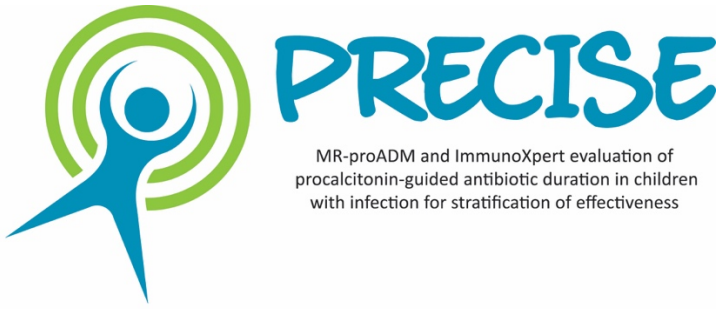
MR-PRo-adrenomedullin (MR-proADM) and ImmunoXpert Evaluation of procalcitonin-guided antibiotic duration in Children with Infection for Stratification of Effectiveness (PRECISE) study (EME Project: NIHR129960)



19.1 Background

The host-response to bacterial infection is highly heterogeneous, there is therefore a need for stratified treatment strategies instead of the traditional "one-size-fits-all" approach. A precision medicine approach can improve patient outcomes by identifying endotypes in whom the intervention is likely to be beneficial, harmful or ineffective.

A mechanistic sub-study called PRECISE will be embedded into the BATCH trial. It will seek to identify if a PCT-guided antibiotic algorithm is beneficial, harmful or ineffective in certain endotypes of endothelial dysfunction and host immune response subgroups. Subgroups that do not benefit from the intervention will be identified, so potential harm is avoided, resources are not wasted, and subgroups that do benefit are optimised.

From a clinical point of view, it is important to identify subgroups in whom a PCT-guided antibiotic algorithm might potentially be harmful, so that alternative treatments and diagnostic strategies could be tried.

The endotypes to be examined in the PRECISE sub-study are stratified by endothelial dysfunction (low/intermediate/high MR-proADM) and host immune response (low/intermediate/high ImmunoXpert score: TRAIL, IP-10 and CRP).

These biomarkers have immunomodulatory (MR-proADM, IP-10), immunosuppressive and immunoregulatory effects (TRAIL), as well as playing a part in both the adaptive and innate host immune response to infection (TRAIL, IP-10, CRP). This provides potential for targeted patient management and enhanced clinical trial design.

19.2 Aim and objectives

Aim

The aim of the PRECISE sub-study is to determine if there are specific sub-groups of patients, for whom a PCT-guided antibiotic algorithm may be beneficial, harmful or ineffective. It aims to identify endotypes or sub-phenotypes of infection to facilitate optimisation of antibiotic dosing and duration (when, by how much and for how long). The embedded mechanistic study within an existing RCT allows the theranostic exploration of two commercially available biomarker assays to guide judicious antibiotic use.

Objectives

The **primary objective** is to determine if there are specific sub-groups of patients (based on host response and organ dysfunction) in whom the addition of PCT testing to current best practice based on the NICE AMS guidelines can safely allow a reduction in duration of antibiotic therapy in hospitalised children with suspected or confirmed bacterial infection compared to current best practice alone. To meet this objective specifically, we will assess;

- Duration of IV antibiotics

The **secondary objective** is to assess the effect of additional PCT testing in AMS best practice in specific sub-groups within the BATCH trial (based on host response and organ dysfunction) on:

- Total duration of antibiotics (oral and IV)
- Time to switch from broad spectrum to narrow spectrum antibiotics
- Time to discharge from hospital
- Suspected Adverse Drug Reactions (ADR) (defined using the Liverpool Causality Assessment Tool),
- Hospital acquired infection up to Day 28
- Unscheduled admissions/readmissions (admitted/re-admitted to PICU, or unplanned readmission to hospital within 7 days of stopping IV antibiotics)
- Re-starting IV antibiotic therapy (for any reason within 7 days of stopping IV therapy)
- Mortality (death for any reason in the 28 days following randomisation)
- MR-proADM at randomisation in the intervention and control arm, and at subsequent time points that other blood tests are being performed
- TRAIL, IP-10, and CRP host signature at randomisation in the intervention and control arm, and at subsequent time points that other blood tests are being performed.

19.3 Design

Embedded mechanism of action study within the BATCH trial (a multi-centre, prospective, individually randomised, open-label two-arm randomised controlled trial comparing a PCT-guided antibiotic algorithm versus usual care).

19.4 Setting

We have identified 4 lead BATCH sites (Liverpool, Bristol, Oxford and Southampton) who will recruit for PRECISE. Additional sites will be included if needed.

19.5 Participants

Children recruited into the BATCH trial.

19.6 Recruitment into PRECISE

Parents/ carers of BATCH participants will be asked to read a supplementary information sheet for the PRECISE study. If they agree to take part they will be asked to sign the informed consent section at the bottom of the supplementary information sheet. They will be advised that where possible, leftover blood taken from routine blood tests will be salvaged to use for the PRECISE study, however if there is not enough leftover blood, additional samples may need to be taken. If any additional samples are needed, they will be told that we will always seek their permission first, and will used the method that is most preferable them and their child e.g. finger prick, venepuncture, arterial line (if already in place). They will also be informed that they will receive a £20 high street shopping voucher for the inconvenience, which is unconditional and not dependent on whether they give permission for any additional samples to be taken.

19.7 Sample and Data collection

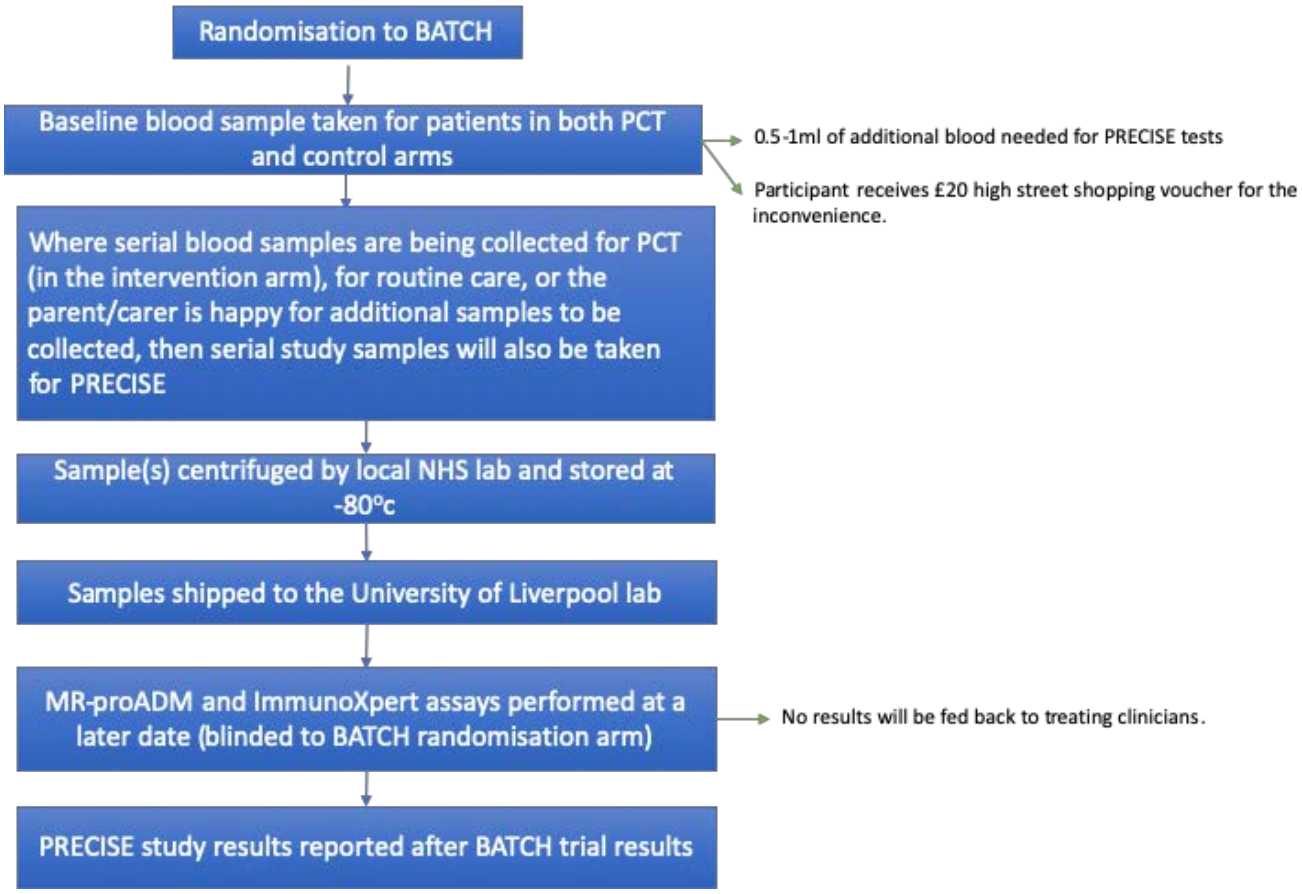
Blood samples will be taken at baseline in both the BATCH intervention and control arms for MR-proADM and ImmunoXpert analysis.

Where serial blood samples are being collected for PCT (in the intervention arm), for routine care, or the parent/carer is happy for additional samples to be collected, then serial study samples will also be taken for MR-proADM and ImmunoXpert analysis.

These PRECISE tests require 0.5-1ml of additional blood. This amount is easily available from a finger prick or venepuncture, even in an infant. The sample volume required for the MR-ProADM test is 26ul of plasma and the ImmunoXpert test requires 200ul of plasma.

The MR-proADM and ImmunoXpert assays will be performed in batches at a later date. The results will not be fed back to treating clinicians. The results will be entered into the BATCH database for secondary analysis after the BATCH trial results are reported (Figure 4).

Figure 4: PRECISE study flow diagram



The prioritisation of samples and hierarchy of tests is detailed below:

1. Routine blood tests
2. BATCH - PCT test
3. PRECISE - MR-proADM
4. PRECISE - ImmunoXpert

19.8 Outcomes

19.8.1 Primary Outcomes

Time until IV antibiotic therapy is stopped will be the primary (time-to-event) endpoint, same as in BATCH trial. Baseline MR-proADM and ImmunoXpert scores will define subgroups for the primary comparison, and serial measurements for additional analyses.

19.8.2 Secondary Outcomes

Total duration of antibiotics (oral and IV), time to switch from broad spectrum to narrow spectrum antibiotics, time to discharge from hospital, suspected adverse drug reactions, hospital acquired infection up to Day 28.

19.9 Sample Size

We will use time until IV antibiotic therapy is discontinued following randomisation as primary (time-to-event) endpoint, similar to the BATCH trial. We want to test whether the effect of the intervention (PCT vs control) on the primary endpoint is different across the pre-defined biomarker sub-groups (see Figure 5) i.e., whether there exists an interaction between intervention arm and biomarker sub-group. For MR-proADM, we assume median antibiotic durations of 2 versus 4 days (control vs PCT) in the low MR-proADM sub-group, 7 versus 5 days (control vs PCT) in the intermediate MR-proADM sub-group, and 10 versus 5 days (control vs PCT) in the high MR-proADM sub-group (Figure 5). To detect an arm–by-sub-group interaction effect of this size with 90% power whilst controlling the type I error level at 5%, we need 25 participants per biomarker sub-group in each trial arm, as calculated with the method of Peterson & George (19). To achieve this sample size, given the assumed proportions of participants falling into each MR-proADM sub-group (as given in Figure 5), and also inflating for 5% dropout, we need to recruit a total of 266 participants.

For ImmunoXpert, we assume median antibiotic durations of 1 versus 3 days (control vs PCT) in the low ImmunoXpert sub-group, 7 versus 4 days (control vs PCT) in the intermediate ImmunoXpert sub-group, and 10 versus 5 days (control vs PCT) in the high ImmunoXpert sub-group (Figure 5). Based on similar calculations as for MR-proADM above, we need 13 participants per biomarker sub-group in each trial arm, and thus a total of 138 when taking into account the assumed proportions of participants in each ImmunoXpert sub-group (as given in Figure 5), and inflating for 5% dropout. Consequently, 266 is the overall sample size target for this study.

19.10 Statistical Analysis

Serial measurement of MR-ProADM and TRAIL, IP-10, and CRP (ImmunoXpert) will provide mechanistic understanding of response to antibiotics due to endothelial dysfunction and organ dysfunction (MR-ProADM), or due to host immune response to bacterial or viral pathogens (TRAIL, IP-10, and CRP (ImmunoXpert)). By determining patients with levels of MR-ProADM that are high or low at randomisation, we can identify subgroups of patients in whom a PCT-guided antibiotic algorithm may be harmful or beneficial respectively. Determining patients whose ImmunoXpert index test score is below 0·35 (likely viral or other host immune response), or above 0·65 (likely bacterial host immune response) at randomisation, and remains so serially, may identify subgroups of patients in whom a PCT-guided antibiotic algorithm may be ineffective, beneficial or harmful.

For the primary analysis, we will fit a Cox proportional hazards model with time until IV antibiotic therapy is discontinued as dependent variable and both intervention arm and biomarker sub-group as independent variables, as well as their interaction. We will fit two separate models, one for MR-proADM and one for ImmunoXpert. This primary analysis will be intention-to-treat with respect to the randomisation in the host trial (BATCH). Additionally, we will perform a similar analysis but with biomarker sub-group definitions based on serial measurements e.g. whether the biomarker value increases, remains high, or decreases over the course of the first 3-4 days. Analyses of secondary outcomes will involve similar regression models depending on the type of outcome variable (e.g. logistic regression for a binary outcome). Full details of all analyses, including strategies to handle missing values, will be set out in a statistical analysis plan that will be aligned with the BATCH statistical analysis plan.

19.11 Key Milestones

Month 1-8: Sample collection and archiving (~4 sites)
Month 8-14: Measurement of MR-ProADM and ImmunoXpert in plasma samples blinded as to randomisation arm
Month 15-18: Data cleaning, statistical analysis, prepare for EME report, dissemination

Figure 5: Hypothesised effects of stratification in PCT-guided antibiotic arm compared to control arm, and assumed proportions of participants falling into each sub-group

MR-ProADM low (50%) (no endothelial dysfunction or organ dysfunction)	Beneficial/Limited value Antibiotic duration ↑ (2 days control arm vs 4 days PCT arm)
MR-ProADM intermediate (20%)	Beneficial/ Harmful Antibiotic duration ↓ (7 days control arm vs 5 days PCT arm)
MR-ProADM high (30%) (Endothelial dysfunction +/- organ dysfunction)	Beneficial/ Harmful Antibiotic duration ↓ (10 days control arm vs 5 days PCT arm)
ImmunoXpert low (20%) (Likelihood of viral or other immune response)	Limited value Antibiotic duration ↑ (1 day control arm vs 3 days PCT arm)
ImmunoXpert intermediate (20%)	Beneficial Antibiotic duration ↓ (7 days control arm vs 4 days PCT arm)
ImmunoXpert high (60%) (Likelihood of bacterial immune response)	Beneficial/Harmful Antibiotic duration ↓ (10 days control arm vs 5 days PCT arm)

20 Protocol/GCP non-compliance

The PI / local researcher should report any non-compliance to the trial protocol or the conditions and principles of Good Clinical Practice to the CTR in writing as soon as they become aware of it. The CTR will assess the nature and severity of any issues of non-compliance in accordance with their SOPs.

21 End of Trial definition

The end of the study is defined as the date of final data capture to meet the trial endpoints. Sponsor must notify REC of the end of a clinical trial within 90 days of its completion or within 15 days if the study is terminated early.

22 Archiving

The TMF and TSF containing essential documents will be archived at an approved external storage facility for 10 years. The CTR will send the TMF and TSFs to Sponsor for archiving. The Principal Investigator is responsible for archival of the ISF at site on approval from Sponsor. Essential documents pertaining to the trial shall not be destroyed without permission from the Sponsor.

23 Regulatory Considerations

23.1 Ethical and governance approval

This Study Protocol has been submitted to a Research Ethics Committee (REC) that is legally "recognised" by the United Kingdom Ethics Committee Authority (UKECA) for review and approval. A favourable ethical opinion will be obtained from the REC before commencement of any study procedures (including recruitment of participants).

This Study Protocol will be submitted through the relevant permission system for global governance via Health Research Authority (HRA).

Approval will be obtained from the host care organisation who will consider local governance requirements and site feasibility. The Research Governance approval of the host care organisation must be obtained before recruitment of participants within that host care organisation.

All substantial protocol amendments must be approved by the REC responsible for the study, in addition to approval by NHS Research and Development (R&D). Minor amendments will not require prior approval by the REC.

If the study is stopped due to adverse events or an urgent safety measure it will not be recommenced without reference to the REC responsible for the study.

The outcome of the study (e.g. completed) will be reported to the REC responsible for the study within 90 calendar days of study closure. In the event of the study being prematurely terminated a report will be submitted to the REC responsible for the study within 15 calendar days.

A summary of the results will be submitted to the REC responsible for the study within one year of completion of study closure.

23.2 Data Protection

The CTR will act to preserve participant confidentiality and will not disclose or reproduce any information by which participants could be identified, except where specific consent is obtained. Data will be stored in a secure manner and will be registered in accordance with the General Data Protection Regulation (GDPR) (EU2016/679). The data custodian and the translational sample custodian for this study is the Chief Investigator.

Participants will always be identified using their unique study identification number and any additional identifiers. This includes collection of NHS number (or equivalent – e.g. CHI number in Scotland), name and postcode to register and trace participants with NHS Digital.

23.3 Indemnity

BATCH is sponsored by The University of Liverpool and will be co-ordinated by the CTR at Cardiff University. The Sponsor does not hold insurance against claims for compensation for injury caused by participation in a clinical trial and they cannot offer any indemnity. As this is an investigator-initiated study, The Association of the British Pharmaceutical Industry (ABPI) guidelines for patient

compensation by the pharmaceutical industry do not apply. However, in terms of liability: NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and they are legally liable for the negligent acts and omission of their employees. Compensation is therefore available in the event of clinical negligence being proven. The Sponsor does not accept liability for any breach in any other hospital's duty of care, or any negligence on the part of employees of hospitals. This applies whether the hospital is an NHS Trust or not.

Clinical negligence is defined as:

"A breach of duty of care by members of the health care professions employed by NHS bodies or by others consequent on decisions or judgments made by members of those professions acting in their professional capacity in the course of their employment, and which are admitted as negligent by the employer or are determined as such through the legal process".

The Sponsor has vicarious liability for the actions of its staff, when through the course of their employment they are involved in the design and initiation of a clinical trial, including but not limited to the authorship of the Clinical Trial Protocol. The University of Liverpool has appropriate insurance in place to cover this liability.

23.4 Trial sponsorship

University of Liverpool will act as Sponsor for study. Delegated responsibilities will be assigned to the sites taking part in this study.

The Sponsor shall be responsible for ensuring that the study is performed in accordance with the following:

- Conditions and principles of Good Clinical Practice.
- Declaration of Helsinki (1996)
- Research Governance Framework for Health and Social Care (Welsh Assembly Government 2009 and Department of Health 2nd July 2005).
- The GDPR (EU2016/679).
- Other regulatory requirements as appropriate.

The Sponsor has/will be delegating certain responsibilities to CTR, the CI, PIs, host sites and other stakeholder organisations as appropriate in accordance with the relevant agreement that is informed by regulation and study type.

23.5 Funding

This project was funded by the National Institute for Health Research Health Technology Assessment (NIHR HTA) Programme (project number 15/188/42) and will be published in full in Health Technology Assessment. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the HTA programme, NIHR, NHS or the Department of Health.

High street vouchers to a maximum value of £20 will be offered to participants taking part in the parental qualitative interviews as a token of appreciation for their time in taking part in the study.

The study will be adopted on the NIHR portfolio.

24 Trial management

24.1 Project Team (PT)

The Project Team (PT) will meet fortnightly and will include the Chief Investigators Trial Manager, Data Manager, Statistician, Administrator and other research staff directly employed to the trial. The project team will discuss all day-to-day management issues and will refer any key management decisions to the Trial Management Group (TMG).

24.2 Trial Management Group (TMG)

The TMG will consist of the CIs, Co-Applicants, Collaborators, TM, DM, TS and TA. The role of the TMG will be to help set up the trial by providing specialist advice, input to and comment on trial procedures and documents (information sheets, Protocol, etc.). They will also advise on the promotion and running of the trial and deal with any issues that arise. The group will normally meet monthly throughout the course of the study. TMG members will be required to sign up to the remit and conditions as set out in the TMG Charter.

24.3 Trial Steering Committee (TSC)

A Trial Steering Committee (TSC), consisting of an independent chair, and three other independent members including a patient representative, will meet at least annually. The first meeting will be before the trial commences to review the Protocol and arrange the timelines for the subsequent meetings. If necessary, additional/more frequent meetings may occur. The TM and TS will attend as observers. The TSC will provide overall supervision for the study and provide advice through its

independent chair. The ultimate decision for the continuation of the study lies with the TSC. TSC members will be required to sign up to the remit and conditions as set out in the TSC Charter.

24.4 Independent Data Monitoring Committee (IDMC)

In order to monitor accumulating data on safety and any trial intervention benefit, an IDMC will be established. The Committee will consist of an independent chair and two/three other independent members. The first meeting will take place before the trial commences in order to review the Protocol and agree on timelines for interim analyses to take place. The main role of the IDMC is to review the data periodically and makes recommendations to the TSC.

IDMC members will be required to sign up to the remit and conditions as set out in the IDMC Charter which will be filed in the TMF.

24.5 Public and Patient Involvement (PPI)

In developing the design of this research study, we actively sought the input of Liverpool GenerationR Young Person's Advisory Group (YPAG). The group consists of 19 young people aged between 12 to 17 year olds. The group have worked with several researchers exploring the topic of developing tests to rapidly detect or diagnose serious bacterial infection in children, including the development of a rapid salivary test to detect serious bacterial infection in children presenting to the Emergency Department (ED) (SPICED study), and a study looking at the diagnostic biomarkers in children on PICU (DISTINCTIVE study). The YPAG are well aware of the problems associated with diagnosing and treating sepsis and when approached by the research team to discuss this study they expressed a preference for a shorter course of IV antibiotics, if it was safe to do so. The group have discussed at length the issues associated with AMR and the need to educate young people and families about the misuse of antibiotics and felt that findings from this study could be developed into educational materials for patients and families.

A parent advisory group consisting of approximately 4-6 parents/carers will be set up and supported by our PPI liaison officer. Their role will be to advise on: the design of parent information leaflets, design of interview schedules and the data generation templates for the qualitative work in the pilot phase, qualitative data analysis, and dissemination strategies. Members of the group will be invited to attend steering group meetings on a rotational basis. We will also involve the Liverpool GenerationR YPAG, throughout the duration of the trial. The group will advise on young peoples' information

sheets for research ethics; interview schedules and the production of educational materials for young people and families on the most appropriate use of antibiotics. Educational materials will be made available in hospitals, GP practices, and schools, distributed to teachers, parents and young people, and posted on the GenerationR website. We will invite parents and young people to contribute actively to dissemination events, including presenting parents/young peoples' views/stories. Members of the YPAG and parents will be supported and trained and supported by our PPI liaison officer.

The parent and YPAG will seek to partner with Antibiotic Action, a charity promoting public awareness about antibiotics and AMR, and utilise their resources. They will be encouraged to register as Antibiotic Champions providing information to peers, schools and other contacts about the importance of antibiotics, how to use them, and the need for new treatments for infections.

25 Quality Control and Assurance

25.1 Risk Assessment

A Risk Assessment has been completed to identify the potential hazards associated with the study and to assess the likelihood of those hazards occurring and resulting in harm. This risk assessment includes:

- The known and potential risks and benefits to participants
- How high the risk is compared to normal standard practice
- How the risk will be minimised/managed

This trial has been categorised as Low + risk, where the level of risk is slightly higher than the risk of standard medical care. A copy of the study risk assessment may be requested from the Trial Manager. The trial risk assessment is used to determine the intensity and focus of monitoring activity (see section 24.2).

25.2 Monitoring

The risk assessment has been used to determine the intensity and focus of central and on-site monitoring activity in the BATCH study. Low+ monitoring levels will be employed and are fully

documented in the study monitoring plan. Investigators should agree to allow study related monitoring, including audits and regulatory inspections, by providing direct access to source data/documents as required. Participant consent for this will be obtained. Findings generated from on-site and central monitoring will be shared with the Sponsor, CI, PI & local R&D.

25.3 Audits & inspections

The study is participant to inspection by the Health Technology Assessment programme (HTA) as the funding organisation. The study may also be participant to inspection and audit by Liverpool University under their remit as Sponsor.

26 Publication policy

All publications and presentations relating to the study will be authorised by the TMG and will be in accordance with the trial's publication policy. In addition to the required final report and monograph for the HTA Programme, we will publish the main study results in international peer-reviewed journals and present at national and international scientific meetings. With the assistance of our collaborators and lay representatives we will disseminate the trial findings to a wide NHS and general audience and vigorously promote uptake of the trial results into clinical care. At the local level, we will interact with and promote the research findings through wider NHS Trusts (Health Boards in Wales), the NIHR Clinical Research Network: North West Coast, North West Coast CLAHRC, North West Coast AHSN (Innovation Agency). The Innovation Agency is the national lead within AHSNs for sepsis through the Patient Safety Collaborative.

Nationally, we will engage with NICE, the Royal College of Paediatrics and Child Health, The British Society for Antimicrobial Chemotherapy, British Infection Society, and the British Paediatric Allergy, Immunity and Infection Group.

Through the Liverpool GenerationR YPAG, we will produce educational materials for young people and families on the most appropriate use of antibiotics. Educational materials will be made available in hospitals, GP practices, and schools. Materials will also posted on the GenerationR website www.generationr.org.uk to be distributed to teachers, parents and young people. With the help of the YPAG, we will develop the website content for a lay audience, and produce an annual newsletter

for children, young people and families. The study findings will be disseminated to children, families and schools through the YPAG.

27 Milestones

Month 1-10: Study and site set-up (at least 5 sites to be open for month 1 of recruitment)

Month 10-19: Internal pilot phase (assessed by progression criteria). Assess acceptability of the PCT results in clinical management, and finalise study management algorithm, based on feedback. Training materials will be developed for clinical staff.

Month 20-44: Continuation of RCT recruitment and data collection to determine effectiveness and cost effectiveness of the intervention**.**

Month 45-50: Data cleaning, statistical analysis, prepare for HTA report.

28 References

1. McMullan B, Andersen D, Blyth C, Avent M, Bowen A, Britton P, et al. Antibiotic duration and timing of the swtich from intravenous to oral route for bacterial infections in children: systematic review and guidelines. Lancet Infectious Diseases. 2016;16(8):e139-52.
2. Singer M, Deutschman C, Seymour C, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801-10.
3. Kumar A, Roberts D, Wood K, Light B, Parrillo J, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human spetic shock. Critical Care Medicine. 2006;34(6):1589-96.
4. Fischer J, Ramser M, Fanconi S. Use of antibiotics in pediatric intensive care and potential savings. Intensive Care Medicine. 2000;27(7):959-66.
5. Goldmann D, Weinstein R, Wenzel R, Tablan O, Duma R, RP. G, et al. Strategies to Prevent and Control the Emergence and Spread of Antimicrobial-Resistant Microrganisms in Hospitals. A challenge to hospital leadership. JAMA. 1996;275(3):234-40.
6. Carrol E, Thomson A, Hart C. Procalcitonin as a marker of sepsis. International Journal of Microbial Agents. 2002;20(1):1-9.
7. Department of Health. UK 5 Year Antimicrobial Resistance Strategy 2013-2018. 2013.
8. Deaprtment of Health. Start Smart - Then Focus: Antimicrobial Stewaedship Toolkit for English Hospitals. 2015.
9. Trasy D, Tanczos K, Nemeth M, Hankovszky P, Lovas A, Mikor A, et al. Early Procalcitonin kinetics and appropriateness of empirical antimicrobial therapy in critically ill pateints: A prospective observational study. Journal of Critical Care. 2016;34:50-5.
10. Huang M, CHen C, Chien J, Wu K, Chang Y, Wu K, et al. Serum Procalcitonin and Procalcitonin Clearence as a Prognostic Biomarker in Patients with Severe Sepsis and Septic Shock. Biomed Research International.2016(1758501.).

11. Westwood M, Ramaekers B, Whiting P, Tomini F, Joore M, Armstring N, et al. Procalcitonin testing to guide antibiotic therapy for the treatment of sepsis in intenstive care settings and for suspected bacterial infeaction in emergency department settings: a systematic review and ocst-effectiveness analysis. Health Technology Assessment. 2015;19(96).
12. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M, et al. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ. 2008;337:a1655.
13. O'Cathain A, Hoddinott P, Lewin S, Thomas K, Young B, Adamson J, et al. Maximising the impact of qualitative research in feasibility studies for randomised controlled trials: guidance for researchers. Pilot and Feasibility studies. 1. 2015;32(1-13).
14. Ritchie J, Lewis J. Qualitative Research Practice: A guide for social science students and researchers. London: Sage Publications; 2003.
15. Gale N, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. BMC Med Res Methodol. 2013;13:117.
16. Freemantle N, Calvert M, Wood J, Eastaugh J, Griffin C. Composite outcomes in randomized trials: greater precision but with greater uncertaintly? JAMA. 2003;289(19):2554-9.
17. Cordoba G, Schwartz L, Woloshin S, Bae H, Gotzsche P. Definition, reporting, and interpretation of composite outcomes in clinical trials: systematic review. BMJ.2010(341):c3920.
18. Chuang-Stein C, Stryszak P, Dmitrienko A, Offen W. Challenge of multiple co-primary endpoints: a new approach. Stat Med. 2007;26(6):1181-92.

19. Peterson B, George SL, (1993) Sample size requirements and length of study for testing interaction in a 2 x k factorial design when time-to-failure is the outcome [corrected]. Control Clin Trials 14: 511-522