Health Technology Assessment Programme

National Institute for Health Research

HTA no 15/32

Antibiotics for acute otitis media with discharge

Introduction

The aim of the HTA Programme is to ensure that high quality research information on the effectiveness, costs and broader impact of health technology is produced in the most efficient way for those who use, manage, provide care in or develop policy for the NHS. Topics for research are identified and prioritised to meet the needs of the NHS. Health technology assessment forms a substantial portfolio of work within the National Institute for Health Research and each year about fifty new studies are commissioned to help answer questions of direct importance to the NHS. The studies include both primary research and evidence synthesis.

Research Question:

What is the clinical and cost effectiveness of topical antibiotics as compared to oral antibiotics in children with acute otitis media presenting with acute ear discharge?

1. **Intervention:** Topical antibiotics (applicants to specify) plus other symptomatic treatment as required.
2. **Patient group:** Children with acute otitis media and discharge (otorrhoea). Applicants should consider stratifying, or sub group analysis, by age.
3. **Setting:** General practice and other relevant primary care settings.
4. **Control:** Oral antibiotics (applicants to specify) plus other symptomatic treatment as required.
5. **Study design:** Randomised controlled trial with an internal pilot phase to test ability to recruit. Applicants should clearly define progression criteria to the full trial. Applicants could consider whether a no treatment arm is also appropriate.
6. **Important outcomes:** Duration and severity of symptoms; repeat infections.

   Other outcomes: Patient/parent satisfaction with treatment; adverse events; simple economic evaluation to inform NHS decision making.
7. **Minimum duration of follow-up:** 3 months.

NHS decision problem to be addressed by this research:

Acute otitis media (AOM; acute inflammation of the middle ear) is a common condition that mainly occurs during the first two years of life and causes pain, malaise, irritability, fever and vomiting. A well-recognised complication is that a child who is screaming and in a great deal of pain finally settles and the ear starts to discharge green pus. In this case the eardrum has burst, releasing the pressure and relieving the pain.

Eardrum perforation due to AOM may resolve spontaneously, but antibiotics in the form of medicine or drops are widely prescribed. However, the best mode of delivery, orally or topically, is not known. It would be very helpful to parents and the NHS to know what the best clinical approach is in order to help guide prescribing practice for this condition. A simple randomised controlled trial to determine the best way of treating AOM with discharge is proposed.

Notes to Applicants

The NIHR Health Technology Assessment Programme is funded by the NIHR, with contributions from the CSO in Scotland, NISCHR in Wales, and the Public Health Agency in Northern Ireland.

For many of the questions posed by the HTA Programme, a randomised controlled trial is likely to be the most appropriate method of providing an answer. However, there may be practical or ethical reasons why this might not be possible. Applicants proposing other research methods are invited to justify these choices.

Applicants are asked to:

1. Follow the Medical Research Council's (MRC) Good Clinical Practice guidelines (http://www.mrc.ac.uk/documents/pdf/good-clinical-practice-in-clinical-trials/) when planning how studies, particularly RCTs, will be supervised. Further advice specific to each topic will be given by the HTA Programme at full proposal and contract stages.

2. Note that trials involving medicinal products must comply with "The Medicines for Human Use (Clinical Trials) Regulations 2004". In the case of such trials, the DH expects the employing institution of the chief investigator to be nominated as the sponsor. Other institutions may wish to take on this responsibility or agree co-sponsorship with the employing institution. The DH is prepared to accept the nomination of multiple sponsors. Applicants who are asked to submit a full proposal will need to obtain confirmation of a sponsor(s) to complete their application. The DH reserve the right to withdraw from funding the project if they are not satisfied with the arrangements put in place to conduct the trial.

The MHRA (info@mhra.gsi.gov.uk, http://www.mhra.gov.uk) can provide guidance as to whether your trial would be covered by the regulations. The NIHR website (http://www.ct-toolkit.ac.uk/) also contains the latest information about Clinical Trials regulations and a helpful FAQ page.

In line with the government's transparency agenda, any contract resulting from this tender may be published in its entirety to the general public. Further information on the transparency agenda is at: http://transparency.number10.gov.uk/#

Applicants are recommended to seek advice from suitable methodological support services, at an appropriate stage in the development of their research idea and application. It is advisable to make contact at an early a stage as possible to allow sufficient time for discussion and a considered response.

The NIHR Research Design Service (http://www.rds.nihr.ac.uk/) can advise on appropriate NIHR Programme choice, and developing and designing high quality research grant applications.

Clinical Trials Toolkit

Researchers designing or undertaking clinical trials are encouraged to consult the Clinical Trials Toolkit (www.ct-toolkit.ac.uk). This NIHR resource is a website designed to help researchers navigate through the complex landscape of setting up and managing clinical trials in line with regulatory requirements. Although primarily aimed at those involved in publicly funded Clinical Trials of Investigational Medicinal Products (CTIMPs), the Toolkit will also benefit researchers and R&D staff working on trials in other areas, who will find useful information and guidance of relevance to the wider trials environment.

Research networks

The HTA Programme expects, where appropriate, that applicants will work with the relevant research network.

Making an application

If you wish to submit an Expression of Interest on this topic, complete the on-line application form at www.nets.nihr.ac.uk/funding/hta-commissioned and submit it on line by **12 May 2015**. Applications will be considered by the HTA Commissioning Board at its meeting in **July 2015**.
IMPORTANT: For Expression of Interest applications, if shortlisted, investigators will be given a minimum of **eight weeks to submit a full proposal**. The full proposal will be considered at the Commissioning Board in **November 2015**.

Applications received electronically after 1300 hours on the due date will not be considered.

Please see GUIDANCE ON APPLICATIONS overleaf.

Guidance on applications

Required expertise

HTA is a multidisciplinary enterprise. It needs to draw on the expertise and knowledge of clinicians and of those trained in health service research methodologies such as health economics, medical statistics, study design, behavioural science and qualitative approaches. The HTA Programme expects teams proposing randomised controlled trials to include input from an accredited clinical trials unit, or one with equivalent experience. Applicants are also expected to engage a qualified Trial Manager for appropriate projects. A commitment to team working must be shown and applicants may wish to consider a collaborative approach between several institutions.

Public involvement in research

The HTA Programme recognises the benefit of increasing active involvement of members of the public in research and would like to support research projects appropriately. The HTA Programme encourages applicants to consider *how* the scientific quality, feasibility or practicality of their proposal *could* be improved by involving members of the public. Examples of how this has been done for health technology assessment projects can be found at www.nets.nihr.ac.uk/ppi. Research teams wishing to involve members of the public should include in their application: the aims of active involvement in this project; a description of the members of the public (to be) involved; a description of the methods of involvement; and an appropriate budget. Applications that involve members of the public will not, for that reason alone, be favoured over proposals that do not but it is hoped that the involvement of members of the public will improve the quality of the application.

Outcomes

Wherever possible, the results of HTA should provide information about the effectiveness and cost-effectiveness of care provided in its usual clinical setting and for the diverse subjects who would be eligible for the interventions under study. The endpoints of interest will in most cases include disease specific measures, health related quality of life and costs (directly and indirectly related to patient management). Wherever possible, these measurements should be made by individuals who are unaware of the treatment allocation of the subjects they are assessing. We encourage applicants to involve users of health care in the preparation of their proposal, for instance in selecting patient-oriented outcomes. Where established Core Outcomes exist they should be included amongst the list of outcomes unless there is good reason to do otherwise. Please see The COMET Initiative website at www.comet-initiative.org to identify whether Core Outcomes have been established. A period of follow up should be undertaken which is sufficient to ensure that a wider range of effects are identified other than those which are evident immediately after treatment. Where relevant, researchers should explore the effect of the intervention in relation to health inequalities. These factors should guide applicants in their choice of subjects, settings and measurements made.

Longer-term follow up

Researchers to consider building in provision, if appropriate, for a simple mechanism for long-term follow up using routine data bases/sets; including obtaining consent for this from participants at trial entry.

Sample size

A formal estimate should be made of the number of subjects required to show important differences in the chosen primary outcome measure. Justification of this estimate will be expected in the application.

Communication

Communication of the results of research to decision makers in the NHS is central to the HTA Programme. Successful applicants will be required to submit a single final report for publication by the HTA Programme. They are also required to seek peer-reviewed publication of their results elsewhere and may also be asked to support NETSCC, HTA in further efforts to ensure that results are readily available to all relevant parties in the NHS. Where findings demonstrate continuing uncertainty, these should be highlighted as areas for further research.

Timescale

There are no fixed limits on the duration of projects or funding and proposals should be tailored to fully address the problem (including long-term follow-up if necessary). Applicants should consider however that there is a pressing need within the NHS for this research, and so the duration of the research needs to be timely.

Feasibility and Pilot studies

We expect that when pilot or feasibility studies are proposed by applicants, or specified in commissioning briefs, a clear route to the substantive study will be described. This applies whether the brief or proposal describes just the preliminary study or both together. Whether preliminary and main studies are funded together or separately may be decided on practical grounds.

Feasibility Studies are pieces of research done before a main study. They are used to estimate important parameters that are needed to design the main study. Feasibility studies for randomised controlled trials may not themselves be randomised. Crucially, feasibility studies do not evaluate the outcome of interest; that is left to the main study. If a feasibility study is a small randomised controlled trial, it need not have a primary outcome and the usual sort of power calculation is not normally undertaken. Instead the sample size should be adequate to estimate the critical parameters (e.g. recruitment rate) to the necessary degree of precision.

Pilot studies are a version of the main study that is run in miniature to test whether the components of the main study can all work together. It is focused on the processes of the main study, for example to ensure recruitment, randomisation, treatment, and follow-up assessments all run smoothly. It will therefore resemble the main study in many respects. In some cases this will be the first phase of the substantive study and data from the pilot phase may contribute to the final analysis; this can be referred to as an internal pilot. Or at the end of the pilot study the data may be analysed and set aside, a so-called external pilot.

For a full definition of the terms 'feasibility study' and 'pilot study' visit the NETSCC website glossary page www.nets.nihr.ac.uk/glossary

In preparing for a substantive evaluation attention should be paid to appropriate guidance on how to develop interventions (such as the MRC guidance on developing and evaluating complex interventions and the IDEAL framework: www.ideal-collaboration.net/framework/).

Diagnostics and Imaging

In evaluating diagnostic and imaging techniques, the emphasis of the HTA Programme is to assess the effect on patient management and outcomes (particularly where changes in management can be shown to have patient benefits). Improvements in diagnostic accuracy, whilst relevant, are not the primary interest of this commissioned research programme. Applicants should justify where they consider improvements in diagnostic accuracy to be relevant to these objectives. Where there is poor evidence to link diagnostic improvements to patient benefits, part of the primary research may be to assess the effects of such changes on patient outcome.

An assessment should also be made of changes in other resources (particularly other subsequent therapies) used as a result of changes in diagnostic methods.

IMMEDIATE ORAL, IMMEDIATE TOPICAL OR DELAYED ORAL ANTIBIOTICS FOR ACUTE OTITIS MEDIA WITH DISCHARGE: The Runny Ear Trial (REST Trial).

Site Agreement to Participate in Recruitment

This is a contract Dated the [XX] day of [XX] 201[X]	(the "Commencement Date")
Between the University of Bristol, whose administrative offices are at Senate House, Tyndall Avenue, Bristol, BS8 1TH	("Bristol")
And agreed by: [Primary Care Site - full legal name of organisation and registered address]	(the "Site")
And is in reference to,	
the randomised controlled trial entitled: REST: IMMEDIATE ORAL, IMMEDIATE TOPICAL OR DELAYED ORAL ANTIBIOTICS FOR ACUTE OTITIS MEDIA WITH DISCHARGE: The Runny Ear Trial.	(the "Trial")

BACKGROUND

Bristol is leading the Trial. Bristol and the Site each desire that the Site participate in the Trial in accordance with the terms of this contract.

Bristol shall be performing its role in the Trial through its Centre for Academic Primary Care in its Bristol Medical School (Population Health Sciences). Professor Alastair Hay is the Chief Investigator of the Trial.

Bristol and the Site each acknowledge and agree that Bristol is the sponsor of the Trial for all research governance purposes, including without limitation for the purposes of the UK Policy Framework for Health and Social Care Research and the Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended from time to time).

The Trial is being funded by the Secretary of State for Health (the "Funder") through the National Institute for Health Research (NIHR), Health Technology Assessment (HTA) programme (project number 16/85/01).

Centre for Academic Primary Care
School of Population Health Sciences, Bristol Medical School
University of Bristol, Canynge Hall, 39 Whatley Road
Bristol, BS8 2PS
Email:

The Trial has received NHS REC approval from the South Central Oxford A Research Ethics Committee (REC reference number 18/SC/0181, date of approval 23rd May 2018). It is registered on the European Clinical Trials database as 2017-003635-10 and on the International Clinical Trials register as ISRCTN12873692. REST is an NIHR portfolio-adopted study (CPMS ID 37299).

Responsibilities of the Site:

Conduct of the Trial

1. The Site will provide the facilities and staff resources necessary for the Site to conduct the Trial in accordance with the Protocol and this contract shall ensure that any of its staff involved in the performance of the Trial provides evidence of having received training appropriate to enable them to perform their role in the Trial. This will include professional training (as evidenced by a signed and dated copy of the staff members current CV), Trial training (provided by the Trial team and evidenced by a training record created following the training), training on the TRANSFoRm platform (provided by the Trial team) and recent GCP training (as applicable). The Site's lead GP (hereinafter "PI") will accept responsibility for oversight of all staff at the Site involved in the Trial.

2. The Site will ensure **that the eligibility and consent of children to take part in REST study is done under the following conditions**:

    a. By a GCP-trained GP who has been trained in the study procedures OR:
    b. a qualified, GCP-trained nurse or other healthcare professional trained in the study procedures with oversight from a GCP-trained doctor (oversight in this instance is signature of the PI on the delegation log to confirm oversight) Any discussion re: eligibility between the delegated person and doctor must be documented to indicate oversight.

3. The Site will ensure participants are **prescribed treatment** according to the randomisation allocation
   sites to follow standard prescribing procedures.

4. The Site will pay attention to the information given to parents of children who will potentially participate in the Trial, regarding all aspects of Trial participation as specifies in the Parent Information Sheet.

5. The Site will ensure that all clinicians involved in the Trial have legal protection for their clinical responsibilities (including their clinical care as part of this Trial) within their cover for medical malpractice. This is likely to either be insurance (MDU) or discretionary indemnity (MPS).

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6. The Site agrees to conduct the Trial in accordance with the Protocol and Trial Specific Working Instructions (TSWI).

   The Site will only deviate from the Protocol should this become necessary to protect the safety, rights or welfare of Trial participants. All deviations from the Protocol shall be recorded by the Site and reported to Bristol in accordance with the TSWI provided to the Site

7. The Site will conduct the Trial in accordance with Good Clinical Practice (GCP), all applicable laws and regulations, and the reasonable instructions of Bristol.

8. A Trial Site File containing essential documents for the conduct of the Trial shall be provided to the Site by Bristol and, from time to time and as appropriate, Bristol shall provide to the Site revised or amended copies of any documents contained within the Trial Site File. The Site will maintain and update its Trial Site File with any revised or amended documents supplied by Bristol. Bristol will also promptly inform the PI and main contact at site of such amended documents. Within the Trial Site File, the Site will store any participant data in numerical order of Participant ID.

9. The Site will allow access to Bristol or their nominee (UH Bristol) to all information relating to the Trial for the purposes of monitoring the Trial, subject always to the requirements of confidentiality of participant data.

10. The day-to-day clinical care of all children who participate in the Trial will remain the responsibility of the Site and the clinicians in the Site, and shall not be affected by this contract or by the performance of the Trial.

11. The Site will ensure that clinicians at the Site who are participating in the Trial will complete the data collection forms for any eligible children willing to take part in the study,

12. The Site will ensure that clinicians at the Site who are participating in the Trial will provide screening data for all potentially eligible children presenting at the Site, whether or not it is possible to recruit them, via the TRANSFoRm Platform.

Participant consent

13. The Site will ensure that the parent of each participating child provides informed consent before the child is entered into the Trial, and that children who are old enough to understand what is being asked of them within the Trial (normally school age, but may be younger or older depending on cognitive development) are asked for their assent.

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14. The Site will ensure that copies of the informed Consent Form (and Assent Form for children of school age and above, or who are old enough to understand what is being asked of them within the Trial) are managed according to the TSWI.

15. The Site acknowledges that Bristol may retain participant consent and Trial related documents for at least 15 years after the completion of the Trial, in line with the relevant regulatory guidance.

Recruitment of children

16. The following targets refer to the number of children to be recruited to the REST Trial. The Site agrees that it will attempt to recruit at least **3** eligible participants into the Trial within the Trial recruiting period. There is no upper limit to the number of participants that can be recruited to the RCT by the Site, and sites are encouraged to recruit eligible children at every opportunity.

17. The Site agrees to record basic information on all potentially eligible children presenting at the Site with ear pain, including those whose parents have been invited but have not agreed to participate, and those who are deemed to be ineligible, via the TRANSFoRm Platform.

Safety reporting (Adverse Events, Serious Adverse Events and Suspected Unexpected Serious Adverse Reactions)

18. The Chief Investigator, on behalf of the Sponsor and with the assistance of UH Bristol as part of a SLA provision, assumes responsibility for appropriate reporting of safety events to the regulatory authorities. All safety events will be reported in line with the Research Safety Reporting Working Instructions of UH Bristol (see REST Trial Adverse Event Working Instructions, of which a summary is provided in the Trial Site File). The Site agrees to notify Bristol of any Serious Adverse Events, within 24 hours of the Site becoming aware of such a Serious Adverse Event, using the SAE Initial Report Form provided, and to complete the Follow-up Report Form within 5 working days from becoming aware of the SAE.

Participant data/information

19. The Site will ensure that employees of Bristol, the Funder and/or appropriate regulatory authorities are able to review participant records of Trial participants for the purposes of monitoring or audit, subject always to compliance with the provisions of the Data Protection Act 1998 and any successor UK legislation intended to implement the General Data Protection Regulation (GDPR) (Regulation (EU) 2016/679).

20. Subject always to the necessary informed consent being obtained for each child participating in the Trial, the Site will collect data from the medical records of Trial participants as required by the Protocol, completing the REST Primary Care Notes Data Extraction for relevant ear data for

each participant (if relevant) at a period of four or five months after recruitment, in response to instruction from Bristol.

21. When requested by Bristol, the Site will assist in providing data from clinical records for Trial participants, provided that the parent of the Trial participant has consented to the provision of such data, and that such data is required for the conduct of the Trial.

22. The Site agrees to Bristol's use of descriptive and demographic data relating to the Site (routinely gathered within the Trial) and shall provide all reasonable assistance to Bristol in gathering this information.

Confidential Information

23. The Site will treat all identifiable participant and Trial participant data in strict confidence and store it in a secure place in accordance with GCP, the Data Protection Act 1998 and any successor UK legislation intended to implement the General Data Protection Regulation (GDPR) (Regulation (EU) 2016/679).

Site file and Trial paperwork

24. The Site agrees that, at the end of the Trial and at the request of Bristol, it will return to Bristol any unused recruitment materials and the Site File with all the Trial paperwork. The Trial paperwork will be archived by Bristol according to the Trial archiving plan.

<u>Responsibilities of Bristol:</u>

Conduct of the Trial

25. Bristol agrees that it will ensure that the relevant HRA Approval, Ethics Approvals, MHRA Approval, R&D / Trust permissions, and Honorary Contracts / Letters of Access and/or Research Passports for the Trial, are in place prior to the start of any recruitment at the Site.

26. Bristol shall ensure that any research nurse or members of the research team attending the Site for training, monitoring or other purposes will have undergone enhanced DBS disclosures as appropriate and ICH-GCP training and will have the appropriate access letter or honorary NHS contract allowing them to work at the Site.

27. Bristol will contact the parents of the children who have been recruited to the Trial (for whom informed consent and/or assent has been obtained), up to 4 times during the 14 days including and following the day of recruitment, by telephone, and additionally by text or e-mail (depending on the parent's preferred method of contact), in order to support their completion of the daily

Symptom and Recovery Questionnaire, in accordance with the Protocol. They will also contact parents at 3 months to remind them to send in their child's stool samples. Bristol will ensure that any staff contacting the parents of the children recruited to the Trial have appropriate training, Honorary Contracts / Letters of Access, and/or Research Passports as required.

28. Bristol will supply the Site with all Trial specific paperwork and equipment necessary for the Site to conduct the Trial. Bristol will also provide the Site with training on the TRANSFoRm platform, a handbook and contact details should they need any assistance during the Trial. Any unused Trial equipment will, at the end of the period of the Site's involvement with the Trial, be returned to Bristol.

29. Bristol agrees to provide the Site with advice and support in relation to the Trial and the TRANSFoRm platform.

Financial compensation: Service Support and Research Reimbursements

30. Reimbursement to the Site for time spent conducting the Trial.
    a. The Site will be reimbursed **per participant recruited** the amount of £67.08 for Research Costs (*in addition, £20.00 may be claimed from the Clinical Research Network (CRN) for Service Support Costs as detailed below):

Trial activity	**Research Cost**
Receptionists Identifies Participant and books into REST appt	£7.08
Opportunistic intervention at consultation	£12.00
Consent	
CRF (use of REST portal for eligibility, baseline data + randomisation)	£48.00
Total	£67.08

Research costs paid by Bristol, will be contingent upon the number of completed consent and case report forms received by Bristol. These payments will be made quarterly in arrears, by Bristol. The Trial team will draft invoices on behalf of the Site, agree the invoices with the Site, and submit them to Bristol on behalf of the Site. All payments are inclusive of VAT where applicable.

*Service Support Costs claimed from the CRN are payable directly to Sites by the CRN and Bristol will assist Sites in claiming these Service Support Costs.

b. The Site will be reimbursed for Site set up training on a **per Site** basis as follows:

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Trial activity	Research Cost
Initial meeting to discuss Trial Feasibility and decide to take part	£66.68
Practice team training in recruitment procedures and full set up	£266.64
Monitoring Protocol adherence during Trial	£83.92
Recruitment of each child to the Trial	£83.75
Close-down visit - data quality checks	£21.96
TOTAL=	**439.20**

There will also be a payment to Clinicians who agree to take part in an **optional interview** of £80.00 per hour per clinician.

Research costs paid by the Bristol, will be contingent upon the number of completed consent and case report forms received by Bristol. These payments will be made quarterly in arrears, by Bristol. The Trial team will draft invoices on behalf of the Site, agree the invoices with the Site, and submit them to Bristol on behalf of the Site. All payments are inclusive of VAT where applicable.

31. Bristol will also provide the Site with a quarterly update regarding payments due for recruitment activity.

Participant data/information

32. Bristol and the Site shall comply with the requirements of the common law of confidentiality, the Data Protection Act 1998 and any successor UK legislation intended to implement the General Data Protection Regulation (GDPR) (Regulation (EU) 2016/679) and, as appropriate, the NHS Confidentiality Code of Practice. Bristol will ensure it keeps all identifiable participant information, confidential. Participant and Site identifiable data will be kept on a secure server or in locked cabinets, and all data for analysis will be anonymised.

Results and Dissemination

33. All data and results arising out of the Trial shall, in the first instance vest in and be the sole property of Bristol and will be regarded as confidential information belonging to Bristol. Bristol may, at its sole discretion, re-assign or licence said data and results to third parties. The REST Trial team will agree upon appropriate dissemination, including publication, of Trial results.

Term and termination

34. This contract shall commence upon the Commencement Date and shall continue in effect until Trial closure as detailed and defined in the Protocol unless Bristol indicates that it wishes the Site to withdrawal from the Trial or the Site indicates that it wishes to withdraw from the Trial, in each case such withdrawal shall be effective upon that party providing written notice to the other party. Termination of this contract, howsoever caused, shall not affect the continuing obligations of each of the parties in respect of the obligations of data protection and confidentiality, as laid out herein.

35. This contract shall be governed and construed in accordance with the laws of England and Wales and the parties hereby submit to the exclusive jurisdiction of the English Courts.

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Email.

Signatures

The undersigned agree to all terms of this agreement.

Signed by:

_____	_____	_____
(sign)	**(print name)**	**(date)**
For and on behalf of the Site		
(Practice Manager/lead GP)		

Signed by:

____	**Anna Wilkinson**	**26.09.2018**
		_____
(sign)	**(print name)**	**(date)**

For and on behalf of the University of Bristol

Centre for Academic Primary Care
School of Population Health Sciences, Bristol Medical School
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Privacy Impact Assessment

Primary contacts for advice and guidance

Henry Stuart
Information Governance Manager
Secretary's Office

Matt Osborn
Information Security Manager
IT Services

Screening questions

These questions are intended to help you decide whether a PIA is necessary. Answering 'yes' to any of these questions is an indication that a PIA would be a useful exercise. You can expand on your answers as the project develops if you need to.

1. **Will the project involve the collection of new information about individuals?**

2. **Will the project compel individuals to provide information about themselves?**

3. **Will information about individuals be disclosed to organisations or people who have not previously had routine access to the information?**

4. **Are you using information about individuals for a purpose it is not currently used for, or in a way it is not currently used?**

5. **Does the project involve you using new technology that might be perceived as being privacy intrusive? For example, the use of biometrics or facial recognition.**

6. **Will the project result in you making decisions or taking action against individuals in ways that can have a significant impact on them?**

7. **Is the information about individuals of a kind particularly likely to raise privacy concerns or expectations? For example, health records, criminal records or other information that people would consider to be private.**

8. **Will the project require you to contact individuals in ways that they may find intrusive?**

Step one: Identify the need for a PIA

Explain what the project aims to achieve, what the benefits will be to the organisation, to individuals and to other parties.

You may find it helpful to link to other relevant documents related to the project, for example a project proposal.

Also summarise why the need for a PIA was identified (this can draw on your answers to the screening questions).

The REST study is a 4-arm randomised controlled trial comparing immediate oral antibiotics, delayed oral antibiotics and topical antibiotic drops in children with Acute Otis Media with Discharge (AOMd).

In this study we would like to find out whether giving an antibiotic ear drop or delayed antibiotic by mouth is as good as immediately giving antibiotics by mouth for children with AOMd. AOMd is a common and painful infection for children so it is important that any new treatment works at least as well as the standard, immediate treatment.

At the moment, nearly all UK children with AOMd seen by their GP or nurse are treated with antibiotics by mouth however taking antibiotics by mouth can cause severe side-effects like rashes, diarrhoea and vomiting and more rarely, sever allergic reactions, They also ad to the growing problem of antibiotic resistance.

The NHS has paid for and approved this study because evidence suggests the treatment might work. It is not guaranteed that children participating in the study will benefit directly, but they will be helping to improve future treatment for children with ear discharge. The benefit to the University of Bristol in carrying out this research study is to help maintain our position in the Research Excellence Framework ranking being among the UK's top research universities.

The study will run in GP practices across the UK and aims to recruit children aged 12 months to 16 years presenting to their GP with AOMd.

The GP or Nurse will invite a child of the correct age and presenting with AOMd to take part in the study at the consultation. The parent attending with the child will be asked some questions about the child's illness and general health (eligibility check) and the doctor or nurse will look in the child's ears and check if it is safe for them to take part in the study. If the child is aged 6-16 years and can understand what is involved for them, they may be asked to sign their own consent form).

Parents will be asked to complete a questionnaire (online or on paper) about their child's symptoms, ear discharge and any antibiotic or oral painkilling medicines, to be filled in on the day of recruitment and for the next 13 days (14 in total).

Our lawful basis for processing has been given by the HRA. The process does achieve its purpose, it is the most secure and efficient way to ensure the quality of the data.

The alternative would be collecting the data using paper CRF's. The specifications of the platform have been reviewed against the Protocol. As part of the trial study design, only the data points necessary for the study have been included and the functioning of the system is designed so it can only extract data that it has been programmed to extract i.e. contact details, date of birth, NHS numbers. Our statistics team have reviewed the system against the protocol for data quality purposes and minimal personal identifiers are being used. The statistics team will regularly check he data for quality purposes.

The DPIA has been executed due to the following reasons; (i) GP practices taking part in this research study who consent participants (parents/children), will need to collect additional information from participants above and beyond that would normally be collected during a standard consultation (ii) Participants (parents/children) whom consent to take part in the research study will be compelled to provide information about their child's health and the family's socioeconomic back ground (iii) Information collected during the GP consultation will be collected on the TRANSFoRm platform and will be shared with the research team conducing this study (iv) the study includes a review of the participants health records.

For a GP surgery to be green-lighted to take part in the study, the surgery must sign a site agreement which lays out their responsibilities as research site. A principal investigator at each site has oversite for the research carried out at that practice. All GPs who consent participants to the REST study must complete study specific training, including the use of the TRANSFoRm platform.

Step two: Describe the information flows

You should describe the collection, use and deletion of personal data here and it may also be useful to refer to a flow diagram or another way of explaining data flows. You should also say how many individuals are likely to be affected by the project.

Data collection during GP consultation for the REST study will be via the TRANSFoRm platform. This platform encapsulates certain features of a clinical trial management system by interacting with the GP's EHR. The tool provides automatic eligibility checking, part-filling of eCRFs, and study workflow management and has been validated against Good Clinical Practice guidelines.
All REST quantitative data will be collected using such a system – namely, the EU FP7 funded TRANSFoRm Program (www.cdisc.orgtransformproject.eu)29. TRANSFoRm uses a Data Node Connector (DNC) to integrate with primary care EHR electronic medical records (also increasingly used in Walk-in and Out-of-Hours centres), ensuring data validity and accuracy, and facilitating the nationwide engagement of the large number of primary care sites needed for REST. An additional module enables Patient Reported Outcome Measures (PROMs) to be collected via web and smartphone (iOS, Android). The system has a full provenance trail and is fully GCP/MHRA validated. The trial data will all be stored by TRANSFoRm on a secure server held by Kings College London.

REDCap is a secure, web-based electronic data capture (EDC) system designed for the collection of research data. Although the system has been developed by Vanderbilt University, the Department of Population Health Sciences (PHS) (University of Bristol, 'UoB') has set up its own infrastructure to host the REDCap application so that all elements reside within UoB. Participants contact details will be stored on the secure REDCap system based at the University of Bristol.

Patient identifiers will be kept on a separate system (REDCap) from the clinical data (TRANSFoRm) and data protection requirements will be further enforced by best practice trial management procedures. The TRANSFoRm platform does not integrate at all with REDCap and the data is stored on servers in two different organisations thereby physically separating clinical and personal data.

Participation will be invited by recruiting site staff and will be entirely voluntary with parents (or those legally allowed to consent for children (www.hra-decisiontools.org.uk/consent/principles-children-EngWalesNI.html) being given full information regarding what trial participation involves, their right to withdraw and research dissemination plans. Consent forms will be generated within the TRANSFoRm system and populated with relevant details i.e. study ID and contact details from the medical records. Full written consent will be obtained from those legally allowed to consent on children's behalf. Consent will be expected to be obtained from all children over the age of 6 wherever possible, with written justification of reasons if consent is not obtained. Signed and completed consent and contact details will be sent to the study lead centre via fax or secure email.
A copy of the consent forms will be kept by the research team for the duration of the study and for up to 15 years after the study has closed.

All study employed research staff with participant contact will have passed Disclosure and Barring Checks.

Following eligibility and consent, children will be randomised, stratified by age. The sequence will be supplied to the TRANSFoRm platform to be allocated to each successive participant recruited. A system for checking the correct randomisation allocation will be built in to the TRANSFoRm platform. Clinicians will not be able to determine treatment allocation pre-randomisation.

Parent and child's personal details will be used to contact them during the study follow-up period and to send out the three-month stool sample kit and questionnaire. The details will be transferred to a secure study administration database called REDCap at the University of Bristol. The information given to researchers will be securely stored for 15 years after the trial ends, on site at the University and protected in accordance with the University's guidelines and the Data Protection Act.

Personal details, e.g. names and addresses will be stored separately to any other information we are given and will be kept for no longer than three years at which point all identifiable information will be destroyed.

The data does not include any special category data. The data collected at the baseline will be name, contact details and NHS number. These will be extracted from the medical notes. All other forms, including eligibility will be in the form of radio buttons for the clinician to select – there will not be any information extracted from patient medical notes in these forms. The data will be collected per participant and only at the time of the baseline visit.

We aim to recruit 399 individuals so we will be collecting this information for each participant recruited to the REST study. We will be recruiting children from GP practices across England. At month three, use of hospital services will be collected by review of the patients HER.

The individuals are patients of GP surgeries that the University is working with. All GP surgeries signed up to take part in the study have signed a site agreement agreeing to the terms and conditions of the study. The parents of these individuals will be provided with patient information leaflets and GDPR documents which will give them all the information they required about they study as well as information on how their data will be used. Children will be given child friendly information leaflets.

These patient information leaflets and GDPR document will provide all the information required for the parent to make an informed decision about whether they are happy for their child to take part. If they agree to the child participating in the study, they will be asked to sign a consent form confirming they are willing to be involved in the study.

The participants taking part in this study will be children however we will be asking a parent to consent to them being involved (a child over the age of six may also consent to involvement). At any point a parent can withdraw their child from the

study team by letting their doctor or nurse know. They do not have to give a reason and their future medical care will not be affected. The Principal Investigators (PI) also have the right to withdraw children from the trial drug in the event of inter-current illness, Adverse Events (AEs), Serious Adverse Events (SAEs), Suspected Unexpected Serious Adverse Reactions (SUSARs), protocol violations, administrative reasons or other reasons. The reason for withdrawal will be documented in the TRANSFoRm system via a specific 'withdrawal form' and coded in the EHR with a specific READ/Snomed CT code.

Details on withdrawal processes are all given in the parent information sheet, but Parents/children will have limited rights to access change or move their child's information, as the research team need to manage the data collected during the study in specific ways for the research to be reliable and accurate. If a child is withdrawn from the study, the research team will keep the information about the child that has already been obtained. To safeguard the child's rights, the research team will use the minimum personally-identifiable information possible.

All REST quantitative data will be collected using the TRANSFoRm system which has been validated using the Good Clinical Practice (GCP) standard. The system has no known security flaws and no current issues of public concern. While the concept is novel, the system has already been used in another clinical trial.

TRANSFoRm uses a Data Node Connector (DNC) to integrate with primary care Electronic Health Records (EHR) from SystmOne software (EMIS currently in development, ensuring data validity and accuracy and facilitating the nationwide engagement of the large number of primary care sites needed for REST. An additional module enables Patient Recorded Outcome Measures (PROMs) to be collected via web and smartphone (iOS, Android). The system has full provenance trail and is fully GCP/MHRA validated. Each DNC has been constructed with the participation of the system vendor. The basic components of the system are:

i) A study system (TSS) that manages projects, sites and workflow;
ii) Middleware that manages authentication and messaging;
iii) A system for triggering and storing PROMs
iv) A DNC specific to each EHR system that links clinical systems to the TSS via their Application Programming Interface (API); and
v) An online back-up data collection system.

For REST, a set of .xml files will be developed, specifying the data elements to be captured and their linkage to the TRANSFoRm Clinical Data Information Integration Module (CDIM) structured according to the Clinical Data Interchange Standards Consortium (CDISC) Operational Data Model (ADM). Further ODM files containing questions for the PROMS will be developed, and structured searches will be developed for any data elements that are to be pre-populated by the data in the EHR.

The GCP-validated clinical database (TRANSFoRm), trial management database (REDCap) and randomisation system are designed to protect patient information in line with the Data Protection Act 2018. Data will not be transferred from the GP system to TRANSFoRm until the parent/carer has consented to theirs and their child's participation. Trial staff will ensure that the participant's anonymity is

maintained through protective and secure handling and storage of patient information at the trial centres. Data is anonymised as soon as it is practical to do so in line with the Data Protection Act 2018. The study participants will be identified only by a patient ID number on the C/eCRF (both on the paper and web-based forms). Participants contact details will be stored on the secure REDCap system based at the University of Bristol.

All study documentation will be retained in a secure location during the conduct of the study. Paper versions saved on site will be archived by the University of Bristol at the end of the trial according to local policy for paediatric clinical trials; with all data retained for at least 15 years post trial closure in line with University procedures.

To comply with the fifth principle of the Data Protection Act, personal data will not be kept for longer than is required for the purpose for which it has been acquired. Data will be held in compliance with the sponsor's standard operating procedures (SOPs). Formal trial specific SOPs will be developed to detail each element of the data handling procedure.

All non-essential data will be destroyed on completion of the study.

We have decided to use TRANSFoRm in this study as we know that there are advantages of using electronic platforms for clinical trials, whereby source data is obtained directly from the health records. These benefits include;

- Increased accuracy in accordance with the data protection principles;
- Reductions in the need for intensive data management;
- Increased safety (by ensuring trial data is within the clinical record);
- Easier trial monitoring; EHR management of trial workflow, prompts and alerts for recruitment and follow-up, and patient recorded outcomes; and
- The use of Clinical Data Interchange Standards Consortium (CDISC) standards for data capture.

There will be no international data transfers taking place.

Consultation requirements

Explain what practical steps you will take to ensure that you identify and address privacy risks. Who should be consulted internally and externally? How will you carry out the consultation? You should link this to the relevant stages of your project management process.

You can use consultation at any stage of the PIA process.

The Data Monitoring and Ethics Committee meets twice a year, shortly before each Trial Steering Committee (TSC) to advise and make recommendations to the TSC regarding trial safety issues or other reasons for the trial not to continue.

We work with a dedicated technical team at KCL who have expert knowledge in this software and will support GP practices that are participating in installing this and to provide ongoing support for the duration of the study. We have consulted with security experts within TPP (also known as System One) who have an agreement that authorises us to use their API. SystmOne is a centrally hosted clinical computer system developed by Horsforth-based TPP (The Phoenix Partnership). It is used by healthcare professionals in the UK predominantly in Primary Care.

GP practices are provided with an installation guide for TRANSFoRm platform and a technical team of experts are available to consult with practice managers/ IT support person at practices during the install process.

We will be consulting with members of staff at GP practices to feedback to us how they feel the software works and whether they would be happy to use this in future trials.

Annex 1

Linking the PIA to the data protection principles

Answering these questions during the PIA process will help you to identify where there is a risk that the project will fail to comply with the DPA or other relevant legislation, for example the Human Rights Act.

Principle 1

Personal data shall be processed fairly and lawfully and, in particular, shall not be processed unless:

a) at least one of the conditions in Schedule 2 is met, and

b) in the case of sensitive personal data, at least one of the conditions in Schedule 3 is also met.

Have you identified the purpose of the project?

How will you tell individuals about the use of their personal data?

Do you need to amend your privacy notices?

Have you established which conditions for processing apply?

If you are relying on consent to process personal data, how will this be collected and what will you do if it is withheld or withdrawn?

If your organisation is subject to the Human Rights Act, you also need to consider:

Will your actions interfere with the right to privacy under Article 8?

Have you identified the social need and aims of the project?

Are your actions a proportionate response to the social need?

Principle 2

Personal data shall be obtained only for one or more specified and purposes and shall not be further processed in any manner incompatible with that purpose or those purposes.

Does your project plan cover all the purposes for processing personal data?

Have you identified potential new purposes as the scope of the project expands?

Principle 3

Personal data shall be adequate, relevant and not excessive in relation to the purpose or purposes for which they are processed.

Is the quality of the information good enough for the purposes it is used?

Which personal data could you not use, without compromising the needs of the project?

Principle 4

Personal data shall be accurate and, where necessary, kept up to date.

If you are procuring new software does it allow you to amend data when necessary?

How are you ensuring that personal data obtained from individuals or other organisations is accurate?

Principle 5

Personal data processed for any purpose or purposes shall not be kept for longer than necessary for that purpose or those purposes.

What retention periods are suitable for the personal data you will be processing?

Are you procuring software that will allow you to delete information in line with your retention periods?

Principle 6

Personal data shall be processed in accordance with the rights of data subjects under this Act.

Will the systems you are putting in place allow you to respond to subject access requests more easily?

If the project involves marketing, have you got a procedure for individuals to opt out of their information being used for that purpose?

Principle 7

Appropriate technical and organisational measures shall be taken against unauthorised or unlawful processing of personal data and against accidental loss or destruction of, or damage to, personal data.

Do any new systems provide protection against the security risks you have identified?

What training and instructions are necessary to ensure that staff know how to operate a new system securely?

Principle 8

Personal data shall not be transferred to a country or territory outside the European Economic Area unless that country of territory ensures and adequate level of protection for the rights and freedoms of data subjects in relation to the processing of personal data.

Will the project require you to transfer data outside of the EEA?

If you will be making transfers, how will you ensure that the data is adequately protected?

IRAS ID: 229293

The Runny Ear Study is funded by the National Institute for Health Research's HTA Programme HTA

REST STUDY SAE/SUSAR REPORTING INSTRUCTIONS FOR RECRUITING SITES

(SEE UNIVERSITY HOSPITALS BRISTOL NHS FOUNDATION TRUST, RESEARCH SAFETY REPORTING STANDARD OPERATING PROCEDURE (LATEST VERSION)
http://www.uhbristol.nhs.uk/research-innovation/information-for-researchers/setting-up-and-running-a-clinical-research-study/templates-and-sops/sops/

An event/reaction is serious if it:

- **results in death,**
- **is life threatening,**
- **results in persistent or significant disability/incapacity,**
- **requires hospitalisation,**
- **prolongs a current hospitalisation**
- **consists of a congenital anomaly or birth defect**

These instructions apply to any Serious Adverse Event reported by a patient, via hospital admission/A&E letters or identified at the REST 3-month Primary Care Notes Review for the period up to 28 days post-study entry.

1. The delegated clinician will report SAEs to UH Bristol monitor and the Bristol trial centre. The Summaries of Medicinal Product Characteristics for ciprofloxacin 0.3% drops, oral amoxicillin and oral clarithromycin list the common side-effects for the trial medications: see the REST protocol (current version found in Site File), Section 8: Trial Treatments, page 32 onwards. Rare or systemic complications of acute otitis media with discharge (AOMd) that result in hospital admission will be treated as SAEs: see protocol Section 10.4.4: "Expected" adverse reactions and events, page 47 onwards for the list of common symptoms that would be expected and rare/systemic complications.

2. The delegated clinician must notify UH Bristol monitor **immediately** (by email: **research@uhbristol.nhs.uk** or telephone:) of reported / notified SAEs. This report can be brief – the purpose is simply to notify UH Bristol monitor (acting on behalf of the trial sponsor) that the event happened.

3. If notifying by email, the instructions below must be followed: -
   - SAE reports should be sent only to research@uhbristol.nhs.uk and bristolccg.RestStudy@nhs.net
   - The format of the message should be as follows:

   A. REST study
   B. Advance notice of SAE report to follow by encrypted email
   C. Participant Identification Number: XXXXXXXXX (**DO NOT include the patient's name or any other patient identifiable information)**
   D. Brief details of SAE if known

4. **All of sections 1-12** of the SAE/SUSAR Initial Report Form (please use the form which can be found at http://www.uhbristol.nhs.uk/research-innovation/information-for-researchers/setting-up-and-running-a-clinical-research-study/templates-and-sops/templates-and-guidance/TMPL_025 SAE/SUSAR initial report) must be completed and submitted by email to UH Bristol monitor **within 24 hours of becoming aware of the event (see contact details below).**

5. The recording and submission of the Initial Report Form must be logged on the patient's electronic medical record by the delegated clinician.

6. The Bristol study centre will log all retrospective SAE reports onto the TRANSFoRm data platform.

Completing the SAE Initial Report Form

1. Responsibility for reporting SAEs and SUSARs at GP practices:
   - Healthcare professionals involved in study recruitment.

2. Staff reporting a SAE will, **as soon** as they become aware of the event:-
   - **immediately** contact UH Bristol monitor (by email to **research@uhbristol.nhs.**uk or telephone) to briefly report that the event happened;

   - complete the Initial Report Form sections 1-7, and section 10 if necessary, and email the form **directly to UH Bristol monitor within 24 hours of becoming aware of the event**;

   - **At the same time** as sending it to UH Bristol monitor, fax a copy of the **unsigned** Initial Report Form to the Bristol study centre on 0117 928 7341 or scan and send it from a clinical staff "….@nhs.net email" account to the Bristol study centre secure email account (bristolccg.RestStudy@nhs.net);

   - The Bristol study centre must confirm in writing that the report has been received (see contact details below).

3. **The Co-Chief Investigator (Co-CI)** at the Bristol study centre will review the Initial Report Forms sent in by all GP sites, complete sections 8, 9 and 11 and sign the forms. The Bristol study centre will send **signed** Initial Report Forms **for all GP sites** by email direct to UH Bristol monitor **as soon as possible (within 5 working days for SAEs or 2 working days for life-threatening SUSARs)**.

4. If the Co-CI at the Bristol study centre is unavailable, the study team will send the Initial Report Forms to the **second Co-CI at the University of Southampton**, who will review the Initial Report Forms, complete sections 8, 9 and 11 and sign the forms. The Co-CI will send the **signed forms** by email **directly to UH Bristol monitor as soon as possible (within 5 working days for SAEs or 2 working days for life-threatening SUSARs) with copies sent to the Bristol study centre.**

5. The Co-CIs will delegate responsibility for completing and signing the Initial Report Forms (and Follow-up Report Forms) to another academic GP in the REST study team, in the event of them both being away and unavailable.

6. **Contact details** for UH Bristol monitor and Bristol study centre are: -

UH Bristol monitor	tel: email**:** research@uhbristol.nhs.uk
Bristol trial centre	fax: Email (not secure): Email (secure): bristolccg.RestStudy@nhs.net

UNDER NO CIRCUMSTANCES SHOULD SAFETY REPORTING PAPERWORK BE FAXED, EMAILED OR POSTED TO ANY OTHER DESTINATIONS

7. File the original Initial Report Form paperwork in the Trial Site File / Trial Master File respectively.

Follow-up of SAEs and completion of Follow-up Report Form

1. All SAEs need to be followed up until they are resolved.

2. A follow-up report is NOT necessary if the SAE is resolved at the time of the Initial report.

3. The Bristol study centre is responsible for ensuring that SAEs are followed-up within the required timescales.

4. If any SAEs remain unresolved beyond the required timescales, UH Bristol monitor will instruct the CI / Trial Manager accordingly.

5. The Trial Manager and Trial Research Nurse will co-ordinate with GP practices in completing the SAE Follow-up Report Form.

6. **Reporting staff in GP practices** (Ideally the same person who completed the Initial Report Form) will:-
   - complete the Follow-up Report form, **as soon as possible**, and **at the latest within 5 working days, or 2 working days if a life-threatening SUSAR,** of becoming aware of initial event;
   - for **SUSARS all sections** on the Follow-up Report form must be completed, and for **other SAEs sections 1, 2 and 3** must be completed;
   - fax or email a copy of the **unsigned** Follow-up Report form to Bristol study centre;
   - email Bristol study centre, who must reply in writing to confirm the report has been received.

7. The Co-CI at the Bristol study centre will sign and send the Follow-up Report form by email direct to UH Bristol monitor **immediately on receiving the report, or within 24 hours (the Follow-up Report must be sent to UH Bristol no later than 5 working days after the Initial Report Form)**.

   The Initial Report and the Follow-up Report Forms may be done together, if within 24 hours of becoming aware of the event.

8. If the Co-CI at the Bristol study centre is unavailable, the study team will send the Follow-up Report form to the **second Co-CI at the University of Southampton**, to sign. The Co-CI will send the **signed form** by email **directly to UH Bristol monitor immediately on receiving the report, or within 24 hours (the Follow-up Report must be sent to UH Bristol no later than 5 working days after the Initial Report Form)**.

9. Reporting staff at both GP practices and the Bristol study centre must file the original document in the Trial Site File / Trial Master File respectively.

10. The Trial Research Nurse will co-ordinate with GP practices for the completion and return (as above) of further Follow-up Report Form(s) for data collected **later than 5 days post-SAE** until the SAE has resolved or a decision for no further follow-up has been taken (UH Bristol monitor will co-ordinate with the Trial Manager / Co-CI).

11. A paper copy of the Follow-up Report Form(s) with signatures will be sent to the sponsor by the Bristol study team.

STANDARD OPERATING PROCEDURE FOR:

Recording and Reporting of Deviations, Violations, Potential Serious Breaches, Serious Breaches and Urgent Safety Measures

SOP Details:

Number: SOP-REST-XXXX	Version: 1.0	
Author(s): Kathryn Curtis		Date: 27/11/2018
Authorised by: Title:		Date:
Date operational:		
Date to be reviewed:		

Review History:

Review Date:		Reviewed By:	
Review amendments:			
Amended date:		Amended by:	
Authorised date:		Authorised by:	

Review Date:		Reviewed By:	
Review amendments:			
Amended date:		Amended by:	
Authorised date:		Authorised by:	

Review Date:		Reviewed By:	
Review amendments:			
Amended date:		Amended by:	
Authorised date:		Authorised by:	

Review Date:		Reviewed By:	
Review amendments:			
Amended date:		Amended by:	
Authorised date:		Authorised by:	

1. DEFINITION OF A PROTOCOL DEVIATION

A violation can occur when there is a variation in practice from Trial Protocol/SOPs. A violation can be classified as major if there is significant occurrence which affects participant safety or scientific integrity of research.

Any violations that may impact on subject's safety or affect the integrity of the study data must be reported to the Sponsor. Examples include but are not limited to:

- Failure to obtain informed consent, i.e. no documentation in source data or an informed consent form
- Enrolment of subjects not meeting the inclusion/exclusion criteria
- Undertaking a trail procedure not approved by REC and/or the MHRA (unless for immediate safety reasons)
- Failure to report and SAE/SUSAR to the UH Bristol

2. REPORTING PROTOCOL DEVIATIONS

- Please report any deviation from the Protocol to the Bristol Study team **as soon as you are made aware.**
- Complete the "Record of Protocol AND/OR GCP Deviation form located in the site file.
- Please include as much information as possible and return the form by **Fax <u>or</u> Encrypted email:** [redacted]

REST
the runny ear study

RECORD OF PROTOCOL AND/OR GCP DEVIATION
PAPER COPY TO BE RETAINED IN THE TMF

1. TRIAL DETAILS			
Trial full name:			
EudraCT number (or N/A):			
REC number:			
Other reference number(s) (or N/A):			
Sponsor:			
Sponsor reference:			
Chief Investigator:			
Trial start date:	___ / ___ / _____ *dd / mm / yyyy*		
Current protocol version and date:	version		___ / ___ / _____ *dd / mm / yyyy*

2. REPORTING DETAILS	
Date Bristol Study Team became aware of incident(s):	___ / ___ / _____ *dd / mm / yyyy*
Reported to (tick all that apply): Sponsor ☐ Chief Investigator ☐ Other (specify) ☐	
Reported by:	
Date reported:	___ / ___ / _____ *dd / mm / yyyy*

3. DETAILED DESCRIPTION OF DEVIATION	
Site name (and number/code if applicable):	
PI name:	
Other involved parties (or N/A):	

In this section include details of:

- *Relevant incident/s*
- *The location of the incident/s*
- *Who was involved and the nature of the incident/s*
- *The outcome of the incident/s*
- *Any information given to participants*

4. SUMMARY OF DISCUSSIONS/AGREED ACTIONS:

Summarise here the reasons for urgent safety measures, any agreed preventative and corrective action(s) and the plan for further action(s) (or if a Sponsor's CAPA form has been completed already this may be attached here):

5. SUPPORTING DOCUMENTS:

List here any relevant supporting documents, e.g. email correspondence. Ensure they are printed and retained with this form in the TMF

6. PERSON COMPLETING REPORT:

Print name		
Signature		
Job title		
Date		

Detailed TRANSFoRm technical specification for REST v1.4

This is a working document, which will accompany the short TRANSFoRm technical specification for REST and Appendix 1. This document will be updated as required during the trial.

Overview

The TRANSFoRm platform encapsulates certain features of a clinical trial management system by interacting with the GP's electronic health record (EHR). The tool provides automatic eligibility checking, part-filling of eCRFs, and study workflow management). The system has a full provenance trail (listed in Provenance capture section below) and is fully GCP/MHRA validated. All REST quantitative data will be collected using the EU FP7 funded TRANSFoRm Program (www.transformproject.eu). The TRANSFoRm platform will support the project compliance with the new General Data Protection Register (GDPR), due to come into force May 2018.

TRANSFoRm uses a Data Node Connector (DNC) to integrate with primary care EHR (also increasingly used in Walk-in and Out-of-Hours centres), ensuring data validity and accuracy, and facilitating the nationwide engagement of the large number of primary care sites needed for REST. An additional module enables Patient Reported Outcome Measures (PROMs) to be collected via web and smartphone (iOS, Android). Each DNC has been constructed with the participation of the EHR system vendor.

The basic components of the system are: (i) a Study System (TSS) that manages projects, sites and workflow; (ii) middleware that manages authentication and messaging; (iii) a system for triggering and storing PROMs; (iv) a DNC specific to each EHR system, that links clinical systems to the TSS via their Application Programming Interface (API); and (v) an online back-up data collection system. For REST, a set of .xml files will be developed, specifying the data elements to be captured, and their linkage to the TRANSFoRm Clinical Data Information Integration Model (CDIM), structured according the Clinical Data Interchange Standards Consortium (CDISC) Operational Data Model (ODM), and the timeline according to the CDISC Study Data Model (SDM). Further ODM files containing questions for the PROMS will be developed, and structured searches will be developed for any data elements that are to be pre-populated by the data in the EHR. See Figure 1.

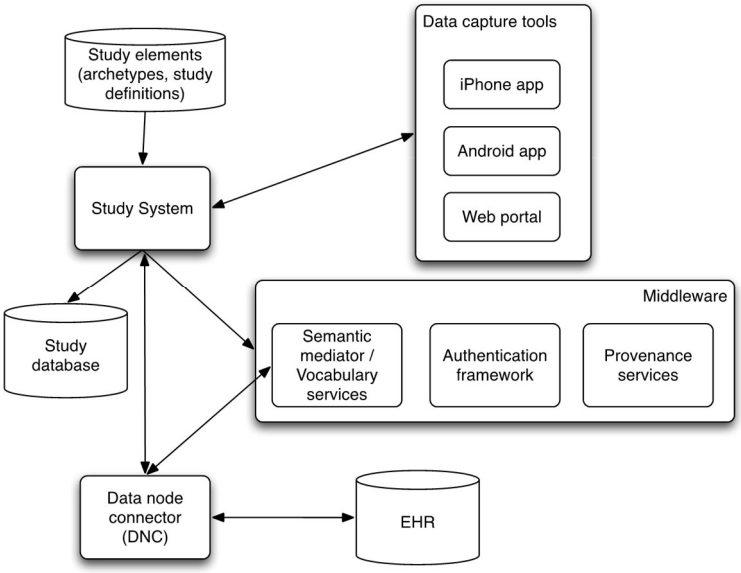

Figure 1: Schematic of the TRANSFoRm system architecture

REST-specific features and work flow for the trial

The basic system will comprise forms for pre-eligibility check, eligibility confirmation, consent, randomisation, 2 clinician-entered study forms (referred to as ESL and CROM 1) and 15 patient reported outcome measures (referred to as PROM 1-15). These will be ordered as follows:

1. A record will be kept the number of times a clinician has ignored the REST pop-up.
2. Pre-eligibility check (whether otitis media is with discharge and if parent/guardian available to consent). A READ code or equivalent will be added to the notes to allow subsequent audit.
   2.1. If a participant declines or is not eligible, the system will prompt a participant information sheet (PIS) for the qualitative study, which will include a number to text if they are happy to take part in a qualitative interview.
3. Eligibility screening, keeping a tally being of screen failures and eligible children who declined to take part in the trial (NB the child will not have a participant ID at this stage as they have not been consented). The reasons for not participating in the trial will be recorded from a drop down menu or as free text. This data will be kept in accordance with GDPR regulations. A READ code or equivalent will be added to the notes to allow subsequent audit.
4. If the participant is eligible, a prompt to print the PIS will appear.
5. Add in a prompt asking if clinical/GCP oversight was required – a yes/no box. If yes is ticked, we need to record the date and what the issue was and who was providing the oversight
6. Subsequently, a prompt to print two copies of the Informed consent form (ICF) (and assent form where relevant) will appear.
7. A participant ID will be issued.
8. Randomisation occurs by TRANSFoRm (not displayed at this point).
9. CROM 1 completed.
10. Randomisation allocation displayed to the clinician.
11. Dialogue pop up for the clinician saying what group the child was randomised into, prescription issued and the system will prompt the correct medicines advice sheet to be printed from a PDF (there will be 3 different ones for the 3 different randomisation allocations).
    11.1. Prompt for the clinician to give the parent/carer the bag containing the paper diary, information about how to download the app/fill out online/paper, stool sample and return envelope.
12. TRANSFoRm sends parent a text welcoming them to the trial.
13. TRANSFoRm sends the study team an email to say a participant has been recruited. For each participant recruited, TRANSFoRm will allow the study team to easily view a summary screen including all contact details, confirmation consent is complete, randomisation allocation and date of recruitment and a list of anything outstanding and when it was due.
14. Prompt to scan and save the ICF in the participant's notes (along with a copy of the PIS) and to fax/email a copy to the study team
15. PROMs 1-14, entered either via the app, web or paper via the study research nurse, over the next 14 days.
    15.1. TRANSFoRm will record whether this data has been recorded from the paper dairy or from the research nurse's record from the daily phone call and identify which member of the research team has recorded this.
    15.2. PROMs 1-14 will be completed. TRANSFoRM to prompt study team to send voucher.

16. PROM 15 – TRANSFoRM will send a reminder to the study team to send PROM 15 and the stool sample and a return envelope. This is completed 3 months after the child has entered the trial.
17. CROM 2 completed by the practice staff at least 3 months after the child has entered the trial (this is not time critical and the practice staff might choose to do several at once). The EHR will pre-populate much of this. SAE will be defined as overnight hospital admission or death. Tech team will put an alert onto dashboard if this happens.

Specific additional features/notes are listed below:

1. Field validation will be included to ensure 'sensible' values have been added and that all forms are completed.
2. The submit buttons will be clear and the form will be structured so that it cannot be closed without being saved.
3. The code triggers for inclusion are intentionally broad as otitis media with discharge is not coded frequently. As the EHR trigger would be for otitis only, the clinician will check otitis media with discharge as part of the pre-eligibility screening (step 2).
4. CROM 1 contains baseline information collected at recruitment stage from patients who have been consented. Randomisation should happen before CROM 1 but is not to be displayed to the clinician until afterwards.
5. Decliners should receive a printed information sheet inviting them to be contacted. Need a dialog message and document to print (step 2.1). This will be implemented this in such a way that the step can be switched off remotely so when recruitment to the qualitative study is complete the function can be inactivated.
6. Information dialogue should be presented to the clinician saying what group the child was randomised into, together with links to info-sheet PDFs that they need to print out, only the sheet appropriate for the randomised group will be presented.
7. CROM 2 will be filled after at least 3 months by a practice manager for everyone by opening the records, confirming the EHR pre-populated data, and adding extra information only if necessary. The forms are checked and signed off by a clinician (as they will contain data about any SAEs).
8. A dashboard for the study team will be implemented to display the current state of the study, e.g. which PROMs are running late.
9. Email notifications will be needed for recruitment events.
10. Study team members will need to be able to enter the data for any PROM - will be used for paper diaries. They will need a username and password for each participant, in case they are completing a paper diary.
11. Data collection will include the following elements:

    - consent and assent to the trial and baseline information collected prior to randomisation. Baseline information will be recorded in the participants TRANSFoRm profile via their medical record;
    - randomisation status of the participant recorded via the TRANSFoRm profile;
    - parent/carer completed PROM 1 on days 1-14 as one document;
    - trial specific data required to answer the primary and secondary outcomes via a READ/Snomed CT code search of the TRANSFoRm profile in conjunction with a hand review of EHR;
    - results of the analysis of participants stool sample at day 14 and month 3;

- PROM 2 at month 3;
- health resource use at days 7, 14 and month 3. Health resource data will be collected via TRANSFoRm (days 7 and 14) and by hand review of EHR (month 3).
- Interviews with parents/carers that accept and decline trial participation.
- A study management form to allow research nurses to log calls, notes and vouchers sent.

The full list of data items, with their associated input form renderings is provided in Appendix 1.

Provenance tracking

- Provenance entry created *for each popup closure event, logging the trial, clinician and practice.*
- Entry for each form completion.

Additional explanation/notes

- The software will be added to the practice PCs by the EHR vendors as part of an update. This circumnavigates the need for the CCG to test the software.
- The software will sit on the practice PCs in a dormant inactive state until the practice has received the 'green light' from the Sponsor. The TRANSFoRm team will then activate the software to a live setting.
- Pop ups will generate several rather than 1 long one because a single long form would be too slow loading in the browser.
- The 'workbench' allows the study team to see how many participants have been recruited (by site and clinician, as well as in total) and how many times the pop ups have popped up.
- Also have a summary view including all contact details, confirmation consent is complete, randomisation allocation and date of recruitment and a list of anything outstanding and when it was due.
- A participant can fill out the PROM on either the web interface or app or both (or entirely on paper).
- The clinician interviews don't need to be included on the TRANSFoRm workflow and will be administered by the qualitative study team only.
- REDCap will ONLY be involved with:
    - Site recruitment
    - Phone calls
    - Addresses
    - Vouchers/ stool kits sent out

  It is a basic management tool and doesn't need to integrate at all with TRANSFoRm.

Additional support provided by the TRANSFoRm team

- Ongoing maintenance of the TRANSFoRm software will be provided with xxxxx time , including the DNC and app (both iOS and Android).
- Ad hoc technical and running support of the TRANSFoRm software (including the app (iOS and Android)), including answering questions from practice staff, the study team and

participants' carers. NB the study team will not be fielding these questions. The training video and training manual will be updated if there are FAQs which need to be included.

- The trial data will all be stored by TRANSFoRm on a secure server held by Kings College London.
- This data will be backed up every night.
- The TRANSFoRm team will write a user manual for the practice staff and the participants to use.

Timeline

All timeline points will be signed off at the monthly Technical Development meetings**.**

1) Prepare main and back-up servers; Oct 17 – May18
2) Development of data collection forms; Jan 18 – Mar 18
3) Monthly technical meetings; Jan 18 – Mar 2020
4) Encode data definitions into ODM; Jan 18 – Mar 18
5) Develop CDIM, CDISC, ODM (CROMS and PROMS) and SDM models for data collection; Jan 18 – Apr18
6) Develop structured searches for any data elements that are to be pre-populated by the data in the EHR; Jan18-Apr18
7) Test setup on simulated study scenarios on both TPP and Vision EHR systems; April 18 – May 18
8) Test set up of the workbench for the study team; April 18 – May 18
9) Deploy on single demonstration EHR system and produce training video and document; May 18 – July 18
10) The study team to sign off how the software works (both practice level and the workbench for the study team), the training video and training manual; July 18.
11) Perform Good Clinical Practice validation of the system and have this signed off by the Sponsor; May 18 – Jul 18
12) Deploy in practices start – August 18
13) Deployment, maintenance and support ongoing Sept 18 – June 20.

Abbreviations and definitions

API	Application Programming Interface
CDIM	Clinical Data Information Integration Model
CDISC	Clinical Data Interchange Standards Consortium
CRF	Case/clinical record form
CROM	Clinician Reported Outcome Measures
ESL	Eligibility Screening
CROM 1	Baseline data collection, demographic information and child contact details
CROM 2	3 month primary care notes review
DNC	Data Node Connector

EHR	Electronic Health Record
EHR Vendors	TPP (Also known as SystmOne) and Vision [N.B We will not be using Emis or Emisweb for this trial]
GCP	Good Clinical Practice
GDPR	General Data Protection Register
ICF	Informed Consent Form
ODM	Operational Data Model
PCRN	Primary care notes review
PIS	Participant information sheet
PROM	Patient Reported Outcome Measures
PROM 1-14	SRQ filled out on a daily basis for 14 days, numbered sequentially 1-14 for each day
PROM 15	SRQ (also called OM-6), completed at 3 months
RN	Research nurse
SDM	Study Data Model
SRQ	Symptom Diary Questionnaire (Completed by the participant)
TMG	Trial management group
TSS	Study specific system managing the project

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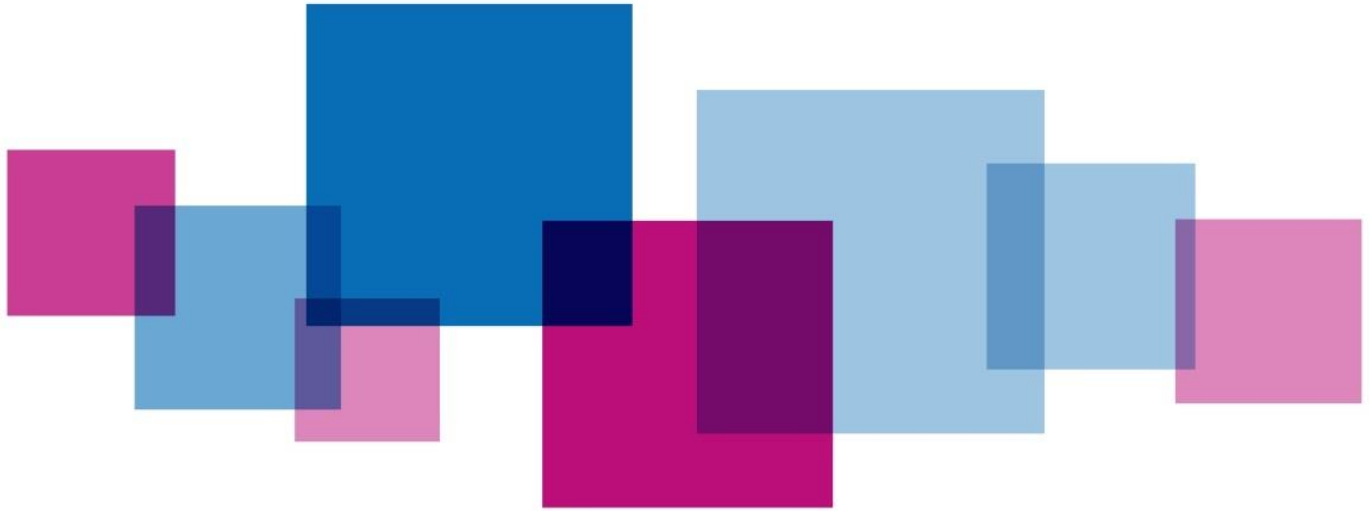
Contractual Escalation Policy



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IMPORTANT:

The CCG R&E Team encourages Chief Investigators (CI) and/or the Research Project Manager to raise concerns at an early point, and we will be in touch outside of project management groups to check-in with collaborator progress.

This document is guidance, and to be used in agreement between the CI, Project Manager and CCG.

Background:

Collaborators usually act in good faith, and often when project deadlines are missed, it is for genuine reasons despite colleagues doing their best.

However, this is a subtle area of relationship management, and it can be difficult to detect the difference between collaborators who will deliver their obligations a bit later than planned, and those who won't/can't or don't intend to deliver.

The R&E Team's experience is that it is not unusual for a collaborator to repeatedly report they have *nearly* completed their allocated tasks at each Management Group Meeting, repeatedly explaining that a few more days or a week longer is all they need in order to achieve their goal.

When those collaborators are the only experts on their area of work in the research team, it is difficult for the CI/Project Manager and others to judge if this is a realistic report or not.

Escalation may not be necessary, but when it is, it is important that it is only performed in agreement between the CI/Project Manager and the CCG Host, and is undertaken as a team effort.

The *gut-feeling* of the CI/Project Manager is an important aspect to consider at all times.

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It is helpful to document what decisions are made as they are made, with brief explanations as to the thinking behind the decision. This can be especially helpful in retrospect when **no escalation action** was the decision taken. If things go wrong later, having a record of the reasons which dissuaded the team from taking escalating action can be helpful for all.

This guidance is intended to preserve the relationship between the CI/Project Manager and the co-applicant, recognising that the intention is to resolve the issues so that the project aims are achieved, and the CI/Project Team can work with the co-applicant.

Escalation level	**Action(s)**	**Works on**	**Risk**
0	Project deadlines raised at project management group, and agreed together.	Good will, funding agreement, peer pressure	Low priority project for Third Party.
1	Project Manager to raise with co-applicant/collaborator, to investigate if there are issues preventing the work or unexpected delaying factors, unforeseen circumstances etc. Revised plan agreed between the CI/Project Manager and co-applicant/collaborator. Revised plan raised, discussed, & agreed in Project Management Group meeting.	Cooperation, open communication and sharing of problem and plan for resolution. Goodwill and reputation amongst peers.	Slippage on grant milestones. If the project is low priority for the Third Party, this approach may not achieve increase in priority
2	CCG management group member to raise concerns in project management group meeting as contract host. CCG member explains role of the host, to act on behalf of the funder to make sure the project achieves the contracted milestones.	Introduces contractual obligation pressure.	This could introduce an unwelcome dynamic to the wider collaborating group (to be managed by the CI

			and Project Manager and CCG). If the project is low priority for the Third Party, this approach may not achieve increase in priority
3	CI/project manager to speak to collaborator stating pressure from CCG. And/or CCG to contact collaborator raising concerns on the slippage, and inquiring about remedying actions, and stating that we take our role as host seriously, and having had a couple of contracts terminated due to slippages we are keen to avoid this. Offering help/support in the first instance, whilst being clear that alternatives include ending the contract and finding an alternative partner to deliver the work. Final revised plan agreed between the CCG, CI/Project Manager and co-applicant/collaborator. Final revised plan discussed in Project Management Group meeting.	Contractual obligation pressure.	The increased communication and time spent addressing the problem may exacerbate genuine collaborators who simply have more to do than they have time to achieve.

	Also, CCG raises concerns with Contract Department and Collaborator's Line Manager/Head of Department. CCG explains our final agreed plan & what the next steps in escalation would be. CCG to discuss alternative providers with the CI/Project Manager.		
4	CCG Pause invoices. CCG raise with NIHR and explain situation, suggest options of a) continue with original but seek extension, b) look for alternative partner (may need extension request) c) close project.	Creates pressure for Third Party from their own finance department and contracts department	Resentment or negativity impact on quality of work delivered.
5	CCG request that Project Management Group add agenda item on the collaborator, with a vote on ending their participation.	Contractual/financial consequences	Ongoing/future collaborations
6	CCG terminates contract with collaborator, reclaiming funding where possible.	Contractual/financial consequences	Ongoing/future collaborations

Terms:

Third Party – this can be a co-applicant, a collaborator, a sub-contractor or project team member (usually employed at a Site other than where the CI/Project Manager is employed).