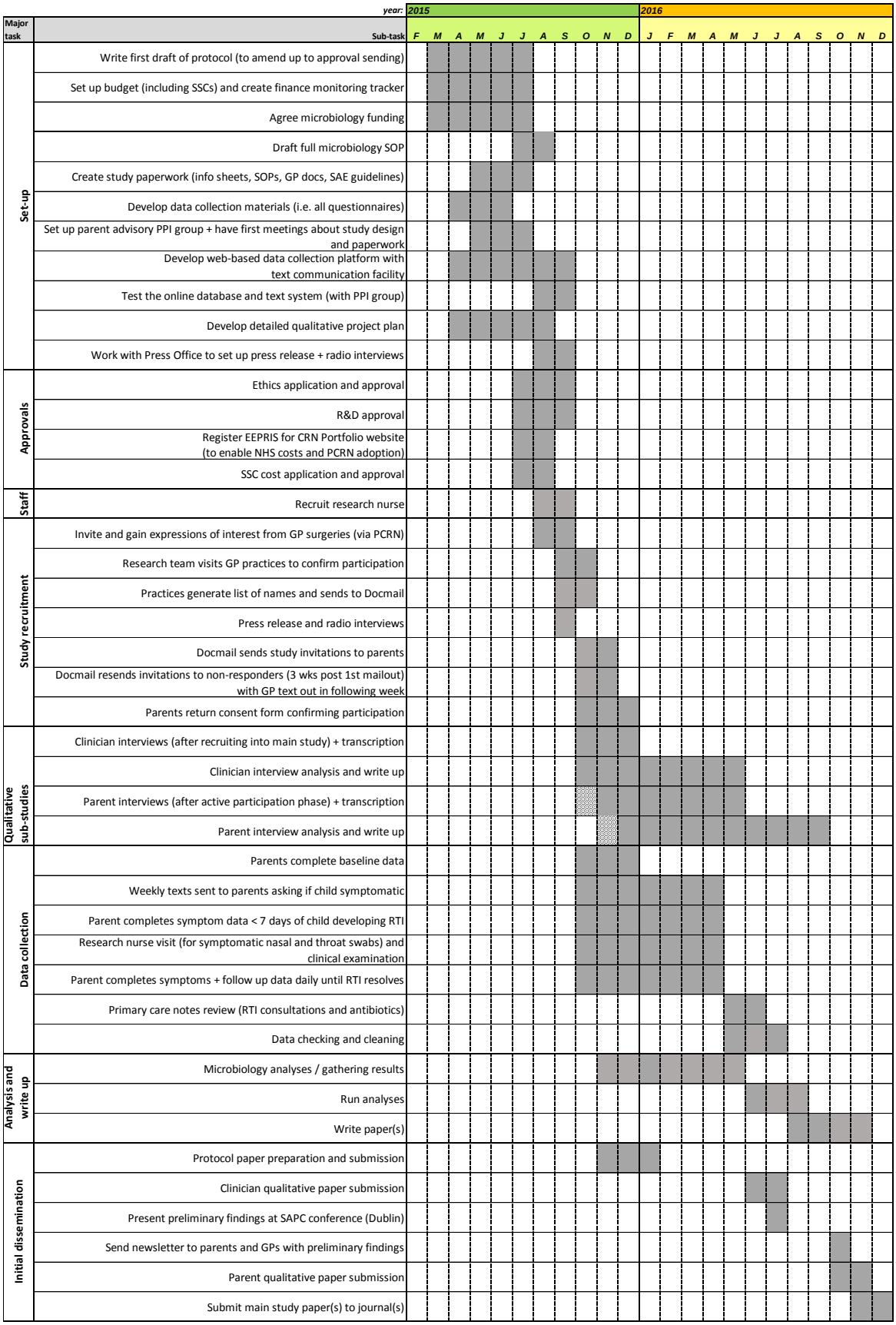
vii) **Parent (and child) interviews:** Of the parents who (on study enrolment) consented to being invited to interview, a maximum diversity sample will be invited for one semi-structured interview (in person at parent's home or convenient location). With parent's consent and child assent, competent and willing children will be interviewed opportunistically at the same time.

viii) **Clinician interviews:** Clinicians in participating GP practices will be invited for one semi-structured interview (in person or via telephone) at surgery recruitment stage.

4.1 Figure 1: Participant Flow Diagram



4.2 Figure 2: GANTT Chart of EEPRIS Study milestones



5 BACKGROUND

Scale of the problem:

General practitioners' (GPs) workload and intensity is increasing as primary care has seen a rise in consultation rates (without corresponding increase in GP staff time), and increased complexity in patient cases over recent years [1]. In addition to this growing burden on primary care clinicians, there is a growing public health threat of increasing antimicrobial resistance (AMR), largely attributable to the over-prescription of antibiotics [2].

Respiratory tract infections (RTIs) are the most common problem managed by primary care with the majority occurring in children [3]. Children experience on average 6 to 8 RTIs annually and NHS costs and costs to parents for paediatric RTIs are significant [4]. The use of primary care services for RTIs and antibiotic prescribing are inseparable - primary care is responsible for 80% of all antibiotics prescribed and 80% of patients with RTI are given antibiotics [5]. Due to the large numbers, even a small change in consultation rates and improved targeting of antibiotic prescribing for paediatric RTIs could have a significant impact on primary care resources and help reduce the growing threat of AMR.

The 10-fold variation in the number of consultations for RTIs between GP practices, along with the variation in antibiotic prescribing between clinicians [6] and GP surgeries [5] suggests uncertainty for parents regarding when to consult and uncertainty for clinicians regarding diagnosis and effective treatment of RTIs in primary care. GPs tend towards prescribing antibiotics in the face of uncertainty for paediatric RTIs, due to a perception that not prescribing carries greater potential threat [7]. Cabral et al [7] recommended that clinician interventions to reduce unnecessary antibiotic prescribing in this group should increase confidence in the safety of *not* prescribing - as an adjusted social norm for GPs to align their prescribing behaviour with. Lucas et al [8] recommend clinician interventions designed to reduce clinical uncertainty regarding social or clinical outcomes and highlight the need for clinicians to clarify parent motivations to prevent the misinterpretation of parental concerns for medical advice as a request for a prescription. Cabral and colleagues found that parents' information needs are not met in most consultations with clinicians in terms of understanding their child's illness, appropriate care for their child, and when to consult [9], [10]. Therefore interventions which address these information needs among parents are needed.

Rationale for research of this kind:

Despite modern microbiological knowledge, delays between microbiological sampling and results as well as cost considerations mean there is a near absence of microbiological testing for RTIs in primary care. Improving the availability of microbiological information in the primary care consultation has the potential to improve the targeted use of antibiotics and improve clinicians' ability to reassure, specifically since parents and carers (hereafter termed 'parents') find that commonly used microbiological diagnoses (e.g. "it's just a virus") in the absence of microbiological evidence undermine clinician credibility [9].

There is currently an absence of surveillance of infectious diseases. Clinicians usually do not establish or know: (i) the microbiological cause; (ii) the proportion of cases seen in primary care (for any given episode); (iii) the relative contribution of socio-demographic, clinical and microbiological factors to primary care consultation for RTIs. The Chief Medical Officer's 2011 Annual Report [11] identifies the need for enhanced surveillance of infectious diseases, with a focus on tackling AMR and improving antibiotic stewardship, and recommends research to enhance infectious disease surveillance. However, the cost effectiveness of microbiological sampling for RTIs is an important consideration.

Using enhanced microbiological surveillance and improving the use of primary care services and antibiotics for children with RTIs has arisen as a research priority regionally and nationally in response to:

(i) Priorities identified by patient and public involvement (PPI) work conducted in Bristol with parents and NHS commissioners as part of the 'Respiratory Infections Health Integration Team (HIT)' led by Professor Hay [12];
(ii) Regional and national Clinical Commissioning Group (CCG) priorities (to promote self-care and improve the use of NHS services for minor illness in children)[13] ;
(iii) Evidence produced by the 'TARGET' NIHR Programme Grant (led by Professor Hay) on which this application builds [14];
(iv) The Department of Health UK Five Year Antimicrobial Resistance Strategy and Action Plan: 2013 to 2018 [15]; and
(v) The 2013/2014 PHE priorities document [16].

A planned future intervention

Development of an online intervention of real-time surveillance summary symptoms of community paediatric RTIs with associated microbiological data is planned. The information presented would be a summary based on recorded surveillance data (not individual patient level). The overall aim of such an intervention is to improve the treatment and management of paediatric RTIs (by enhancing clinician and parent knowledge of circulating RTIs). It also has potential to provide a 'microbiological platform' to assist the evaluation of new vaccine strategies (e.g. intranasal paediatric influenza vaccine).

The intervention would have clinician-facing information and distinct parent-facing information. The aim of the clinician-facing intervention would be to provide information about currently circulating RTI microbes and their real-time symptom profile. It is hypothesised that such an intervention will increase clinician confidence regarding the targeting of antibiotic prescribing and need for secondary care referral when children present with RTI symptoms, as well as aiding advice-giving within the consultation. The aim of the parent-facing intervention would be to reduce consultation rates by potentially increasing parent confidence to manage RTIs at home.

A main aim of the current feasibility study is to inform the development and future trial of this proposed real-time online intervention. It is important to explore the feasibility and acceptability of such an intervention in principle – both to clinicians and parents, using qualitative methods, to inform the design and development of a future intervention at the pre-trial stage [17] [18].

How EEPRIS is informed by previous research

Widespread population internet connectivity has great potential for enhancing our knowledge and management of circulating infectious illnesses through community participation in illness surveillance (via real-time online symptoms self-report). This approach has been successfully applied to influenza in adults – for example Gripenet [19] and the FluSurvey project [20], though the majority of this work to date has been based on symptom self-report, and lacks associated microbiological data to identify circulating pathogens.

As yet unpublished analyses from the soon-to-complete successful 'TARGET' NIHR Programme [14] show that upper respiratory tract microbes detected on throat swabs taken from children presenting to primary care with acute cough and RTI are associated with clinical characteristics (parent reported symptoms and physical examination signs). In order of increasing strength of association, these include: rhinovirus (TARGET prevalence 12%); *S. pneumoniae* (15%); *H.*

influenzae (24%); *beta-haemolytic streptococci* (8%); respiratory syncytial virus (9%); influenza A (6%) and influenza B (4%). We have also found that outbreaks of specific microbes detected in primary care were contemporaneously detected among other children admitted to local hospitals. We believe that, although the associations are not strong enough to be diagnostic for individual children, they could be strong enough to be used in real-time microbial surveillance.

We hypothesise that microbiological information (viral and bacterial detection via polymerase chain reaction), combined with real-time clinical characteristic information for RTIs currently circulating within a city community, could reduce parental and clinical uncertainty, leading to changes in primary care consultation and antibiotic use.

How EEPRIS differs from previous research in this area

Previous research has focused on paediatric RTIs captured during primary care presentation [21, 22]. This leaves a key area of uncertainty in the *duration* of paediatric RTI symptoms in the community, as well as the *proportion* of these seen in primary care. McNulty [23] suggests around a fifth of adult RTI present to primary care but we do not know the corresponding proportions for children.

Minor illness home care is recognised as an important priority to encourage in the parents of young children by the National Children's Bureau [24]. This report states that parents often lack confidence in home management of infections due to a lack of understanding about how long common illnesses are likely to last, and the normal profile of symptoms development. In order to better manage parents' expectations of what is normal (to promote home management of infections), we need prospective data on paediatric RTIs in the community. Our study will provide this information as well as presenting a comparison of the duration of RTI symptoms between consulting and non-consulting children, which has not previously been done.

There is some evidence that clinician-taken throat and parent-taken nasal swabs have similar microbial detection rates [25] as do self- and staff-collected nasal swabs [26]. A real-time community paediatric RTI surveillance programme not based on primary care consultations would be reliant upon the acceptability, cost and clinical utility of parent-taken swabs *in the community* which would be *posted* to a laboratory for analysis. TARGET evidence shows sending swabs through the post may be acceptable and successful.

A recent American project found that saliva and nasal community-taken and posted samples for acute RTI in adults are clinically comparable, and that saliva sampling was preferable to nasal sampling for participating adults [27]. While these results are encouraging, there is a need to test whether the same applies to a paediatric population, and to conduct further comparisons of sample types to assess clinical utility as well as patient acceptability to inform an online paediatric RTI intervention.

EEPRIS is evaluating an approach to paediatric sampling which is likely to be acceptable and practical for wide scale community surveillance. Samples need to be easy for parents to take; sample kits must be safe for use on children in the absence of clinical supervision; and the postal process should not introduce new delays to sample processing or refrigeration that reduce sample quality. At present the least intrusive sample for parents to collect which is of biological utility is thought to be a saliva sample taken via a simple sponge collection device. EEPRIS adds to previous work by evaluating the clinical utility of this method. Nasal swabs, if taken just inside the entrance to the nostril, may also be an acceptable form of sampling for parents. We intend to compare the clinical validity of saliva samples and nasal swabs taken by parents using low risk sample kits (i.e. dry tubes without chemical agents or gels that could be accidentally ingested) against the 'gold standard' clinical sample (nurse-collected; using optimal preservative agents in the tubes and transported via optimal clinical protocol, i.e. direct to the laboratory in a clinical cold box or with

interim overnight refrigerator storage). Saliva samples and nasal swabs from asymptomatic cases (collected by parents after RTI resolution and posted to the laboratory) will provide a matched comparison between each case while symptomatic and after resolution of RTI.

We propose to conduct analyses similar to the TARGET throat swab microbial-clinical characteristics presented above, this time using both parent-taken and nurse-taken saliva samples and nasal swabs. Samples will be analysed using polymerase chain reaction (PCR) on an array of common viruses and bacteria.

What the EEPRIS study contributes

EEPRIS is a feasibility study of enhanced paediatric RTI surveillance. This study will inform the design of a future definitive cohort study with nested RCT of an online intervention (of real-time community surveillance summary symptoms with microbiological data). Towards this end, EEPRIS will assess recruitment and retention rates, and provide a cost estimate for the large scale study and intervention. Within EEPRIS, we are collecting symptoms data in real-time and analysing samples in batches (not necessarily immediately on arrival in the laboratory). The next stage in the development of the intervention would be to both analyse the data and produce meaningful outputs rapidly, in order to present the information online as close to 'real time' as possible. EEPRIS is testing the initial practicalities of this process, and the cost projection within EEPRIS will take the future plan into account.

As EEPRIS tests the *process* of gathering data for the future cohort study with online intervention, we will also gather and analyse qualitative information to inform the *design, delivery, utility* and potential *impact* of such an intervention through structured interviews with clinicians and parents who are involved with the study.

An important contribution of EEPRIS is the comparative microbiological (viral and bacterial) detection across sample types to provide evidence on the optimal community sampling of paediatric RTIs.

In addition to these scientific contributions, the EEPRIS study would like to answer two questions:

1. How many children with respiratory tract infection (RTI) consult?
2. What is the duration of RTI symptoms in the community?

Potential benefits to patients and NHS:

This feasibility research will provide:

1. New knowledge regarding the duration and symptom presentation of paediatric RTI illnesses in the community (to compare with those that reach primary care)
2. New knowledge regarding the numbers of children who consult with RTI.
3. New knowledge regarding the clinical utility and cost of parent-collected samples in the community.
4. New evidence regarding parent and clinician attitudes to, and perceptions of, a potential future intervention (that includes real-time enhanced community RTI microbiological surveillance) to modify and improve the use of NHS services for children with RTIs.
5. Evidence of the feasibility and cost of large scale community surveillance of paediatric RTIs.
6. Preliminary evidence of the contribution of factors (socio-demographic, clinical and microbiological) that drive the use of NHS services for paediatric RTIs.

Together with the future fully powered definitive cohort study with nested RCT, the research will provide:

7. Evidence of the effectiveness of an online intervention (that includes real-time enhanced community RTI microbiological surveillance) designed to modify and improve the use of NHS services for children with RTIs, including improved antimicrobial stewardship.
8. New knowledge regarding the contribution of factors (socio-demographic, clinical and microbiological) that drive the use of NHS services for paediatric RTIs.

6 STUDY OUTLINE

EEPRIS is a prospective, feasibility cohort study assessing the feasibility of data collection with a nested qualitative study to inform the design of a future definitive cohort study with a nested RCT. The study evaluates enhanced paediatric RTI microbiology surveillance among a prospectively recruited, representative cohort of children with RTI, recruited via primary care.

7 AIMS AND OBJECTIVES

The aim of the EEPRIS study is to assess the feasibility of collecting and using real time paediatric RTI microbiological surveillance data – the purpose of such data being to develop a clinician and parent-based intervention to improve primary and secondary care utilisation for paediatric RTI).

The main aim is to inform the design of a future full scale RTI surveillance cohort study with a nested randomised controlled trial (RCT) of a real-time microbiology and illness profile intervention.

7.1 Main objective

Specifically, the main objective of the EEPRIS feasibility study is to determine recruitment and retention rates to inform the design of a full scale cohort study and RCT. The primary outcome is the number of complete RTI episode data sets collected compared with the number of families and children enrolled.

7.2 Secondary objectives

The **main secondary objectives** are to:

1 Describe the duration of community paediatric RTI symptoms, with a comparison between consulting and non-consulting children.
2 Describe the primary and secondary care consultation rates

Further secondary objectives are to:

3 Compare the microbiological (viral and bacterial) detection in nasal swabs versus saliva samples (to assess clinical equivalence).
4 Compare the microbiological detection of parent-collected *and posted* nasal swabs compared with clinical standard research nurse-collected nasal swabs. (to assess clinical equivalence)
5 Compare the microbiological detection of parent-collected *and posted* saliva samples compared with clinical standard research nurse-collected saliva samples. (to assess clinical equivalence)

6 Compare the sequential microbiological detection of symptomatic samples with a matched comparison between each case while symptomatic and after resolution of RTI.
7 Compare the cost of parent-collected *and posted* saliva samples and nasal swabs compared with clinical standard research nurse-collected saliva samples and nasal swabs.
8 Develop and evaluate (the acceptability of) an online data collection platform.
9 Assess the level of parent website use for data collection
10 Assess the feasibility of data collection regarding likely RCT outcomes to include: Duration of RTI symptoms in the community; use of primary care services for RTIs prior to RTI symptom resolution; prescribing and consumption of antibiotics; use of secondary care services for RTIs prior to RTI symptom resolution; adverse events; costs to the NHS and the family (e.g. over the counter medicines) and consequences (e.g. time off school/nursery, time off work).
11 Conduct preliminary analyses of RCT outcome data collected (as listed directly above)
12 Evaluate costs of the feasibility and inform a cost projection for a definitive large scale cohort study with RCT.
13 Describe parents' level of ongoing engagement with the study in terms of their contribution of data on single or multiple illness episodes per child and/or more than one child per household.
14 Assess the success of the screening procedure.

7.2.1 Qualitative sub-study objectives

Interviews with parents - and with willing and competent children (who sign assent) will assess:

15 The acceptability of the study components, including the paperwork, swab taking, the website and data collection processes. Willingness to be randomised for future RCT.

Interviews with parents – and separately with clinicians – will also assess:

16 Perceptions regarding how the microbiology and real-time illness symptom data could be used as part of a future online intervention that informs parents and clinicians about circulating microbes and illness profiles in the community.

7.3 Objectives of the final, fully powered, definitive study:

1 Investigate the relative contribution of socio-demographic, clinical and microbiological factors to primary care utilisation (walk in centres [WICs], out of hours [OOH] primary care centres, emergency departments and GP practices);
2 Evaluate the impact of an online real-time illness symptoms and microbiological information intervention that informs parents and clinicians about circulating microbes and illness profiles in the community.
3 Describe the clinical and economic burden of vaccine and non-vaccine preventable RTIs in children, and provide a 'microbiological platform' to assist evaluation of new vaccine strategies (e.g. intranasal paediatric influenza vaccine).

8 STUDY OUTCOMES

In order to meet the main objectives (outlined above), the study will assess the following outcome measures:

8.1 Primary outcome

The primary outcome is the number of complete RTI episode data sets collected. A complete data set is defined as: baseline data, completion of online symptoms diary from beginning of RTI to symptoms resolution – or up to the 8 weeks maximum data collection for ongoing symptoms (some data gaps in the middle are acceptable as long as beginning and end of RTI symptoms diary is

complete for the episode) plus nurse clinical examination data, four symptomatic samples (nurse- and parent-taken nasal swabs and saliva samples) and parent-taken aymptomatic nasal swab and saliva sample.

Recruitment and retention rates for the study will be further divided to describe *levels* of study retention by study tasks:

- Response to weekly emails (or texts)
- Parent website use for data collection to include: symptoms list completion on confirmation of incident RTI in a child; ongoing symptoms diary completion until resolution of RTI (or a maximum 8 weeks data collection period for a single RTI)
- Telephone prompting required
- Parent-taken symptomatic nasal swab
- Parent-taken symptomatic saliva sample
- Nurse visit completion (including physical examination and nurse-taken nasal swab and saliva sample)
- Asymptomatic parent-taken saliva sample and nasal swab
- Notes review completion

These data will describe the level and nature of missing data to assess the methods of data collection and inform how best to carry this out in a larger trial.

8.2 Secondary outcomes

The main secondary outcomes:

1 Duration of RTI symptoms, including a comparison between consulting and non-consulting children.
2 Primary and secondary care consultation rates

Further secondary outcomes:

3 Agreement of microbiological detection between nasal swabs versus saliva samples (as Kappa statistic).
4 Agreement of microbiological detection between parent-collected *and posted* nasal swabs compared with clinical standard research nurse-collected nasal swabs (as Kappa statistic).
5 Agreement of microbiological detection between parent-collected *and posted* saliva samples compared with clinical standard research nurse-collected saliva samples (as Kappa statistic).
6 Difference in microbiological presence and load (cycle threshold values) between symptomatic and asymptomatic samples as a matched comparison with each RTI case.
7 Cost of parent-collected swabs compared with nurse-collected swabs
8 Level of acceptability of online data collection platform (simple Likert scale with free text response option)
9 Level of parent use of website for data collection (to include questionnaire completion rates, and percentage of questionnaires completed by administrator over the phone)
10 Completion rates of likely RCT outcome data (use of primary and secondary care services for RTIs prior to RTI symptom resolution; prescribing and consumption of antibiotics; parental health anxiety; parent confidence in managing children's minor illness; adverse events; costs to the NHS [e.g. cost of consultations and prescriptions] and the family [e.g. over the counter medicines] and consequences [e.g. time off school/nursery, time off work]).
11 Preliminary statistical analyses of RCT outcomes outlined above, with a particular interest in factors associated with decisions to consult.

12 Cost of feasibility study with scaled up cost estimate of a definitive cohort study with real-time online RCT intervention.
13 RTI numbers contributed per child and per household (i.e. including enrolled siblings), with sub-assessment of rates of retention in the study (agreeing to ongoing symptoms trigger texts/emails) after completion of one RTI episode data.
14 Numbers of children contributing data who would be expected to be excluded at screening.

Qualitative sub-studies: Outcomes

15 Attitudes to the study, the paperwork, swab taking, the website and data collection processes (parent and children interviews only).
16 Parents' level of understanding of and engagement with a hypothetical online intervention; influence on intention to consult; self-efficacy for home child care; knowledge of RTIs; and attitudes to antibiotics and willingness to be randomised for a future RCT.
17 Clinician engagement with the intended online intervention. Facilitators, barriers and perceived feasibility, efficacy and acceptability of a hypothetical intervention in practice; fit with consultation style and influence on intentions to prescribe antibiotics in response to such an intervention and willingness to be randomised for a future RCT.

9 MAIN STUDY DESIGN

9.1 Study period

Recruitment and baseline data collection is planned to take place between October and December 2015, and in the new year of 2016. Data collection from parents will continue until May/June 2016. This means that each parent with a child enrolled in the study will participate in the study for a maximum duration of seven months, and a minimum duration of the time from enrolment until resolution of the first incident RTI in one child (parents can always withdraw from the study sooner if they wish). On completion of the active participation phase for each parent (either on parent opt-out after symptom resolution of the first RTI, after resolution of further RTIs of the same child or other participating children in the household, or end of study data collection phase if that comes first), a sample of the parents who consented to invitation will be invited to take part in one qualitative semi-structured interview, along with any willing and competent participating child who is old enough to have signed assent.

After the completion of the active participation phase, research staff will conduct a medical notes review on all children who contributed RTI data to the study (which is expected to be completed by the end of July 2016). This will count as a phase of study participation, although data will be gathered from GP surgery records only, and no further requests will be made of participants in this period.

9.2 Sample size and recruitment numbers

9.2.1 Power calculations

EEPRIS is set up to provide descriptive results to inform the design of a fully powered cohort study with nested RCT. In addition to this, the EEPRIS study would like to provide answers for its secondary aims:

1. How many children with respiratory tract infection (RTI) consult?
2. What is the duration of the RTI symptoms in the community?
3. What is the comparative agreement in microbial detection between sample types?

With statistical and practical considerations, a sample size of 300 incident RTIs in the community is set as follows:

1. How many children with RTI consult?

Studies in the US from the 1970s have suggested that approximately 20-30% of RTI in the community consult with a clinician. With what precision can we estimate this in EEPRIS?

π = proportion of interest (i.e. % of RTI that consult)
e = required standard error
n = minimum sample size = $(\pi(1-\pi))/e^2$

Say π=20%, we have the following standard error with a sample size of 300 RTIs:

$e^2 = (0.20(0.80))/300 = 0.00053333$
e = 0.02309394

With this standard error, we gain the following 95% confidence interval around 20% (15%, 25%) (0.20-1.96 se, 0.20+1.96 se); (.15473588, .24526412)

2. What is the duration of the RTI symptoms in the community?

We can estimate a mean/median duration of RTI from the EEPRIS study, however it would be more helpful to know by what time point 90% of cases would have cleared the infection [28].

n = minimum sample size = $(\pi(1-\pi))/e^2$
With a sample size of 300, the standard error is 1.73.

A sample size of 300 RTIs would yield a 95% confidence interval (CI) of 87–93% around an estimate of 90% for the proportion recovered at the relevant time point, using an exact binomial calculation. This sample size calculation uses the same methods used for Hay et al's study on cough duration [29].

3. What is the comparative agreement in microbial detection between sample types?

Kappa statistics are used to indicate agreement between different rates. In the EEPRIS study, we will be looking at the agreement between nurse-taken and parent-taken swabs, as well as nasal and saliva swabs. Each swab will have a binary outcome – either we detect a bacteria/virus or we do not. We expect to find a 10% positive detection rate (for any microbe). We are testing 300 RTIs and will have tables like this:

		Nurse result -ve	+ve	Total
Parent result	-ve			270
	+ve			30
Total		270	30	300

		Saliva result -ve	+ve	Total
Nasal result	-ve			270
	+ve			30
Total		270	30	300

We would like to know how well the 2 swabs match in terms of the final result. Note that we would expect some of the swabs to match purely through chance. The kappa statistic accounts for those 'chance' matches. Kappa takes values from -1 to +1, where 0 represents the agreement you would expect purely by chance. Kappa values have the following interpretations:

Kappa	**Interpretation of strength of agreement**
<=0	Poor
0.01-0.20	Slight
0.21-0.40	Fair
0.41-0.60	Moderate
0.61-0.80	Substantial
0.81-1	Almost perfect

Usually, a hypothesis test would take the form

$$H_0: \kappa = 0$$

Which tests against the null hypothesis that kappa=0, meaning agreements are the same as that expected by chance. However, this may not be a reasonable null hypothesis. We would hope that the parent and nurse taken swabs would match more than they would simply by chance.

It is more realistic to test against a null hypothesis of kappa=0.40. If kappa is less than 0.40, we would say that this is clinically 'unacceptable'. We would like to be able to detect a kappa of 0.70, to indicate that the swabs match substantially. In this case, we would require a sample size of 180 to detect a kappa of 0.7 against a null hypothesis of 0.4, with 80% power (see Table 1).

Table 1: With a proportion of positive ratings 0.10 and power 80%, we need these sample sizes:

Kappa to detect	**H_0: κ =0**	**H_0: κ =0.4**	**H_0: κ =0.5**	**H_0: κ =0.6**	**H_0: κ =0.7**
0.4	50				
0.5	32	1617			
0.6	22	405	1519		
0.7	17	180	380	1340	
0.8	13	102	169	335	1090
0.9	10	65	95	149	273

These figures are taken from [30]

9.2.2 Recruitment numbers

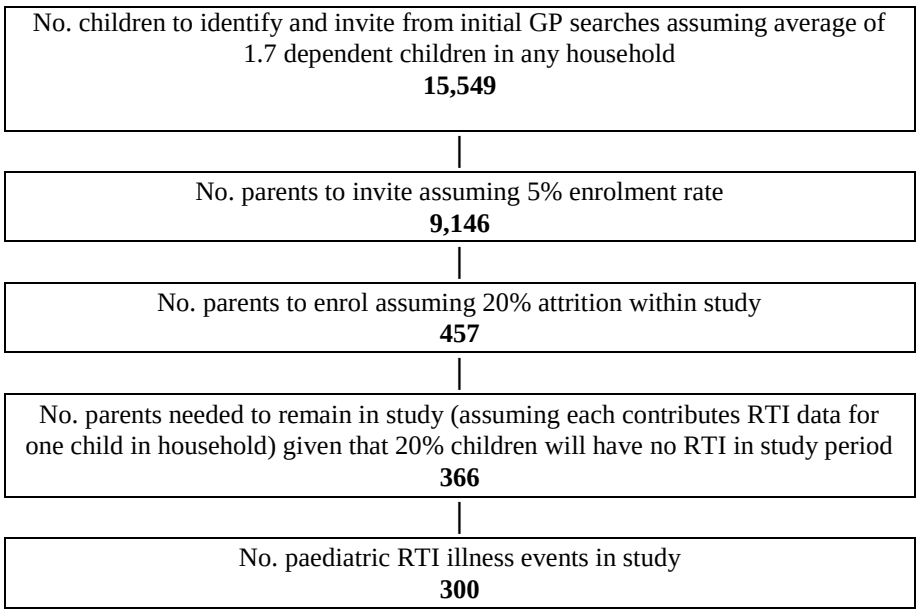
This is a feasibility study, aiming to recruit enough participants to record 300 incident RTIs over one winter period. In order to achieve this number, based on a conservative estimate of 80% of recruited children developing at least one RTI over winter [31], a 20% parent attrition rate after study enrolment, and a conservative estimate that each parent will contribute data for one child only, the aim is to **recruit a total of 457 parents** to take part in the study. The average number of dependent children is 1.7 per UK household [32]. If each of the 457 parents enrols all their children in the study we will have approximately **777 children in the study**. (We are assuming that each household may enrol all their children but then will contribute RTI data to the study for just one child and not more).

Our expected 5% mailout response rate predicts that we will need to send invitation letters to reach 9,146 parents to reach our recruitment targets. Given that the mailout system will be arranged around numbers of eligible children identified, the initial mailout must be factored up by the average number of children in each household (1.7) meaning 15,549 children will be identified during the GP surgery search process and this number of pre-filled in consent forms with invitation packs will be sent to parents (via Docmail). We aim to consolidate mailouts at one pack per household, with a separate pre-filled-in consent form included for each eligible child in the household. In the event that this is not possible via the GP search, mailmerge and Docmail procedures, we will send a separate invitation pack for each eligible child.

Our study database will notify us if we are close to recruiting 457 parents – or 777 children – sooner than expected to enable us to slow down/ stop further recruitment as necessary.

It is estimated that just under 20% of an average GP patient population will be parents of eligible children for invitation (from a basic exploratory GP database search). With an average GP practice list size of 7,000 [33], each GP surgery is likely to identify 1,400 children to invite. With a planned 12 GP surgeries recruited into the study, 16,800 children are estimated to be identified for invitation, which exceeds our planned target of 15,549.

9.2.3 Figure 3: Projected recruitment and retention rates



9.3 Recruitment methods

One centre (University of Bristol) will recruit 12 GP surgeries within a 10 mile radius of Bristol city centre via the NIHR Clinical Research Network (CRN). There are currently 124 GP surgeries within this geographical area. We intend to source twelve surgeries out of these to help with recruitment to the study.

Participants will be children registered at participating GP surgeries recruited primarily via mailout from the GP surgery to parent(s). Parents are the main point of contact for study participation, and it is parents who complete the main informed consent and provide data for the participating children. Children in school year 3 (age 7/8) or older will also provide assent prior to participation. Using this source of participants keeps the research within primary care, for which the results of the future definitive cohort study are designed to be of use. It is expected that the response rate will be low at approximately 5% of households responding (personal communication, 2014, Professor Paul Little). GP surgeries will provide basic, anonymised, demographic information regarding non-responders. Recruiting via GP surgeries therefore brings the benefit of enabling an assessment of how representative the recruited cohort is for each surgery.

Mailout will be conducted via Docmail®, a secure print and mailout company provided by CFH Docmail Ltd, which is widely used to provide print and mailing services for local government, GPs, dentists, schools, exam boards and banks throughout the UK. The system can be found online (www.Docmail.co.uk) and requires a secure user name and password for businesses to log on and upload their letters and address lists to create mailings. The Docmail website is highly encrypted and once the mailing details have been uploaded, the production facility is a Standard 3 approved printer, being accredited to the following schemes (amongst others): APACS 55: Cheque Printer Accreditation Scheme; APACS 72: PINS Printer Accreditation Scheme; BS ISO IEC 27001:2005 Information Security Management Systems; BS 9001:2000 Quality Management.

10 PARTICIPANT SELECTION

10.1 Participant inclusion criteria

Children:

- aged ≥3 months and < 15 years*
- registered at participating GP surgery*

Parent:

- agrees to participate in all main study processes†
- has a mobile phone and/or regular access to an email account for weekly contact†
- is willing to provide data online (webpage accessed via phone, tablet or desktop) †

10.2 Participant exclusion criteria

Children:

- not signing assent to take part and are age equivalent of school year 3 (age 7-8) or above†
- only temporarily registered with the GP practice (i.e. not likely to remain a patient for the duration of main study participation)*
- with severe life-limiting (terminal) illness*
- at greater risk of serious infection complications including:
  chronic lung disease of prematurity, cystic fibrosis, previous aspiration pneumonia, HIV, splenectomy, sickle cell anaemia, IgA deficiency, hypoplasia of the lung, systemic lupus erythematosus, Alpa-1-antitrypsin deficiency, neutropenia, Hunter's syndrome, CHARGE syndrome, heart failure requiring ongoing medication, congenital heart disease requiring ongoing medication – i.e. still under treatment (GP to confirm on screening), hepatic disease, renal disease, severe developmental delay and tracheostomy; cancer patients (solid tumours and haematological malignancies); immunodeficiency states to include: transplant recipients, autoimmune disease (such as systemic lupus erythematosus) and respiratory patients treated with immunosuppressant medications as groups of immunocompromised patients*

Parent:

- lacking capacity to consent to participation (e.g. through learning difficulty)*†
- who does not speak / understand English language proficiently to enable a full understanding of the research study and questions and procedures required* †

Household:

- for which a study invitation could cause stress or distress to the parents. This will include recent bereavement in the family, any terminally ill child or parent.*
- which may present a risk for a lone working nurse visit (e.g. domestic violence).*

* – *to be screened at GP database search stage*
† – *to be confirmed by parent signing consent, and checked during welcome phone call*

11 RECRUITMENT PROCEDURE

(see Figure 1)

11.1 GP Surgery Recruitment

GP surgeries are eligible to take part in EEPRIS if they are located within 10 miles of Bristol City Centre.

The NIHR Clinical Research Network (CRN), West of England will initially publicise the study to GP surgeries in the Bristol area, through the CRN monthly bulletin and email to practice contacts. An example of the information for the initial information to circulate to generate expressions of interest from practices is shown in Appendix A. Details of practices who express an interest in the study will be passed on to the study team to make contact, send the surgery a GP research information sheet (Appendix B), answer any questions and arrange a recruitment meeting. The aim is to recruit twelve practices by October 2015 (or November if delays make this necessary). GP practices will only be recruited from local areas (CCGs) that have provided research governance approval and that the Sponsor has approved. Efforts will be made to source different GP surgeries to cover a range of areas of deprivation using the Index of Multiple Deprivation.

NHS service support costs (SSCs) and research costs will be offered to GP surgeries for study-related tasks including meetings, study set up, mailout, texts, and other administrative tasks, and for provision of facilities for the notes review process.

11.2 Participant recruitment

11.2.1 Method of recruitment

Children's recruitment methods will be similar to those employed by the successful and soon to be published, 'PRIMIT' study (led by Paul Little). The primary mode of recruitment is via GP surgery mailout. GP surgery staff will be asked to run a search on their patient database to provide a list of eligible children to invite. The list will be subject to GP screening against an agreed protocol (e.g. to exclude recently bereaved families or households in which there is a terminally ill child) before invitations are sent. The surgery will update a standardised participant recruitment letter provided by the research team (Appendix C) with their surgery header and GP signature. These will be sent (addressed "to the parent/carer of [child's name]") to children's addresses via Docmail. Sent in the same envelope will be a participant information leaflet for parents (Appendix D), a children's leaflet (Appendix E), a consent form pre-filled in with each eligible child's details (Appendix F) merged onto the form plus a return envelope (freepost standard). For any child identified who will be aged 7 or older by September 2015 (the equivalent of school year 3 and above), the consent form will have an assent section on the reverse side for them to sign to agree to take part in the study (Appendix G). No children in this older age group will be recruited into the study without their written assent.

The research team will record details of those who consent to participate, do not respond or request not to be contacted from each surgery on an anonymised list of EMIS codes of all the children invited by each practice (produced by the practice staff and provided to the research team once the mailout list is confirmed and sent to Docmail). This updated list will be sent back to each GP surgery to run a repeat mailout letter (Appendix H) to all non-responders (i.e. the original list taking off responders) three weeks after the initial mailout. If the GP surgery is also signed up to an automated patient text system, this second mailout will be followed by a text reminder about the study a week later to the parents of younger children (aged under school year 3) from the second mailout recipients (Appendix I). This is to ensure that the invitation goes to parents, and not directly to any child (as a mobile phone number contact recorded for older children in a medical database

may be the child's number, rather than the parent's). The invitation letters, participant information leaflet and text will all include study team contact details and an invitation to contact the team with queries about the research.

A final anonymised list of EMIS codes updated with whether the study team received an opt-in, opt-out or no response will be sent to practice staff by two months from the final mailout so that their records can be updated as required.

Study recruitment posters (Appendix J) and recruitment cards (Appendix K) will also be made available to patients in each participating GP surgery, inviting patients to contact the study team for more information. Any respondents opting in independently of mailout receipt will be screened by telephone according to the same eligibility screening criteria used in GP database searches. If eligible to be invited, these people will be sent an invitation pack (participant information leaflet, consent/assent form and children's information letter if applicable) by the study team.

11.2.2 Screening for eligibility

Screening for suitability will take place via the GP database search filters, to exclude from invitation any children who are at greater risk of serious infection. The main reason for excluding these children is that this study is aiming towards an intervention designed to reduce RTI consultation rates where appropriate. Children at greater risk of serious infection by definition have a medical reason for a low consulting threshold for these illnesses.

Search filters will also screen out those children who have a severe life-limiting (terminal) illness (for whom a study invitation could cause distress). Age filters will also be applied, as well as exclusions based on temporary (as opposed to full) patient status.

GP surgery staff will also be invited to screen the lists to identify and remove: children who are resident in a households for which a study invitation could cause any stress or distress to the parents (e.g. recent bereavement in family, terminally ill sibling), or which may present a risk for a lone working nurse visit (e.g. domestic violence).

Numbers of children (and households) excluded by the main criteria outlined above will be collected and reported.

Second to the GP search phase, parents will sign their consent to take part in the processes required for participation in the study as detailed on the consent form (see Appendix F). If there is any missing or illegible information on any consent form received, the study team will contact the parent to confirm details and re-send the consent form if necessary.

Our notes review phase (at the end of the study) will check the relative success of our study exclusion and screening strategy, and will form a small outcome of interest for designing a large scale study.

11.2.3 Gaining participant consent

As outlined above, parents will receive in the post an invitation letter, information sheet and consent form, with a children's information leaflet for children to read or have read to them. For any older child for whom we require assent, a consent with assent form will be sent. All will include a freepost return envelope. Parents are invited to contact the research team with any questions or concerns before signing up to the study. It is the GP surgery that makes the initial contact via postal invitation. Responses received by the research team (via post, phone call or email contact) from

parents receiving the invitation letters will be the first contact that the research team will have with any potential participants. Only the information directly provided by parents at this stage is available to the research team. Older children (school year 3 and above) will need to sign their assent in order to be enrolled.

Postal receipt of the study information (with the invitation to contact the team with any questions) and the process of parents completing and returning a consent form to the study team makes up the initial informed consent procedure for the study. The welcome phone call from the study administrator will come after receipt of the signed consent form, and will check the parent's understanding of the study. If any concerns about eligibility arise during the welcome phone call, we will not proceed with any study procedures (i.e. baseline data collection and commencing of weekly prompts) until these are resolved appropriately (e.g. refer to study manager for assessment if unclear). If there is any reason that the parent, child or household is not suitable for inclusion at this stage, the study team will decline to enrol them in the study and explain this decision to the parent.

Each parent will be posted a copy of their signed consent form (with assent where relevant) on study enrolment. A copy of the signed consent (with assent) forms will also be sent to GP surgeries in batches at the end of each month of study recruitment via post or scanned and emailed to the GP surgery via a secure NHS Net email account specifically set up for the EEPRIS Study.

As this is a small feasibility study we unfortunately do not have facility to accommodate non-English speakers, or parents who lack capacity to consent. It is to be noted that we use the word parent to mean a primary care-giver or adult who has legal responsibility for the child. If the main parent lacks capacity, but has an associated carer who could legally provide consent, then they would be able to take part in the study.

11.2.4 Enrolment procedure.

On receipt of a returned consent form, study staff will manually enter the contact details and consent form information into the study administrative database (Admin DB), which will automatically generate a unique code for each participating child. In the event of any ambiguity or incorrect completion of a consent form, the study administrator will telephone the parent to clarify and post out a new consent form for the parent to return.

The parent will then receive a welcome telephone call from the study administrator to confirm eligibility, thank them for taking part, answer any questions about the research and direct them to complete a baseline form online. We will also ask for the parent's contact preferences and about any special needs with respect to research visits and ongoing participation in the welcome call.

The parent will be emailed (or texted) a link to their individual survey page (encrypted link with no login details necessary) to provide baseline data for each child (the electronic copy of consent form data will be attached to the email also).

The administrator will check if there are multiple consent forms from one parent so as not to duplicate welcome phone calls, and will check during the phone call if any other consent forms than those we have received may be due to arrive. Only one welcome call will be made per household (if multiple children are enrolled), and the parent will have been made aware of this on the information sheet as well as during the call. The study administrator will post the parent a welcome pack to include a participant welcome letter (Appendix L), contact cards (to pass to other parents) (Appendix K) and a fridge magnet magnet and poster to remind them about the EEPRIS symptoms to look out for and study processes (Appendices M and M-2) as well as a copy of their signed consent form.

A separate email (or text) will be sent to the parent for each child they have enrolled – to ensure clarity for the baseline data entry.

The consent form has an optional field inviting parents to consent to take part in one audio-recorded interview for the qualitative component of the study. See Parent and child interviews for details of the interview sub-study.

11.2.4.1 Enrolment process for parents opting in independently of letter mailout

Some parents will make contact with the study team from seeing a study poster in a GP surgery (Appendix J) or from picking up contact cards (Appendix K) or finding the study online. In this instance, the parent will not have a pack with a consent form to return. The enrolment procedure will be as follows:

i) Participant expresses an interest via text/ email/ phone call. Administrator logs details on AdminDB:
   - Date
   - Name
   - Contact details
   - How contacted us
   - Where found out about the study
   - Free text for any other info

ii) Administrator conducts a screening phone call to check:
- any missing details from above list (i)
- if the child is registered at a participating GP surgery (if not, we cannot recruit)
- whether parent and child are eligible according to EEPRIS inclusion and exclusion criteria

iii) If eligible, administrator fills in parent and child details on a new consent form

iv) Administrator sends this filled in consent form with an invitation pack to the parent (same as that sent by Docmail).

12 PARTICIPANT REIMBURSEMENT/ THANK YOU VOUCHERS

Participating parents will receive a £15 shopping voucher as a thank you for contributing data for each enrolled child who has an RTI recorded within the study. This is to recognise that it is the parent who contributes the most time and effort for the study (though as it is a generic shopping voucher, the parent will be free to share this with participating children if they choose).

This voucher will be posted to the parent on completion of their active participation phase – i.e. on survey completion after resolution of an RTI and declining to continue in the study, or after data collection ends (30/04/2016), whichever comes sooner. The participant information leaflet for parents (Appendix D) makes it clear that vouchers are a thank you for contributing RTI data to the study and that although it is possible that not all children will develop an RTI within the data collection period, it is likely that participating parents will have the opportunity to contribute in this way as (due to the prevalence of RTIs) it is normal for all children to develop symptoms at least once over the winter period.

If the parent opted to continue with the same child and contributed more than 1 RTI for that child, they will receive £15 in total (not more than this). This approach was regarded as acceptable by our study PPI parent advisory group, and is thought to guard against any risk of bias that could be introduced if ongoing data collection in the same child was seen to be incentivised.

Any parent that takes part in a qualitative interview will receive a separate £5 shopping voucher on completion of the interview, given in person by the interviewer.

For each clinician who contributes one half hour interview within the study, the practice will be reimbursed with £40, in accordance with standard research reimbursement costs, approved by a representative from Avon Primary Care Research Collaborative (APCRC).

13 DATA COLLECTION AND MAIN RESEARCH PROCESSES

GP surgeries will be asked to provide demographics of the original list of eligible parents (and children) for comparison with those who take part in the study.

13.1 Baseline

Baseline data (Appendix N-1) will be collected online from parents at enrolment for each of their children in the study (and prior to the first study RTI). The following will be collected from parents (online):

Demographics
Household demographics: parent education level, occupation, ethnicity, composition of household (number and age of adults and children in the home), presence of smokers in the home, number of bedrooms in the house. (Number of household bedrooms enables a measure of crowding in the house – as number of children per bedroom – which may impact on RTI transmission risk).

For each of the parent's children being enrolled as participants in the study, baseline data will be collected on: age, ethnicity, gender, if the child is full time in the household, or stays elsewhere regularly (e.g. separated parent) and how many nights per week if so. As well as presence of any lifetime diagnosis of asthma, eczema and hay fever diagnoses in the lifetime of the child.

All these data will be used for descriptive statistics of the study sample and to describe study subsamples by recruitment and retention rates.

RTI symptoms present at baseline
The EEPRIS Study is interested in *new* RTI episodes that develop prospectively, so we are not collecting data on any child's RTI that is already present on the date the parent filled in the baseline questionnaire. The baseline questionnaire asks if the child is currently experiencing RTI symptoms. If the answer is yes, the parent will receive a phone call each week checking if these original symptoms have now resolved. When the parent confirms that the symptoms have resolved, then the standard weekly symptoms prompts will be activated.

13.2 Weekly symptoms prompts:

After completion of the online baseline questionnaire, there will be automatic activation of a weekly email (or text) symptoms prompt. Parents will receive one email (or text) per week for each of their children in the study, which asks:

"Hi [parent's first name], has [child's first name] developed any EEPRIS symptoms in the last 7 days? Please click to reply:[insert individual survey link]"

The survey page checks the presence of EEPRIS symptoms as follows:

EEPRIS symptoms:

- *Blocked/runny nose*
- *Earache/ ear discharge*
- *Sore throat*
- *Cough*
- *Chesty symptoms (breathing faster than normal when resting; wheeze or whistling chest)*
  - *over and above what is normal for your child*

Has [child's initials], (year of birth [20XX]) developed any of these symptoms in the last 7 days?
Yes / No

➔ *A "Yes" response automatically forwards to the first 'symptoms and recovery' survey.*
➔ *A "No" response automatically generates the following online text:*
"Thank you for responding, we really value your contribution. We will check again next week. Best wishes, the EEPRIS team"

13.3 Incident RTI symptoms and follow up questions

Once a parent responds "Yes" to the weekly prompt to confirm the presence of RTI symptoms in a child, they will automatically receive a link to a symptoms survey page (Appendix N-2) for that child (a direct encrypted link) via email (or text). Data will be collected on: date of first presentation of any RTI symptom presentation in the child, and a list of symptoms with a seven point severity rating scale (as used in previous studies where zero is "normal/no problem" and six is "as bad as it could be") for each day of the RTI to be filled in at the end of each day (up to maximum of 7 retrospective days) to capture symptoms from illness onset. Symptoms of interest will be runny/blocked nose, earache, ear discharge, sore throat, cough and chesty symptoms (to include breathing faster/shortness of breath; and wheeze/whistling) – with measures of systemic impact to include fever/ chills, fatigue, and disruption to usual activities.

On confirmation of the presence of RTI symptoms, the parent will receive an email (or text) every two days (towards the end of the day at about 6pm) to remind them to complete the symptoms diary, providing a direct (encrypted) link to the survey. This will occur until symptom resolution, defined as two consecutive symptom-free days, or for a maximum of 21 days (from the date of symptoms onset) of ongoing symptoms.

In addition to capturing daily symptoms and severity for the child with RTI, the following questions will be asked:

- School/ day-care attendance
- Parent time off work
- Use of NHS resources (telephone, walk-in clinic, GP surgery attendance, secondary care)
- Antibiotic consumption by child
- Use of other medicine for RTI including over the counter medicines
- RTI symptomatic status of household members

The daily symptoms diary accounts for three weeks of continuous symptoms (including retrospective symptoms filled in on day one of data collection). If the child has continuing symptoms after this time, there will be a brief weekly questionnaire (Appendix N-3) to fill in up to a maximum of 8 weeks from the date of symptoms onset. A weekly email (or text) prompt with questionnaire link will be sent to the parent. If there is no response to two consecutive weekly

prompts for children with ongoing symptoms, the administrator will call to collect data over the telephone.

On resolution of the RTI episode, the parent will be asked

- if they would have wanted paper questionnaires rather than online,
- the level of acceptability of the online data collection platform (simple Likert scale with free text response option) and
- if they feel that taking part in the study changed how they managed their child's RTI.

They will also be asked if they are happy to continue in the study – either with same child or with any other of their children enrolled. If the parent responds positively to continue in the study for either the same child or other children, the weekly emails (or texts) continue (for the same or other children). If the parent responds no to either, the parent will complete their active participation phase for that child (or other children), and the weekly symptoms email (or text) reminders will cease as appropriate.

13.4 Research Nurse visit (examination and swab taking)

When a parent responds "Yes" to the weekly prompt to confirm the presence of RTI symptoms in a child, the Admin DB system will automatically prompt for a research nurse (RN) home visit to be arranged as soon as possible.

The RN will visit the parent and symptomatic child at their home (or other convenient location at the parent's request) to conduct a clinical examination of the symptomatic child, prompt the parent to collect a saliva sample and nasal swab, and for the nurse to take a (clinical standard) saliva sample and nasal swab. The visit must take place before symptoms resolution – defined as two consecutive symptom-free days. The visit will last approximately 30 minutes.

Clinical examination:

The RN will take the following measures from the child (Appendix N-4):

> Pulse, temperature, respiratory rate, O_2 saturation, consciousness level and capillary refill time. The RN will also assess presence/absence of: pallor, grunting, nasal flaring, stridor, inter/subcostal recession, inflammation of pharynx/tonsils, wheeze/whistling in chest, crackles/crepitations, bronchial breathing, nasal discharge, ear ache, ear discharge and rate general wellness (on a 10 point scale).

If the RN is concerned about the child, they may advise that the parent seeks medical advice and record this as a possible study-induced primary care visit.

13.5 Nasal and saliva sampling

13.5.1 Symptomatic samples (taken during nurse home visit)

The nurse will bring to the home visit two sets of parent sample collection kits with instructions and prepaid postage pack (e.g. Royal Mail Safebox^{TM}) for returning them to the laboratory in the post.

The nurse will hand over a kit and ask the parent to follow the instructions (samples recorded as "parent-taken saliva sample" and "parent-taken nasal swab"). The parent should be able to follow the instructions without extra guidance from the nurse, though the nurse will be present at the time of the parent taking these symptomatic samples.

The nurse will also take a saliva sample (sample recorded as "nurse-taken saliva sample") and nasal swab (recorded as "nurse-taken nasal swab") to go for immediate laboratory processing. The RN places these swabs in a coolbox for clinical standard preservation and transport.

The parent and child will be thanked for their time. The child will be offered a sticker for taking part (if age appropriate).

The nurse will also leave a saliva sampling kit (complete with instructions) with the parent together with a pre-labelled Royal Mail Safebox^{TM} (or other pre-paid postal return system appropriate for human specimen transport) for taking a swab once the child has recovered. The parent will be asked to take the next sample when they are prompted via the online form – which will be on confirmation of symptoms resolution.

The parent is asked to post the samples (in the Royal Mail Safebox^{TM}) on the same day to the central laboratory for microbiological analysis.

The RN transports the nurse-taken swabs via cool box straight to the PHE laboratory on the day of collection. Samples need to be dropped off before 5.30pm Monday to Friday and before 12pm on Saturday (laboratory not open on Sundays).

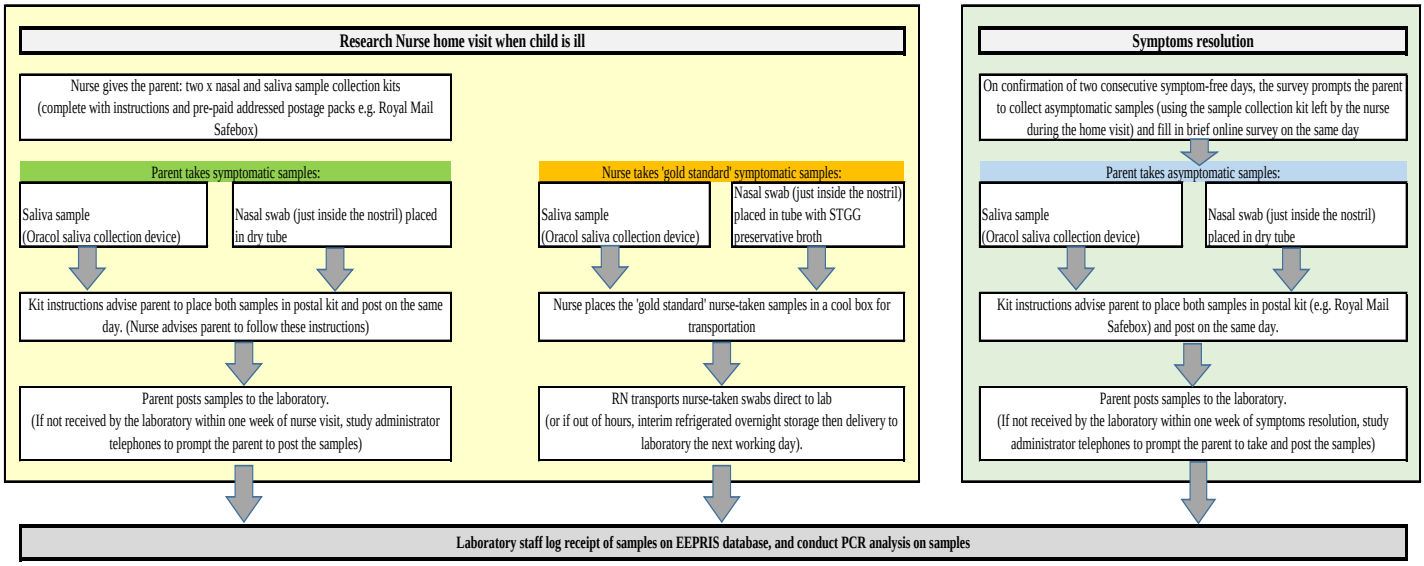
If these drop off times are not met (due to late appointments), the samples will be stored at 4^{o}C overnight in a secure samples refrigerator at the University of Bristol (in a secure room in the basement of Canynge Hall) before being transported by the RN to the laboratory the next day. (Since freeze/thaw cycles may damage the sample, it is better for them to be stored at 4^{o}C than to be frozen during interim storage)

If for any reason they need to be stored for longer than overnight, the nurse should leave them at the laboratory to be processed, rather than storing at 4^{o}C for several days.

13.5.2 Asymptomatic sample

Previous research indicates that microbial shedding will decline along with symptoms resolution [34] and so it is planned to take asymptomatic samples as soon as possible after symptoms resolve. Once the parent confirms resolution of RTI symptoms on the online survey (defined as two consecutive symptom-free days), the survey will prompt the parent to take an asymptomatic saliva sample and nasal swab using the kit that was provided at the RN home visit, and post this to the laboratory in the prepaid postal package, and complete brief symptoms questions on the day of the sample collection.

13.5.3 Figure 4: Flow diagram of sample collection and transportation



13.5.4 Sample labelling

Labelling of the samples will be carried in the following way: The nurse will take with her a roll of randomly generated bar codes that will have been printed on labels that can withstand being stored at -70^{o}C. There will be three exact duplicates of each code, one will be stuck to the sample tube, the second to the form that will accompany the sample to the laboratory (the only other information that will be contained on this form is the date on which the samples were prepared), and the third duplicate will be carefully placed on a form that precisely identifies the sample and study ID number. The nurse will stick these labels on sample tubes and forms whist at the participant's home. The nurse, when at the office, will scan the barcode on the form that identifies the sample so that a record linking the barcode to the sample is made on the Admin Database. Parent sample kits will be pre-labelled with barcodes, and linked in the same way. The labelling system will be tested to ensure we leave no room for error, and the nurse training will emphasize the importance of accurate labelling.

We will do spot checks on the barcode labelling system via internal administrative audit once the study is underway. This will be in the form of cross checking our barcode key with records of sample collection dates and barcodes logged at the laboratory.

13.6 Primary care medical notes review

At the end of the active participation phase (May/June 2016), a medical notes review will be conducted on all children who provided RTI data in the study (Appendix N-5).

The following data will be collected to supplement the parent-reported baseline data: Child immunisation history; chronic co-morbidities, current medications for chronic conditions, RTI consultation history, antibiotic prescriptions in year prior to study enrolment (for RTI or other conditions). The success of the initial screening/exclusion process will also be verified.

For each RTI episode included in the study, medical notes will be reviewed for entries within the duration of each study RTI (from symptom onset date to symptom resolution) to extract: use of primary care services, antibiotic prescribing, secondary care contacts to include likely diagnoses, A&E attendance and hospital admission.

14 LABORATORY PROCESSING OF NASAL SWABS AND SALIVA SAMPLES

14.1 Storage of samples for future analyses

Upon receipt in the laboratory, nasal swabs and saliva samples will have a second, laboratory specific, barcode label stuck to them. The samples will be booked on to the Laboratory Information Management System (LIMS) using a barcode reader system. The following information only will be recorded: EEPRIS barcode, sample receipt date, laboratory barcode.

The unique laboratory barcode generated for each sample will be affixed to each of the original sample vials, and copies of this same barcode will be affixed to any secondary storage vial(s), and also the study request form. Request forms will be date and time stamped and scanned to generate an electronic copy. Hard copies will be filed.

This system has a two-fold benefit: it ensures maximum anonymity of samples, and reduces human error. i.e. no codes are to be typed in, just barcodes to scan. The EEPRIS team will hold the key to which EEPRIS barcode corresponds to which participant ID code, and the laboratory will update a record of EEPRIS barcode matched to laboratory barcode.

To facilitate optimal sample storage, initial sample processing will take place on the day of receipt as follows:

*Saliva samples:*Oral fluid collection devices will be centrifuged to recover oral fluid which will be transferred to a storage vial and stored at -80C.

*Nasal Swabs:*Dry swabs for microbiological studies will be removed from the sheath and the tip snapped off into a tube of Universal Transport Medium and stored at -80C. Swabs in STGG broth and RNAlater will be stored at -80C**.**

14.2 Processing of nasal swabs and saliva samples.

Swabs in universal transport medium and saliva samples will be removed from the freezer, thawed at ambient temperature and pulse centrifuged. Total nucleic acids will be recovered from 200 □l aliquots of each sample using a Kingfisher 96 processor. Eluted nucleic acids will be analysed for microbial nucleic acids by reverse transcription real time multiplex polymerase chain reaction (PCR) in a Taqman low density array (TLDA). Briefly the nucleic acid eluate is added to a reaction mix which in turn is added to one well of the TLDA. The reaction mix is then centrifugally distributed to an array of 48 amplification chambers each of which is pre-printed at the time of manufacture with primers and probes for amplification and detection of a specific microbial target or amplification control (Appendix O). Amplification and detection takes place in an ABi Viia7 analyser. Results, expressed as cycle threshold (Ct) values for each amplification target are downloaded into an Excel spreadsheet which can then be added to a database of results. Results will be reviewed, interpretative comments added as necessary, and emailed to the study administrator as required.

14.2.1 Endogenous and exogenous internal amplification controls

- The system uses the detection of a human mRNA species as an endogenous internal control to determine how well the sample has been collected and preserved before arriving at the laboratory
- The addition of control bacterial/viral nucleic acid to the sample once at the laboratory will be used as an exogenous internal control to determine the effectiveness of the nucleic acid extraction and detection system. This will also allow the detection of inhibitors (eg mucous carried over in lysis buffer) that may be present in the sample

14.2.2 Cycle threshold (C*t*) values

- This is the number of cycles required to raise the level of the target nucleic acid above threshold levels and this allows the detection to be semi-quantitative
- A low C*t* value indicates a larger amount of nucleic acid and therefore larger amount of the virus/bacterium in the original sample, a high C*t* value would suggest lower levels in the sample
- A C*t* value is available because real time polymerase chain reaction (RT PCR) is being carried out

14.2.3 Taqman low density array (TLDA)

(see Appendix O)

- This is the format of RT PCR that will be used on the EEPRIS samples
- Each array uses 48 primers to test for 48 separate targets
- The 384 well array card will allow 8 samples to be analysed at a time

14.2.4 Results feedback

It is to be noted that individual results of the microbiology analysis will not be fed back to the GP or the parents of participating children. This is made clear in participant and GP study information leaflets.

14.2.5 Longer term sample storage

Longer term storage of anonymised study samples and their remains is planned (for those participants who have consented to this) so that these may be used in future infection studies. The ongoing storage of any samples will adhere to standard laboratory procedures and guidelines for tissue banking, in accordance with the Human Tissue Act.

The transport medium that will be used in EEPRIS is not suited to culture of bacteria, but PCR can be carried out on the frozen sample for the detection of host (participating child), bacterial and viral nucleic acids

15 PARTICIPANT RETENTION

15.1 Recording of participant retention information

Number of complete RTI episode data sets compared with the number of families and children enrolled is the primary outcome of interest. The study will capture information on study engagement by each parent. Levels of completion of study procedures will be recorded via the Admin DB database to enable provision of more detailed analysis of the primary outcome including descriptive statistics on participants grouped by data completion rates.

15.2 Detail of follow-up of non-responding participants

In order to minimise data loss, the Admin DB system automatically creates prompts to parents on detection of lag to data completion. If baseline data is not provided within one week of the welcome phone call, an email (and/or text) prompt will be sent. If no baseline data is provided within one week of the prompt, a second prompt will be activated with an alert for the study team to call the participant to prompt them to complete the online questionnaire if not provided in the following week (i.e. within three weeks from welcome phone call). Weekly symptoms prompts via email (or text) are only elicited once baseline data has been provided.

If a parent responds to the weekly prompt to say that their child *is* symptomatic, they will be asked to provide the date of first symptoms (and fill in a symptoms diary retrospectively for all the days of the illness to date), after which email (or text) prompts will remind them to provide daily symptoms diary data every two days. If a week goes by without symptoms diary completion once incident RTI is identified, the parent will receive a phone call reminder (answerphone message only is acceptable) to fill it in online. The study team will be alerted to call the participant to prompt data collection online or obtain the data over the telephone if not provided by the end of one week from a positive response to the first email (or text). The process applies for each additional week of symptoms – i.e. if there is any week in which no symptoms data is provided, a phone call reminder is triggered (answer message only is acceptable).

Reasonable attempts to arrange the RN home visit will be made. If the parent makes no response to a number of contact attempts to arrange it (maximum ten contact attempts at different times/ days/ means of contact), or cancels up to three arrangements and re-arrangements, or is not present in the house for one arranged and one further re-arranged home visit, then the RN visit will be abandoned. This will be recorded as missing data, but the participant will not be withdrawn from the study.

If no asymptomatic sample is received in the post within one week of confirmation of symptom resolution, the study administrator (answerphone message only is acceptable) will call to remind the parent to take it. If there is no sample after a further week, another phone call will be made (attempting to speak to parent if possible). There will be a minimum of three contact attempts (and a maximum of ten contact attempts at different times/ days/ means of contact) to prompt for the collection and return of asymptomatic samples, up to a maximum duration of one month from symptoms resolution. This will be recorded as missing data, but the participant will not be withdrawn from the study.

If a participant moves GP surgery during the study attempts will be made to access their medical records in the new surgery through contacting the Health Records Authority.

16 PARTICIPANT WITHDRAWAL

Parents and participating children will be free to withdraw from the study at any time at their direct request. They will not have to give a reason for withdrawal, although any reason for withdrawal will be recorded within a withdrawal section of the online participant case report form (CRF) if given on a gentle prompt or freely provided.

On study withdrawal of any participant, the research team member informed of the withdrawal will complete an online study withdrawal form in the relevant section of the participant database, to record date of withdrawal, person requesting withdrawal, any reason(s) given.

Participants can choose to withdraw from all or some of the further study tasks. Withdrawal requests will be recorded as opting out of: ongoing texts/emails, phone calls, RN visit, parent or nurse collecting nasal swab, parent or nurse collecting saliva sample during the symptomatic phase; parent collecting saliva sample or nasal swab after symptoms resolution, swab analyses, qualitative interview, and/or primary care notes review. Recording of withdrawal requests by study task will be built into the study administrative database, so that once a participant has opted out of a task, the associated prompts and activities will cease (e.g. no more weekly emails/texts will be generated once it is recorded in the database that a participant has withdrawn from this task).

Parents and participating children who choose to withdraw from the study after enrolment retain the right to make an additional request that any data provided from them for the study to date be destroyed, including any clinical samples. This additional function will be built into the

administrative database also. In the event of requests to destroy data, these data will be destroyed according to usual laboratory and research procedures.

The research team may terminate a participant's active involvement in the study if any medical condition, event or situation occurs such that continued participation in the study would not be in the best interest of the participant, and/or the participant meets an exclusion criterion (newly developed or not previously recognized) that precludes further study participation.

Declining to be interviewed for the qualitative component at the end of the active participation phase will not count as withdrawal, as this in an optional element of study participation. Any reason for refusing interview will be recorded if given on a gentle prompt or freely provided.

17 DATA HANDLING AND RECORD KEEPING

Data collection will be online via Research Electronic Data Capture (REDCap™) and Admin DB database systems which are already in use and managed by the University of Bristol for conducting clinical research. Adapted versions of these databases are being developed for use in this study. The University of Bristol operates a strict policy to safeguard the security and confidentiality of research data and participant identifiable information. Data protection and security remain the priorities throughout the development of the database systems for the current study.

The REDCap™ system captures clinical data and other questionnaire answers, and the Admin DB system holds contact details and identifiable data. This dual system ensures that research data is held confidentially – i.e. separate from identifiable information. Only the immediate study team will have access to the link between research data and participant identifiers. This system enables a restricted system for database access which means that study staff members will have access only to the information that is necessary for their role. For example, laboratory staff entering microbiological data will not need to see other clinical information or contacts details of participants, and so will have their database access restricted on this basis.

All data will be entered online in the first instance. Parents will fill in all questionnaires online via a secure survey function of REDCap. Parents will receive an email (or text) containing a direct link to their individual questionnaire page for filling in. This direct link function ensures that each parent has access only to the survey page(s) relevant for each of their children in the study, and it is impossible for any parents in the study to see any other participant's information or to accidentally input data into the record of any child that is not theirs.

In the event of a parent not completing online data after several prompts, the study team will collect the data via a telephone call and input it online contemporaneously. This direct online data collection (rather than collection onto paper form and then transferring onto the computer) minimises opportunity for data inputting errors. The online questionnaires will be designed to minimise error through use of multiple choice answer options, drop-down lists and progression through the questions dependent on completion of all necessary fields.

Data collected during the RN visit will be entered online at the time via tablet (with mobile internet package). In the event of internet failure during the home visit, the RedCAP data collection system has an offline facility, so there will be no data loss. RN will have paper forms to use as emergency back-up (e.g. tablet run out of battery), and will input the data directly after the visit as soon as internet connection is reached.

Notes review will be conducted by the research nurse (or study research staff) in GP surgeries, using a tablet (with mobile internet) or accessing the database online via the GP surgery computer. In the event of internet or database failure during the surgery visit, the researcher will have paper forms to use as emergency back up, and will input the data directly after the visit as soon as database/ internet connection is reached.

Data will be collected, transported and stored according to requirements set out by the Data Protection Act 1998 (amended in 2005)[35]. Study data and documentation will be archived after study completion and will be stored in password-protected electronic file format for twenty years after study completion in accordance with University of Bristol policy [36]. The University Research Data Storage Facility (RDSF) provides secure, long term storage for research data.

18 STATISTICAL ANALYSIS

18.1 Descriptive statistics and quantitative analysis

As this is a feasibility study, we will present simple descriptive results. The main outcome, for example, being the number (and percentage) of complete RTI episode data sets for our study sample. Levels of completion of study procedures will be recorded via the Admin DB database to enable simple descriptions of the different levels of study retention. These descriptive statistics will then be used to estimate the number of GP surgeries and participants required to participate in a definitive cohort study with RCT.

We will describe the characteristics (to include age, comorbidities, ethnicity and household demographics) of the children and households in the study (Means and standard deviations will be presented for normally distributed variables. Medians and interquartile ranges will be presented where variables are non-normal, and percentages presented for categorical variables). Descriptive characteristics of similar variables (as available from GP database search outputs) will be presented for the GP surgery populations from which we recruited (for sample representativeness and response rates).

Analysis of primary outcome

We will assess whether our outcome is associated with particular baseline characteristics, e.g. does response completion vary by post-code index of deprivation or household crowding? Is age, gender or ethnicity of the child or parent related to response rate? Our primary outcome is a binary variable: presence/absence of a complete RTI episode dataset. As such, we will use χ^2 tests, t-tests and univariable logistic regression to assess associations of baseline characteristics with the outcome.

Analysis of secondary outcomes

Similar strategies will be used for the secondary outcomes and linear regression will be used where the outcome is continuous, e.g. duration of RTI symptoms. Viral/bacterial load by will be compared across symptomatic/asymptomatic samples using paired t-tests/Wilcoxon signed rank tests.

We will assess the clinical equivalence of nurse-collected and parent-collected swabs. To look at presence/absence of microorganisms we will use Kappa statistics to assess the level of agreement between different methods of collecting swabs. If we consider the nurse-collected swabs to be the gold standard, then we can assess the diagnostic utility of the parent-collected swabs by calculating sensitivity and specificity. We will also consider whether the quantity of microoganisms present differs according to the collection method by calculating correlation coefficients and limits of agreement for Bland-Altman plots.

All statistical analyses will be completed using Stata™.

19 QUALITATIVE SUB-STUDIES

19.1 Clinician interviews

19.1.1 Participant recruitment

GP practices that agree to participate in the EEPRIS feasibility study are asked to nominate two or more prescribing clinicians (GPs and nurse prescribers) to be invited to take part in one thirty minute semi-structured audio-recorded interview each - at a time and place convenient for the clinician. A telephone interview option will be offered. The study manager will be the main contact enrolling each surgery in the EEPRIS study and will also conduct the clinician interviews for the nested qualitative research, so can introduce this part of the research in initial contacts with each GP surgery. This dual role of the study manager is thought to enhance the likelihood of gaining clinician consent to interview and maximise data collection possibilities, as clinicians will already be in contact with the study manager which has the advantage of familiarity and time burden reduction in comparison to a different researcher making contact separately for the qualitative work.

The study design aims to maximise data collection while minimising clinician time burden. The Research Information Sheet for Practices (Appendix B) - provided on gaining an expression of interest from the practice, and before study enrolment - informs practice staff of the interview study. The study team ask for clinicians to be nominated for interview, and also asks for permission for their opinions about the proposed future intervention that arise in discussions of the main study to be recorded (via written notes) for the qualitative study. This means that individual interviews can be supplemented by any clinician comments regarding RTI surveillance and the proposed online intervention that are freely-given in EEPRIS meetings and contacts. Comments will be recorded (via written notes) by the study manager (or other study staff) during EEPRIS recruitment meetings and other (e.g. telephone) contacts for those practices and clinicians who agree to this. The study manager will highlight the qualitative data collection plan in the first contacts with any practice staff, and at the beginning of the team meeting to enrol the GP practice into the main EEPRIS study.

Any staff member or GP practice team is free to decline either part of the qualitative data collection (semi-structured interview; or recorded comments within meetings/contacts) while still taking part in the main EEPRIS study. If an individual staff member does not want any of their comments in meetings or contacts to be used as qualitative data, then these wishes will be respected.

The surgery will be offered £40 reimbursement per half hour clinician interview. There are four GPs in an average-sized surgery [37], giving an estimated pool of 48 GPs to invite plus any nurse prescribers (NPs) and locums working at each practice. By inviting all the clinicians in EEPRIS-participating practices, it is estimated that a minimum of twelve prescribing clinicians will be interviewed (one per practice), though we aim to recruit until data saturation, and estimate that two interviews per practice may be appropriate. This gives us approximately twenty four participants. Efforts will be made to cover a range of GPs and NPs and length of service to NHS. Efforts will also be made to recruit across practices (rather than relying on several clinicians from a smaller number of practices). Numbers of clinicians invited from each surgery will be recorded along with any reasons given for not participating. These data will inform a statement of representative sampling and may provide some preliminary information on clinician engagement in the subject of the investigation.

19.1.2 Data collection (the interview process)

A participant information sheet specific to the interview study for clinicians (see Appendix P) will be provided in advance of taking part, and written consent will be sought directly before the start of

each interview (or confirmed verbally and audio-recorded if over the telephone) (see Appendix Q) and basic demographic data will be obtained for each participating clinician. The interview will be arranged at a time to suit each clinician to minimise time burden, so it could be offered directly after the EEPRIS enrolment meeting at the surgery, or at another time at the clinician's convenience - either in person or over the telephone. Data collection is likely to take place between the months of October 2015 and February 2016.

During the interview participating clinicians will be provided with an outline of a microbiology and symptoms profile intervention. This will consist of two written text vignettes of common RTI microbes and associated symptomology profile. These will be provided in hard copy for face to face interviews or by email for telephone interviews, with an explanation that such data would be provided online with real-time symptom profiling of circulating RTIs in the community. Interviews will be semi-structured, based on an outline of key areas of interest informed by components of the Normalisation Process Theory (NPT) [38]. The NPT is a model which can be used to evaluate the implementation of complex interventions. In this case, the first three of the four NPT components are of relevance: i) Coherence – the perceived meaning of the intervention (i.e. does the intervention make sense to clinicians, is it perceived to be of value, does it align with overriding goals and activities?); ii) Cognitive participation – the commitment participants are willing to make (i.e. are clinicians prepared to invest in the intervention? What are facilitator and barriers to its use?); iii) Collective action – the effort that participants will make in response to an intervention (i.e. what perceived effect will the intervention have on clinicians' consulting and prescribing behaviour, is it consistent with existing practices? Feasibility and efficacy of the intervention in practice; commitment to using existing sources of information about circulating illnesses). The fourth component of NPT; Reflexive monitoring, is not thought to be relevant as this is a reflection on the intervention *once it has already been in place* for a time. As we are gaining opinions on an outline intervention based on pre-prepared vignettes, rather than a fully implemented real-time data intervention, the study is interested in gaining opinions to inform the design and development of a full intervention, as well as drawing on clinicians' real experiences of using existing sources of information about circulating illnesses.

See Appendix R for an outline of the topic guide. Topic areas may be added or adapted in an iterative process in response to themes identified in earlier interviews and recorded comments.

19.2 Parent and children interviews

19.2.1 Participant recruitment

A University of Bristol qualitative Research Associate will conduct semi-structured individual face-to-face interviews with parents of children participating in the EEPRIS feasibility cohort study. Willing and competent participating children (age equivalent of school year 3 and above) will be invited to contribute to the interview also.

The intention is to achieve a sample with maximum variation in experiences of the feasibility study and views on the development of the planned intervention and RCT. All parents participating in EEPRIS who opted to sign their consent to the interview study (on the main study consent form) are eligible for inclusion in this study, and any participating children who are old enough to have signed assent will be invited to contribute at the same time as the parents.

Parents will be sent more detail about the interview study (by post/ email) at the time of invitation to interview (see Appendix S). They may decline to be interviewed if they choose, and still remain in the main EEPRIS study.

Efforts will be made to select potential interview participants purposively using baseline data collected on the following characteristics:

- Parent education level
- Employment status (full-time, part-time, full-time carer)
- Socio-economic status (Index of Multiple Deprivation derived from home postcode)
- Ethnicity (white vs non-white)
- Number of children (1 vs >1)
- Age of participating children (pre-school, primary and secondary)

Participant selection based on the above characteristics will be performed once this data has been collected at baseline from all participants who consent to be invited to interview (an optional criterion on the main consent form). These pre-selected participants will be invited to participate in an interview throughout the course of the study period with the intention of achieving a sample with varying levels of study engagement ranging from 0 to more than 1 RTI recorded with symptom data and samples collected.

We will attempt to conduct a sub-sample of approximately 10 interviews during or immediately after an RTI has been recorded to capture experiences of the study in 'real-time', approximately 10 interviews will be conducted after at least 2 months of active study participation and a further 10 will be conducted after at least 4 months of active study participation. Within these interviews it is anticipated that some participants will not have recorded any RTI. If a participant either does not respond or declines an invitation to participate in an interview, an invitation will be sent to another participant with similar characteristics. Any reason given for refusing to participate will be notes (although participants do not have to give a reason for declining). Interviews will be conducted at a time and place convenient to the participant.

Interviews will continue until theoretical saturation of key concepts [39] has been reached which based on previous research in this area [40, 41] is anticipated to constitute a sample of approximately 30 parents.

19.2.2 Data collection (the interview process)

Interviews will be conducted face-to-face at a time and location convenient to the participant (e.g. home or other convenient location). All interviews are audio-recorded and are expected to last approximately 45 minutes.

The interview topic guide (Appendix T) will consist of two sections. The first section will explore the experiences and acceptability of the feasibility study components including views on the use of text messages, emails, research nurse visits, daily symptom reporting and nasal and saliva sampling. This section will explore the positive and negative experiences of the feasibility cohort study and how the study components could be improved. During the first interview section, the views of any participating children will also be sought either directly from an assenting child or indirectly via parent reports. In addition, we will seek to understand the impact of completing symptom diaries on perceptions of child illness (e.g. perceptions of severity).

The second section of the topic guide will involve parents only, as its focus is on the perceived value, acceptability, feasibility and anticipated impact of the planned intervention. To begin this section, participants will be provided with a description of the intervention and presented with examples of the intervention materials (e.g. example vignettes). These materials will be used to facilitate a discussion of the potential value of the intervention, its perceived utility and impact in relation to parents' concern for child health, confidence about when to consult and consultation behaviours. Specific feedback on the vignettes will be sought to understand views on their content (e.g. level of detail), their presentation and how they compare to other information sources used by parents. The interview guide will be applied flexibly to allow for emergent issues to be probed.

19.3 Qualitative data handling and record keeping

All interviews will be audio-recorded using an encrypted digital voice recorder. Recordings will be promptly transferred to electronic storage on the University of Bristol computer network, with password-protected access restricted to the immediate study team. Once transferred, original recordings will be deleted from the digital recorder. Audio recordings will then be transcribed verbatim (by a trusted transcription company used by the University of Bristol). Transcriptions will be checked against audio recordings for accuracy by the interviewer before being anonymised. Anonymised transcriptions may be emailed to participants (if necessary or requested) for accuracy-checking before analysis goes ahead. Data will be collected and stored according to requirements set out by the Data Protection Act 1998. Study data and documentation will be archived after study completion and will be stored in password-protected electronic file format for twenty years after study completion in accordance with University of Bristol policy [36]. The University Research Data Storage Facility (RDSF) provides secure, long term storage for research data.

19.4 Qualitative analysis

The anonymised transcripts from each interview (as well as notes taken during meetings and other interactions with practice staff) will form the data. Notes of initial impressions will be made on reading these data, and possible themes will be identified.

As the interviews are expected to be conducted throughout the duration of the study the analysis will be on-going allowing emergent issues to be explored in subsequent interviews. The framework method, a type of thematic analysis which is defined by the production of a matrix of themes (columns) for each participant (rows) will be used to analyse the parent interview data [42]. This approach enables comparisons of themes between participants and across the entire sample which is useful in this study where it may be valuable to triangulate the views of clinicians and parents to understand areas of agreement and divergence. It is an approach which can be applied inductively or deductively and is not situated within a particular theoretical or epistemological standpoint.

The framework method approach firstly involves a process of familiarisation with the transcripts during which initial impressions are noted. Next, the first few transcripts are assigned codes systematically line-by-line which summarise and interpret the data. These initial codes are discussed amongst the study team, iteratively refined and condensed into broader themes to produce an agreed coding framework which is applied to all subsequent transcripts. Throughout this subsequent coding, modifications will be made to the framework in response to new emergent information. The coded data is then inserted into a framework matrix in QSR NVivo which charts the themes against each participant. Within the matrix a summary capturing the meanings in the data is developed. By condensing the data in this way, reflections on meaningful, pertinent themes as well as connecting or divergent perspectives within and between participants are formed.

20 SAFETY ASSESSMENTS

20.1 Adverse Events (AEs) and Serious Adverse events (SAEs)

Any unexpected Adverse events (AEs) defined as ‘any untoward medical occurrence in a trial participant’ and serious adverse events (SAEs) – defined below - will be monitored by the study team (Appendix U) and reviewed at monthly management group meetings.

20.2 Serious Adverse Event definition

Any untoward and unexpected medical occurrence or effect that: Results in death; is life-threatening (refers to an event during which the participant was at risk of death at the time of the event; it does not refer to an event which might have caused death had it been more severe in nature), requires hospitalisation, or prolongation of existing hospitalisation; results in persistent/significant disability or incapacity; is a congenital abnormality or birth defect.

20.3 Adverse event procedure

At follow up, parents will be routinely asked if they have re-consulted for their child's illness and where this may have been. In addition, whether the child has been hospitalised will also be requested. Once a child has been identified as hospitalised either in A&E or on a ward, the standard SAE process will be followed as described above. All expected SAEs will be reported as part of the outcome to the trial.

About a fifth of adults with RTI will present to primary care [43], but we do not know the rates for children. From earlier work within the TARGET programme, around 1% of children presenting to primary care with RTI will be hospitalised. With a sample of 300 RTI episodes, a generous allowance of up to one third of children with RTI presenting to primary care would anticipate that just one child may be hospitalised for their RTI within the study duration.

In the event that a research team member is informed of a hospitalisation or other SAE occurring within the active participation phase of the study, the research team member will record relevant information about the incident including whether the study was in any way linked to the outcome. The research team member initially collecting this information will report the incident to the PI and/or study manager within 24 hours of its discovery (in accordance with usual SAE procedures). If there is any indication that an SAE could have been linked to study procedures (e.g. a child inhaling a saliva sample), it will provoke a research team-led investigation, with reporting to the sponsor via the usual procedures as detailed on the University of Bristol Research and Enterprise Development website [44].

20.4 Criteria for discontinuation of parts of the study or the entire study

There are no plans for discontinuation of the study or parts of the study, as no new techniques are being tested on participants; the aims and outcomes of the study are unlikely to be affected by any event or new knowledge arising during the course of the study; and the risk of negative outcomes of study participation is minimal.

21 PATIENT AND PUBLIC INVOLVEMENT (PPI)

We have appointed a Parent Advisory Group of eight parents (seven mothers, one father; with a range of child ages to include babies, pre-school and older children), for ongoing work with the study. We recruited these interested parents via advertisements on Netmums and Mumsnet websites, newsletters from the People in Health West of England (PPI specialist group) and the Southville Centre as well as posters in a family friendly café and nurseries in Redfield. (Both Southville and Redfield are areas of Bristol with diverse demographic populations and many young families).

The Parent Advisory Group (PAG) have been a valuable resource for advising on the 'parent facing' aspects of the study. They have (to date) advised on: recruitment strategies, study processes

and thank you vouchers, and contributed to the design and content of the study invitation letter, information sheets, leaflets, welcome pack, questionnaires and reward stickers for children. Our PAG is also poised to test the online database and emailing system and identify any issues to be resolved before it is launched for study data collection. Beyond this, we will ask for their input on our interpretation of study results and dissemination plans.

Our PPI meetings have taken place in family friendly cafés to enable parents to come with their children if necessary. Future meeting venues will be arranged as appropriate for the task(s) involved. PAG members are reimbursed at standard University of Bristol and PPI advisory group rates for all study-related tasks completed plus travel expenses incurred.

22 RESEARCH GOVERNANCE, MONITORING AND ETHICAL APPROVAL

22.1 Research governance and monitoring

The study will be conducted in compliance with the Research Governance Framework for Health and Social Care and Good Clinical Practice (GCP) and will be subject to University of Bristol sponsorship and monitoring procedures. The study management group consists of highly experienced research professionals who will oversee the design and conduct of the study to ensure that the research is of high quality.

22.2 Ethical considerations

The study is low risk in terms of ethical issues. Parents of healthy children are asked to respond to weekly emails (or texts) and fill in online symptoms diaries for the duration of a child's incident RTI developed in a winter period. Children will not be receiving a medication or intervention, and no treatment will be withheld. The cost to parents is mainly in the time taken to fill in questionnaires and any logistical problems with filling in online data (e.g. lack of access to computer or internet connection).

Patient safety

Patient safety will always take highest priority throughout all study procedures. Data protection and participant confidentiality will be maintained (see Data handling and record keeping section**).**

Nasal swab-taking by parents may cause minor distress either to parents or the child, but are not likely to cause physical harm. Saliva sample taking is an unobtrusive process with very low likelihood of causing any distress. The study team will provide clear instructions for parents on swab-taking and the RN will be present during the first parent-taken swab process. This means that the RN can help in the case of any difficulty the parent finds with taking a nasal swab or saliva sample from the child. The RN can aid the parent to take the swab if necessary. The RN will be taking a second saliva and nasal swab in the visit as well as a clinical examination. These procedures are routine and will be undertaken by an experienced professional. The RN will give reassurance, praise and thanks for the samples and clinical information obtained in the research visit (including provision of child reward stickers). In the event of significant child or parent distress around the process, no swabs will be taken. The RN will act according to clinical expertise and NHS guidelines when conducting visits to prioritise patient safety. In the event that the RN, on assessing the child, is concerned about the health of the child, they may advise that the parent seeks medical advice (and record this as a possible study-induced primary care visit).

Parents (and some willing and competent children) will be invited to be interviewed as an optional addition to the main study participation. These interviews are to gain feedback on study processes and a future intervention and will be arranged at a time and location convenient to the participant. Minimal ethical issues are involved in this process. The only cost to participants is their time. The interview topic guides do not cover any sensitive issues. Clinicians will also be interviewed to gain feedback on the outline intervention at their workplace or via telephone, and will be reimbursed for their time.

Participants retain the right to withdraw from the study at any time, with an additional right to request destruction of existing data or samples collected from them.

Research staff safety

The home visits conducted by a research nurse and qualitative interview staff will be guided by the University of Bristol safety policy for researchers working in the field [45]. A lone worker policy will be applied for all fieldwork in accordance with University of Bristol guidance [46]. The nurse and qualitative interview staff will notify the study team (in advance) of the details of all planned home visits and will make contact directly before and after each visit. A pre-specified SOP with emergency contact information will be followed in the event of the nurse failing to make contact within a reasonable time frame of visiting a participant.

Study conduct

Research nurses and all the research team will be DBS checked for participant safety measures (according to the principles of GCP).

Medical notes review will be undertaken by research staff with honorary NHS contracts. The process will be conducted according to NHS and research standards on confidentiality and ethical practice.

The study will be conducted in compliance with the principles of the Declaration of Helsinki [47], the principles of GCP [48] and in accordance with all applicable regulatory requirements including but not limited to the University of Bristol Research Governance and Integrity Policy [49], The Human Tissue Act [50] and the Freedom of Information Act [51].

This protocol and related documents will be submitted for Health Research Authority (HRA) approval to include review by a NHS Research Ethics Committee and appropriate Research and Development (R & D) departments. The study will be conducted in accordance with advice and approvals received. Any subsequent protocol amendments will be submitted to the REC, on the agreement of the Sponsor. Progress reports will be submitted to the REC as required. Progress reports will also be submitted to the funder in line with NIHR reporting requirements.

Copies of these reports will be sent to the Sponsor prior to submission. Copies of all relevant reports will be made available to the Study Management Group (SMG) as appropriate. An end of study declaration will be submitted to the REC within 90 days of the end of the study. A final report at conclusion of the study will be submitted to the NIHR, the Sponsor, the REC and the HPRU within one year of the end of the study.

23 FINANCE

This study is funded by the National Institute for Health Research (NIHR), Health Protection Research Unit (HPRU). The University of Bristol will be responsible for and administer the financial aspects of the grant.

24 INDEMNITY

This is a University of Bristol sponsored research study. The University of Bristol has arranged Public Liability insurance to cover the legal liability of the University as Research Sponsor in the eventuality of harm to a research participant arising from management of the research by the University. The University of Bristol holds Professional Negligence insurance to cover the legal liability of the University, for harm to participants arising from the design of the research, where the research protocol was designed by the University. The University of Bristol's Public Liability insurance policy provides an indemnity to our employees for their potential liability for harm to participants during the conduct of the research.

25 REPORTING AND DISSEMINATION

The written papers from this work will be submitted for publication in quality peer-reviewed health journals, such as BMC Family Practice, International Journal of epidemiology, PLos journals.

There will be a main feasibility study paper which will inform the design of a definitive cohort study (with nested RCT).

Due to their novelty, we anticipate that secondary feasibility study results will be publishable in the world's leading medical and policy journals, including:

1. A paper describing the clinical utility and cost of community swab types
2. Paper(s) describing RTI duration in the community, and numbers of children consulting
3. Paper describing the microbiological (and symptoms) profiling of RTIs (with possible future transmission modelling)
4. A paper describing the contribution of socio-demographic, clinical and microbiological factors to NHS use
5. Qualitative papers describing parent and clinician views of a microbiological information intervention.

Findings from this study are thought to be of interest to several professional groups including clinicians, infectious disease modellers, primary care intervention researchers and behavioural scientists. Application will be made to present study results to primary care and infectious diseases modelling conferences, including the Society for Academic Primary Care (UK).

All study participants will receive a newsletter outlining the main study results, via email or post (at their preference stated at baseline), unless stated that they did not wish to receive this. The PPI group will advise on newsletter content and dissemination to enable the best quality communication of study results to parents. Participating GPs will also receive a newsletter about the results. These newsletters will include a link to the study website where we will post further information and links to papers when accepted for publication.

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27 APPENDIX LIST

Please see Protocol Appendix supplement (separate document) for the following:

A Example invitation for GP expression of interest

B Research information sheet for practices

C Participant recruitment letter from GP

D Participant information leaflet

E PIL for children

F Participant Consent Form

G Participant Consent Form with Assent

H Repeat mailout letter

I Follow up SMS text invitation from surgery

J Recruitment poster

K Contact card for recruitment

L Participant welcome letter

M Fridge magnet for parents

M-2 Welcome pack poster for parents

N Data Collection Forms - 1 Baseline questionnaire

N Data Collection Forms - 2 Symptoms and recovery questionnaire

N Data Collection Forms – 3 Symptoms and recovery questionnaire

N Data Collection Forms - 4 Clinical examination form

N Data Collection Forms - 5 Medical notes review form

O List of microbial targets for PCR studies

P Clinician interviews information sheet

Q Clinician interview consent form

R Clinician interview topic guide

S Participant information leaflet interview

T Parent interview topic guide

U Serious Adverse Events Form